Seminar



1

Pd-catalyzed enantioselective [4+3] intermolecular cycloaddition

Reporter : Xinyue Wang Supervisor : Prof. Junliang Zhang

2023-9-8



1. Background

- 2. Palladium-catalyzed enantioselective intermolecular [4+3] cycloaddition
 2.1 Trimethylenemethane(TMM) donors as three-atom building blocks
 2.2 Vinyl cyclopropanes or aziridines as three-atom building blocks
 2.3 Enals as three-atom building blocks
 2.4 Other three-atom building blocks
- 3. Summary and outlook



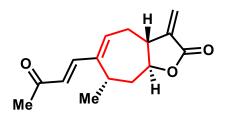
1. Background

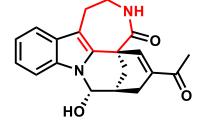
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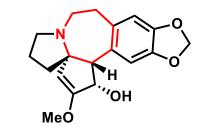
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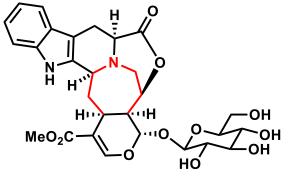
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Selected natural products and pharmaceuticals







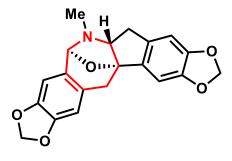


Xanthatin

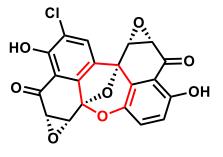
Tronocarpine

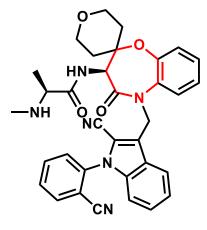
Cephalotaxine

Rubenine









Ribasine

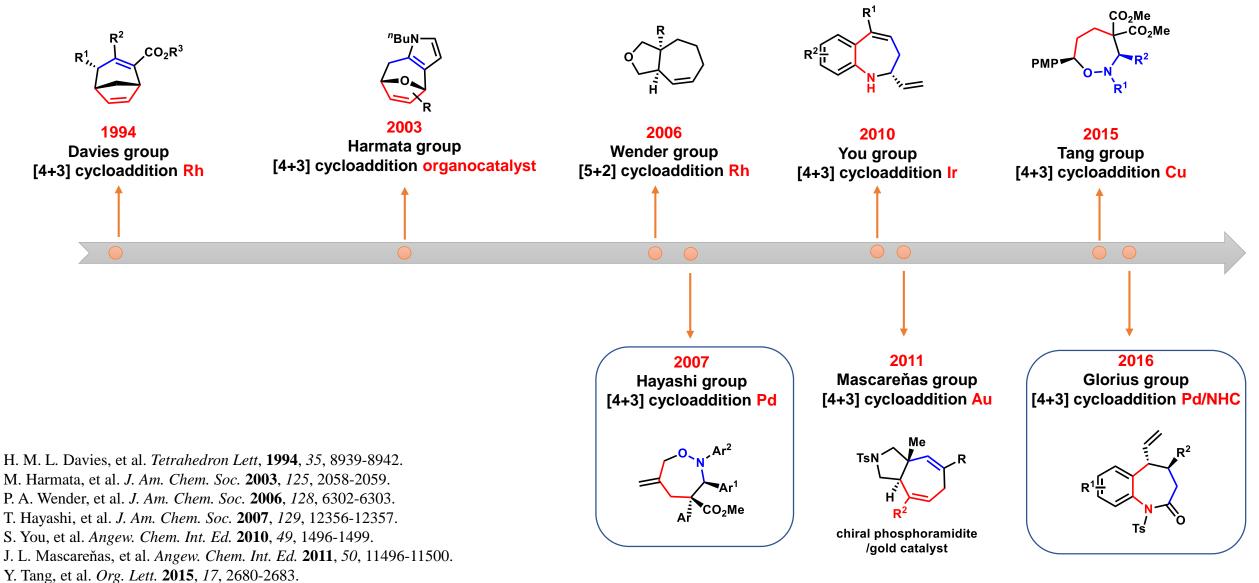
Cephalotaxine

Spiroxin A

Benzoxazepinone

1. Constructing seven-membered rings





F. Glorius, et al. J. Am. Chem. Soc. 2016, 138, 7840-7843.

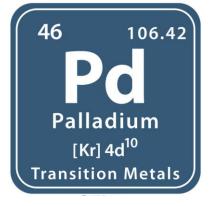
1. Constructing seven-membered rings

[5+2] $Pd_2(dba)_3$ (2 mol%) `✓<mark>N</mark>−Ar¹ L (6 mol%) PAr²2 .CHO ,R² PAr²2 Precat (10 mol%) Θ BF₄ NMPi (30 mol%) \mathbb{R}^1 toluene, rt, 10-12 h $Ar^1 = 2,6-Et_2C_6H_3$ $Ar^2 = 4 - MeC_6H_4$ Precat L R^3 $Pd_2(dba)_3$ •CHCl₃ (2.5 mol%) ····Ar³ L (11 mol%) Ar³ Ме +R³ Ph THF/CHCl₃ (1/3) N_2 -Ph rt, 6 W blue LEDs Ρh Ρh R⁴ Ph. Ph N_2 ····Ar⁴ Pd₂(dba)₃•CHCl₃ (5 mol%) `S−Ph L (12 mol%), acetone, rt, 6 W blue LEDs

F. Glorius, et al. J. Am. Chem. Soc. 2018, 140, 3551-3554.
W. Xiao, et al. J. Am. Chem. Soc. 2019, 141, 133-137.
W. Xiao, et al. Angew. Chem. Int. Ed. 2020, 59, 17429-17434.

1. Introduction







Excellent catalytic ability High functional groups tolerance Mild reaction conditions

Palladium-catalyzed cross-coupling (The Nobel Prize in Chemistry 2010) Wacker process Heck reaction Sonogashira cross-coupling Negishi cross-coupling Suzuki-Miyaura cross-coupling Stille cross-coupling Buchwald–Hartwig cross-coupling . . .



Applied in various reactions

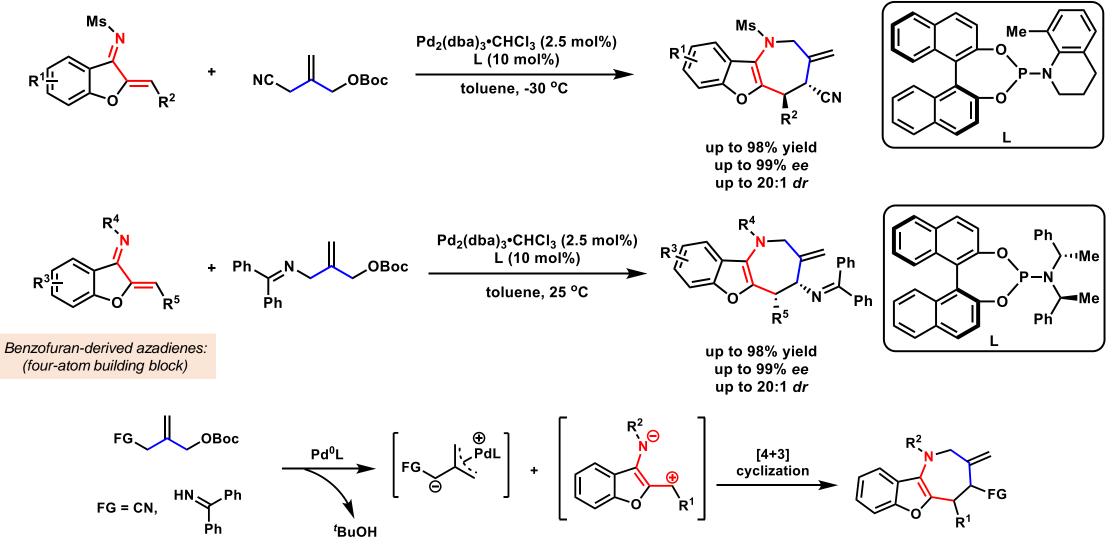


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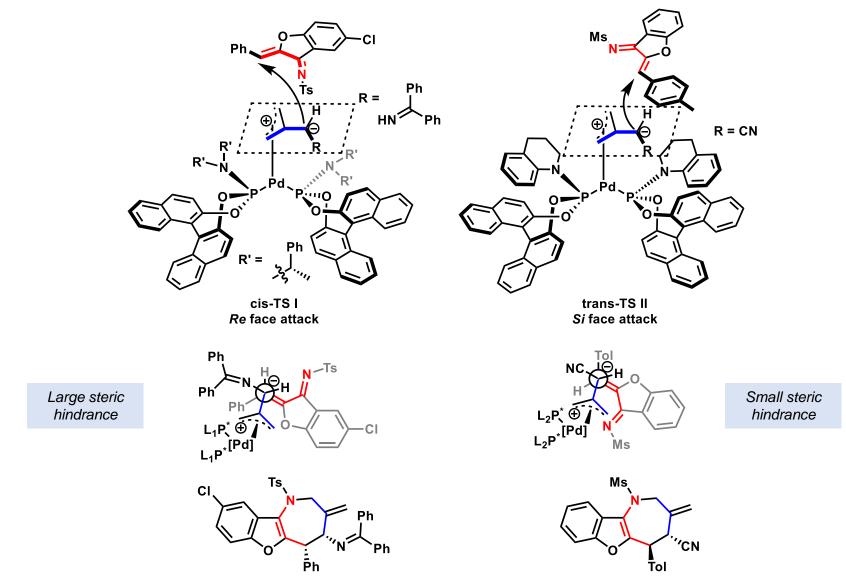
3. Summary and outlook





Opposite diastereoselectivities with different TMM donors

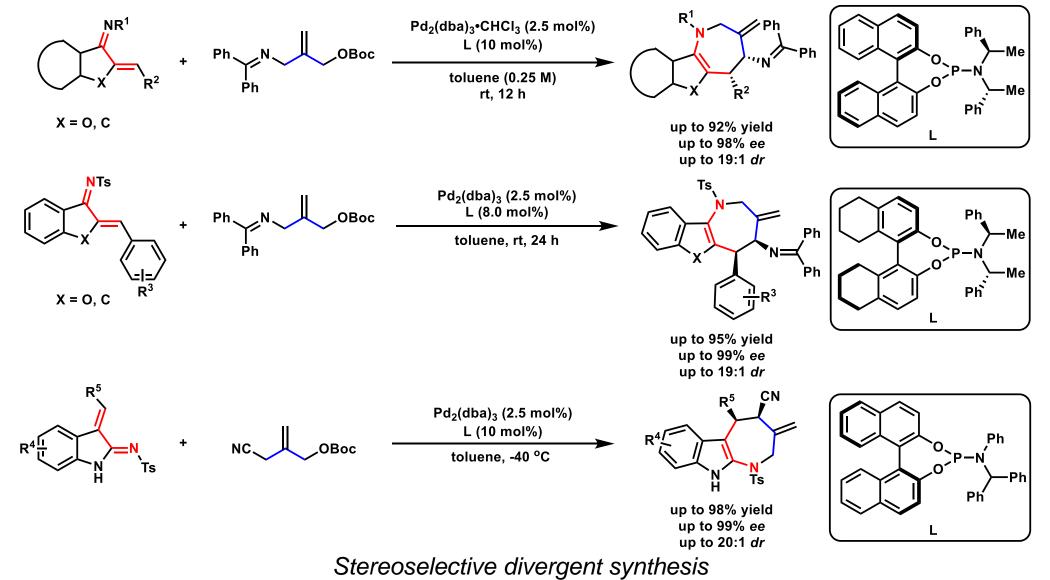




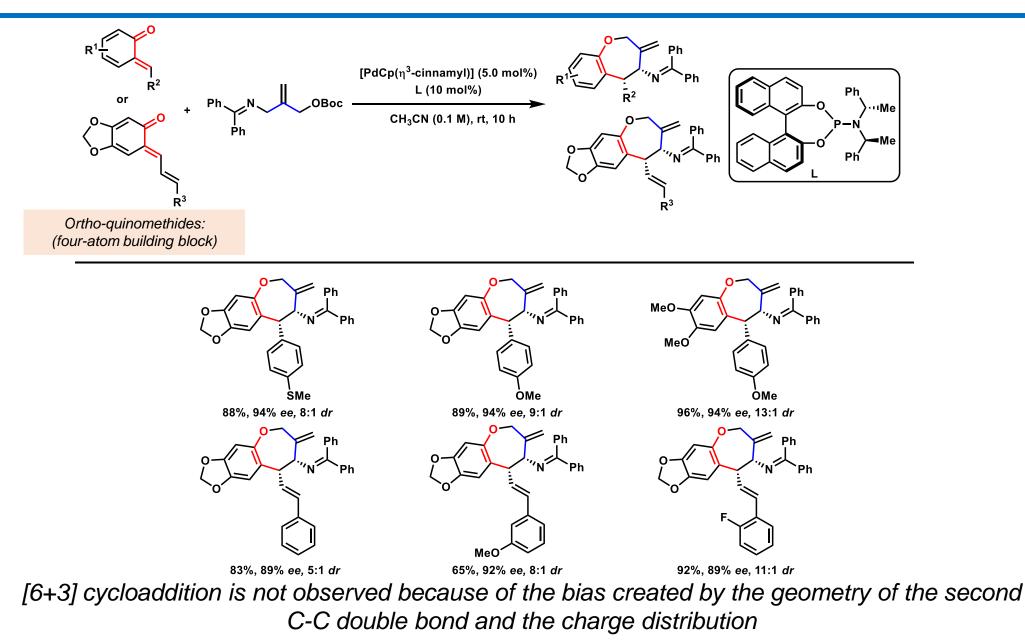
Two possible transition states explain the opposite diastereoselectivities

W. Deng, et al. Angew. Chem. Int. Ed. 2020, 59, 1238-1242.

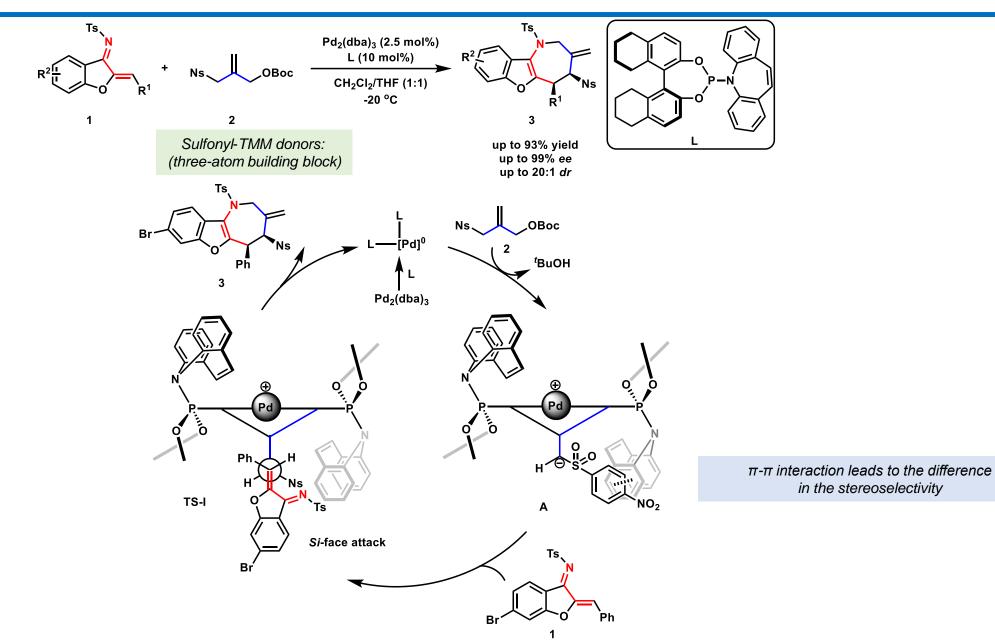




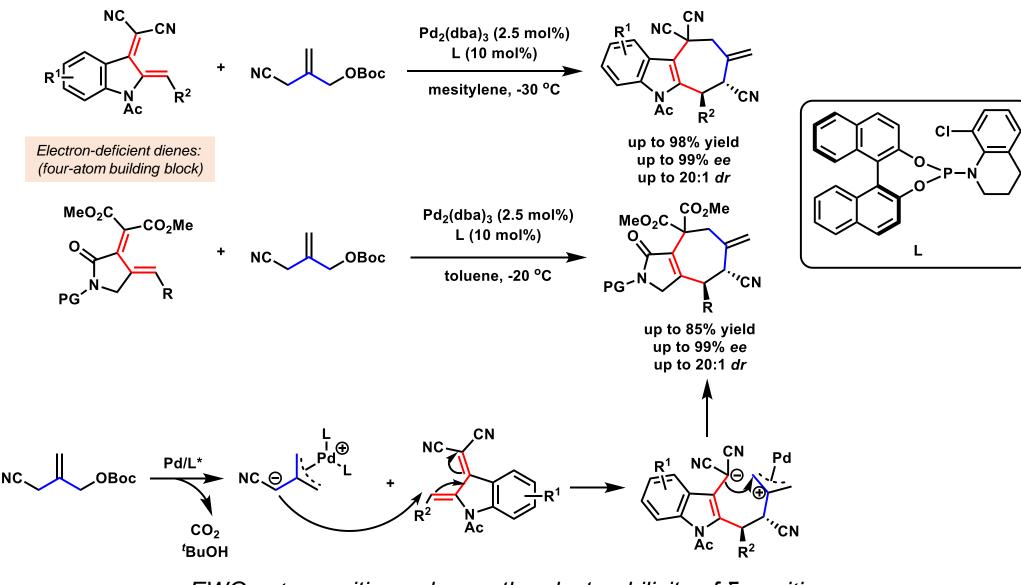
B. M. Trost, et al. Angew. Chem. Int. Ed. 2020, 59, 1243-1247.
Z. Shao, et al. Chin. J. Chem. 2020, 38, 151-157.
W. Deng, et al. Chin. J. Chem. 2020, 38, 1571-1574.





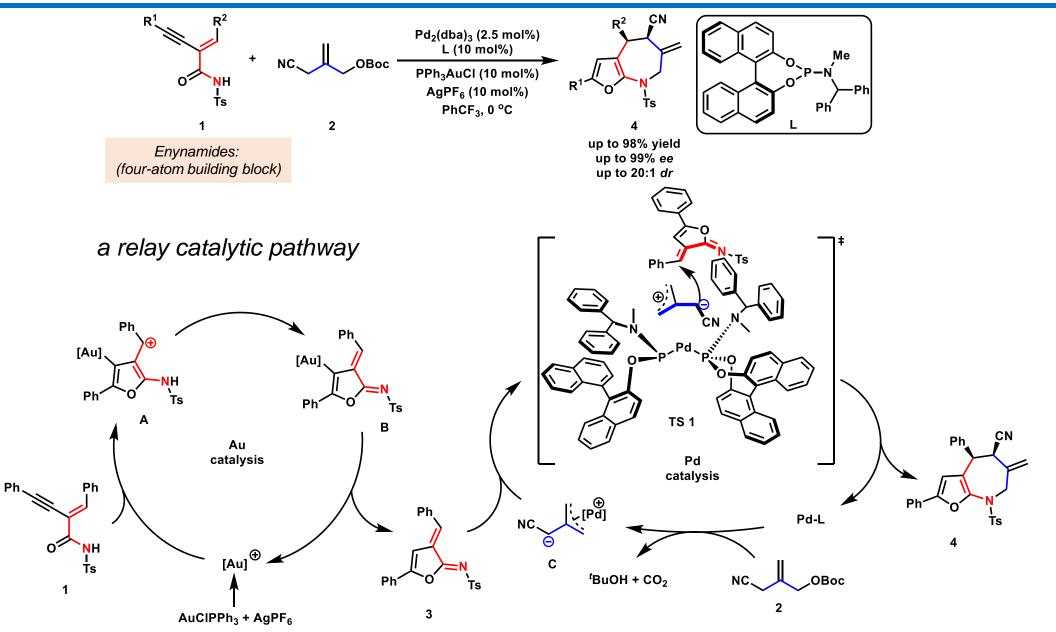






EWGs at α -position enhance the electrophilicity of δ -position





W. Deng, et al. Org. Chem. Front. 2022, 9, 4685-4691.



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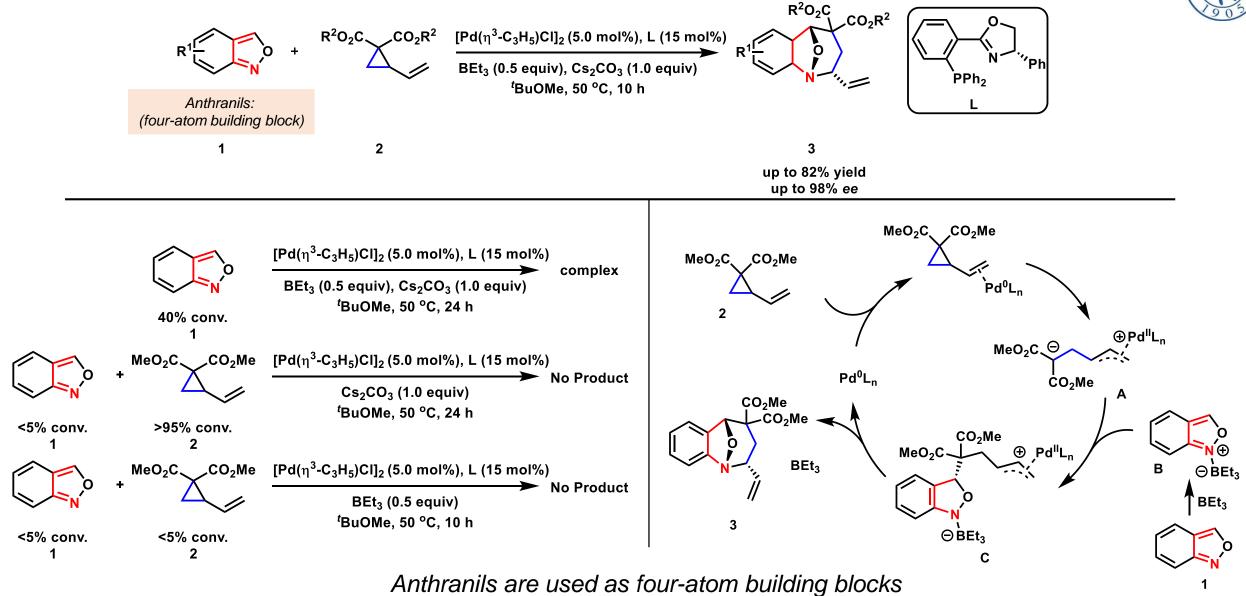
2.3 Enals as three-atom building blocks

2.4 Other three-atom building blocks

3. Summary and outlook

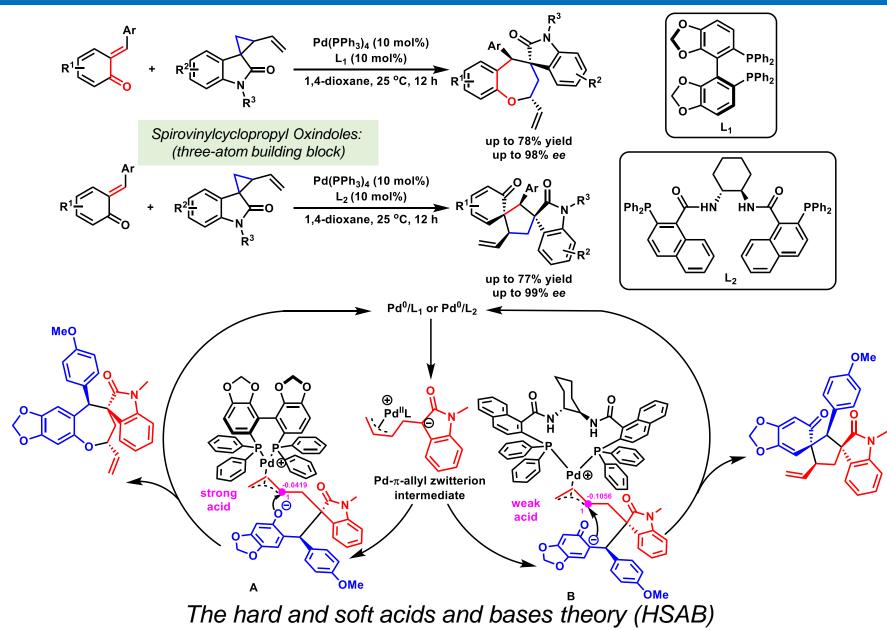
2.2 Vinyl cyclopropanes or aziridines as three-atom building blocks





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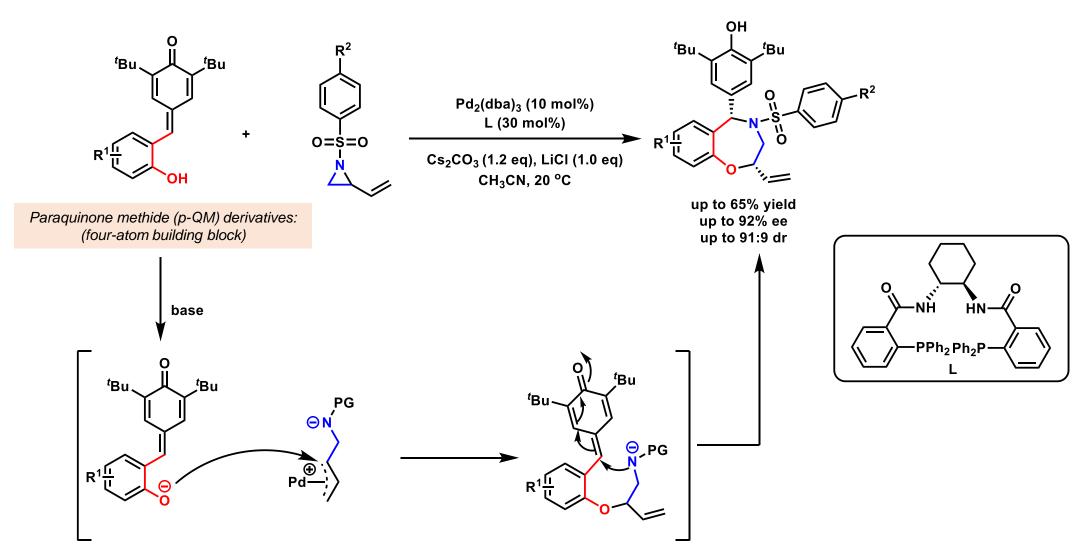




Z. Miao, et al. Org. Lett. 2022, 24, 3097-3101.

2.2 Vinyl cyclopropanes or aziridines as three-atom building blocks





Vinyl aziridines as three-atom building block



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2. Palladium-catalyzed enantioselective intermolecular [4+3] cycloaddition

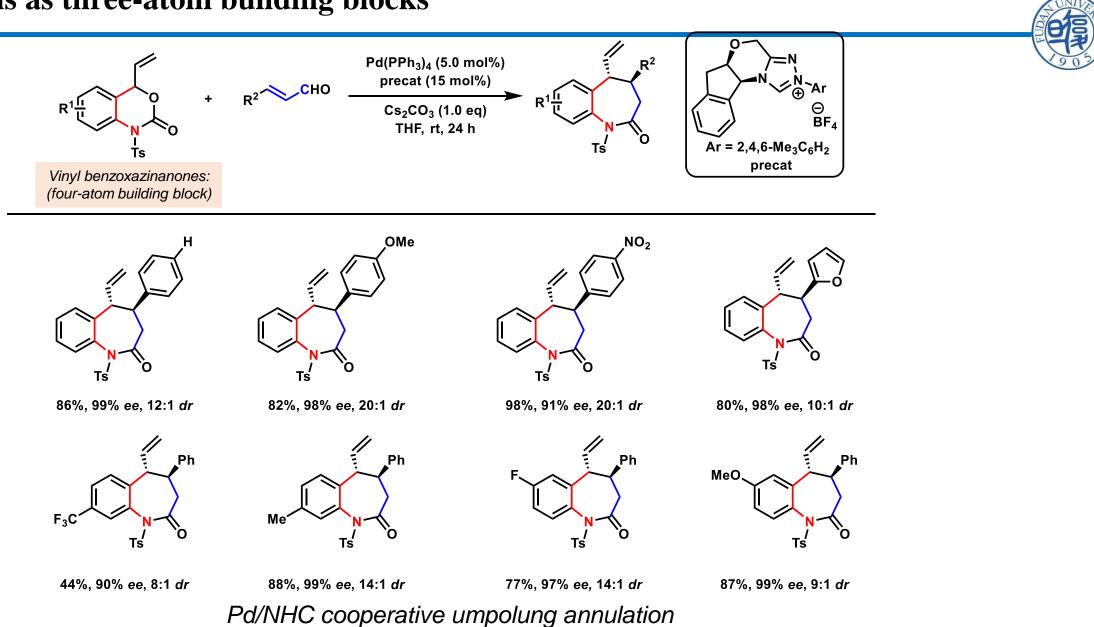
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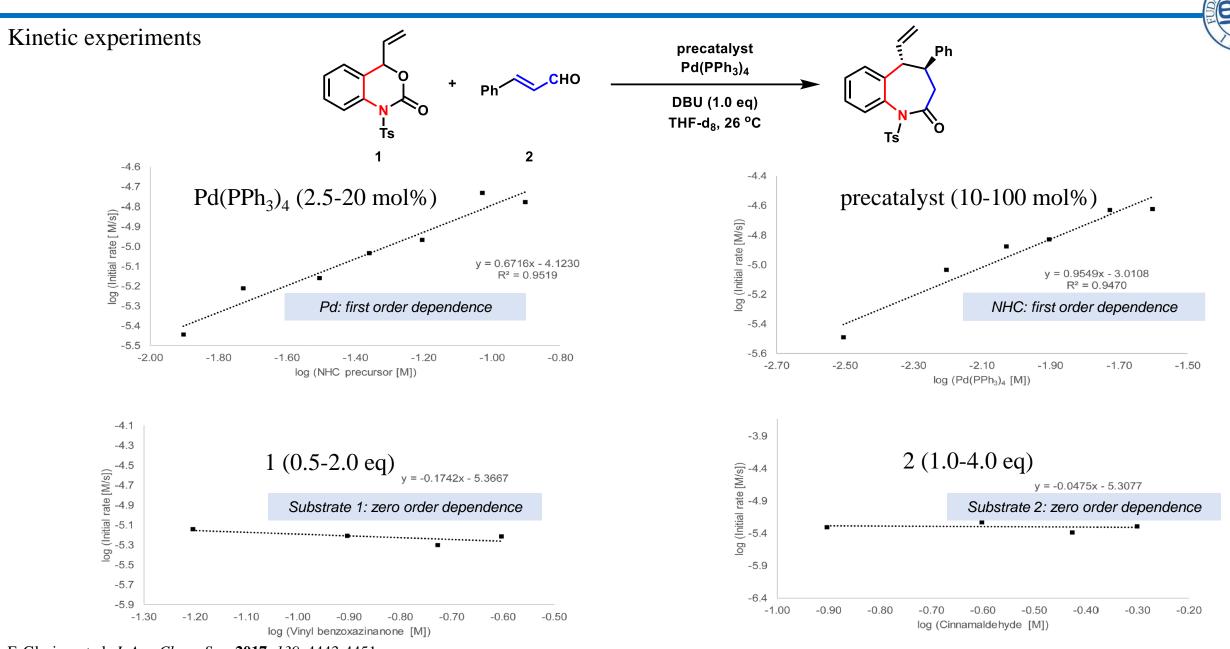
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3. Summary and outlook

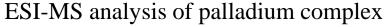


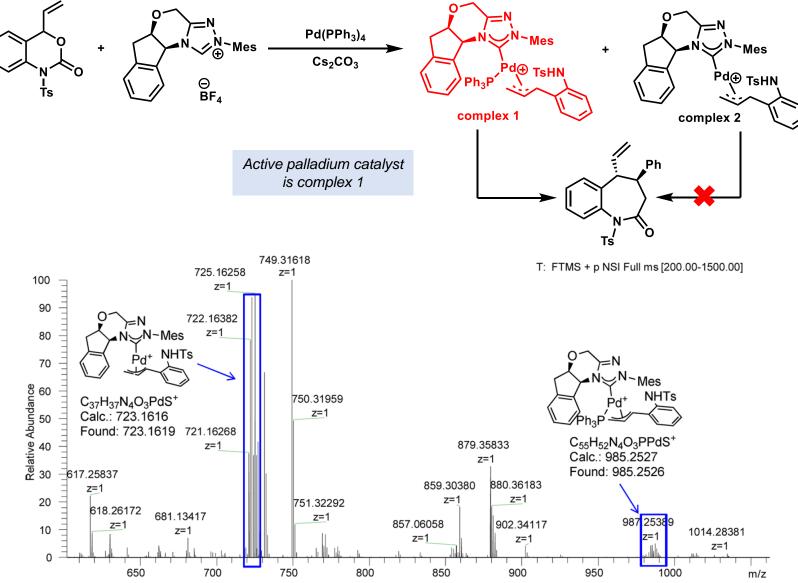
F. Glorius, et al. J. Am. Chem. Soc. 2016, 138, 7840-7843.
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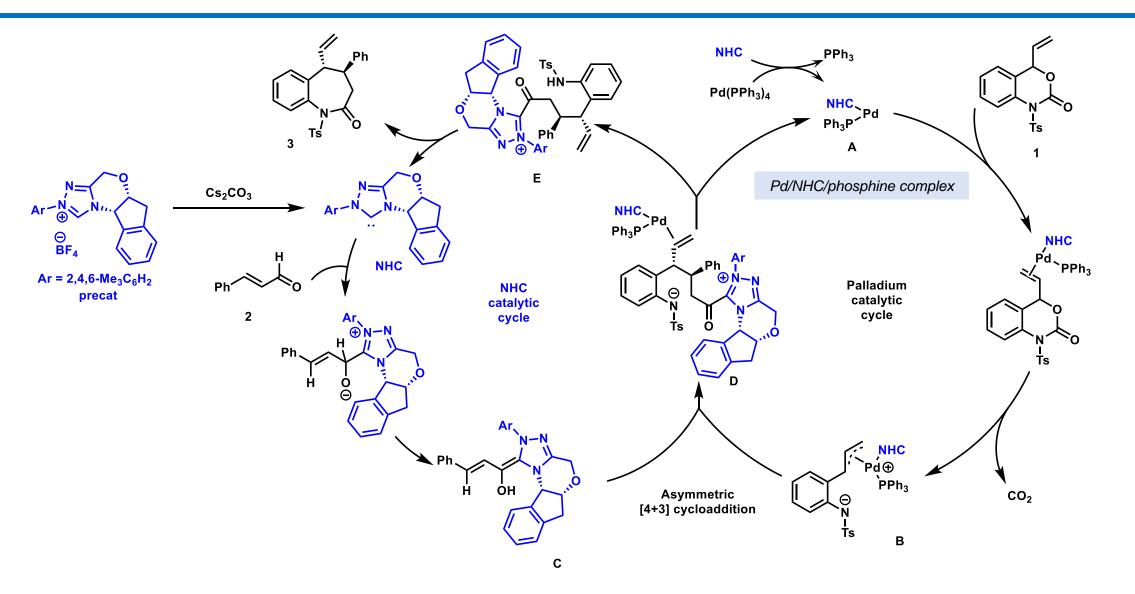
F. Glorius, et al. J. Am. Chem. Soc. 2017, 139, 4443-4451.





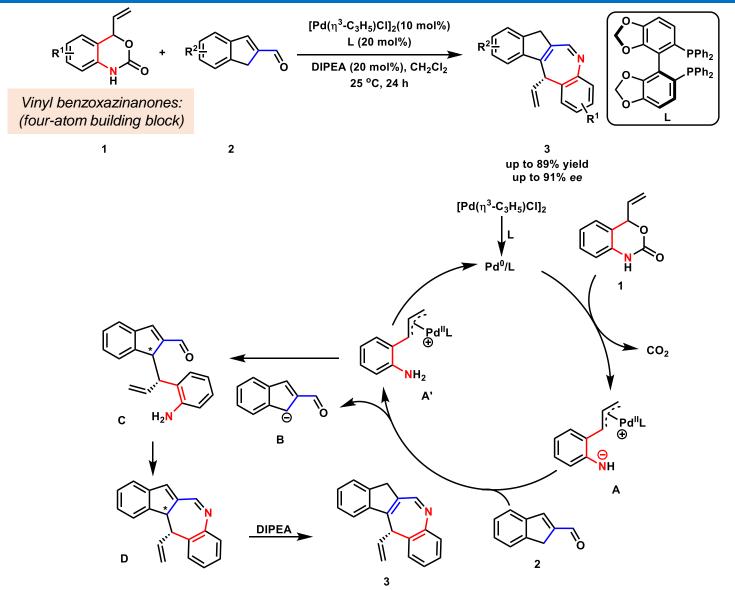


F. Glorius, et al. J. Am. Chem. Soc. 2017, 139, 4443-4451.



Dual role of the NHC (an organocatalyst and a ligand)





Thermodynamic product because the migrating C=C double bond is tetrasubstituted

Z. Miao, et al. Adv. Synth. Catal. 2023, 365, 381-387.



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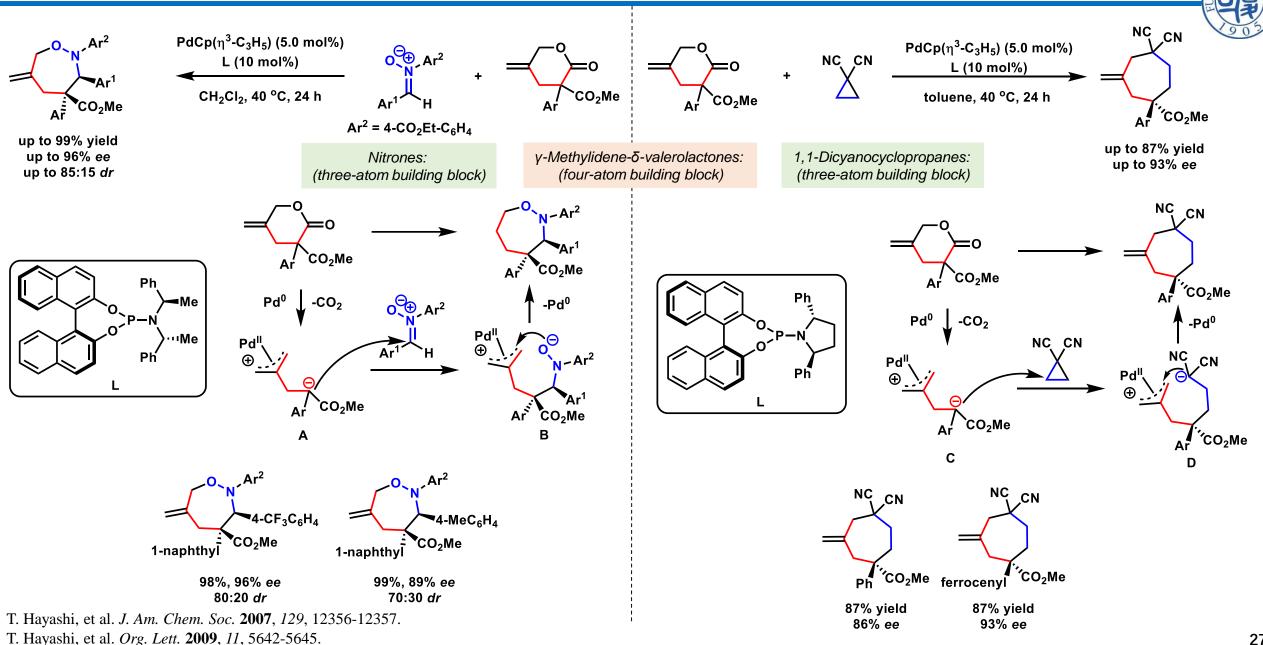
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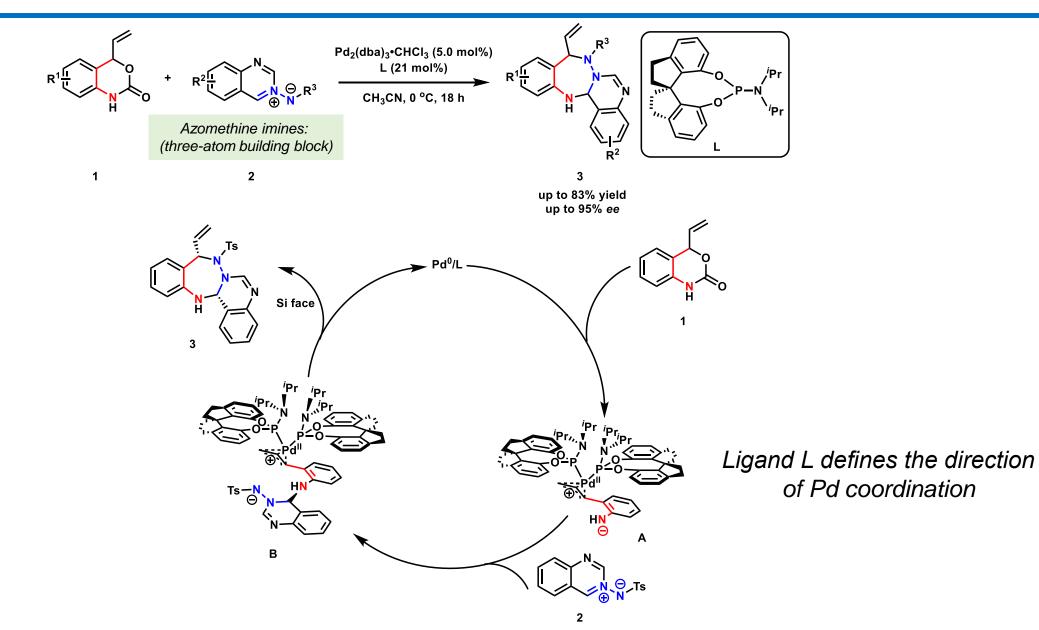
3. Summary and outlook

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2.4 Other three-atom building blocks







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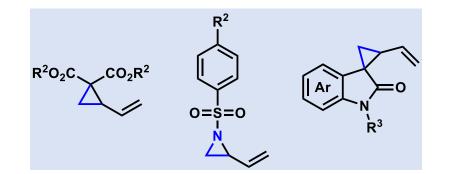
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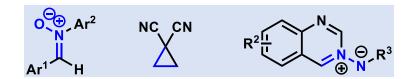
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Enals as three-atom building blocks



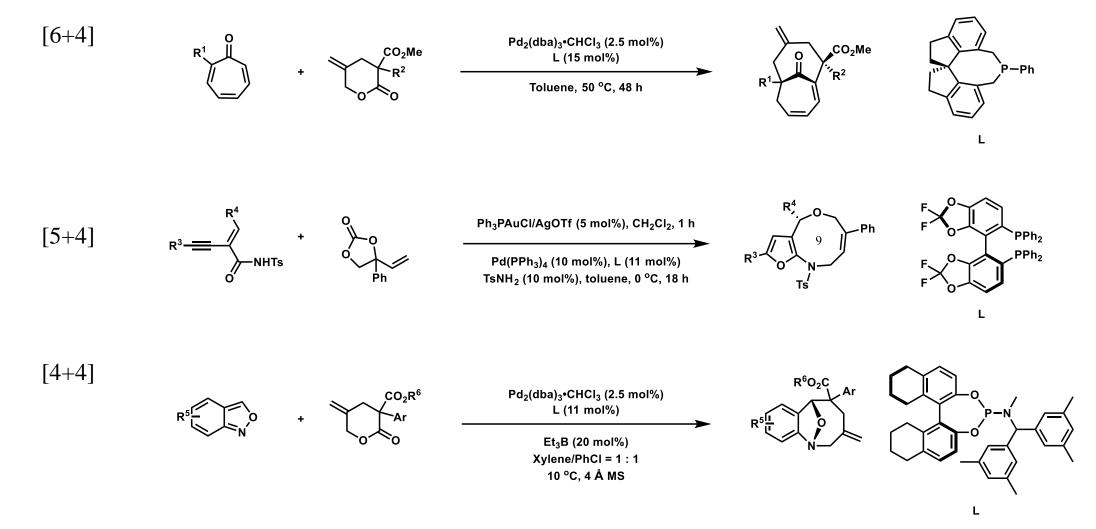
Other three-atom building blocks



3. Outlook



Three-atom building block/four-atom building block used in the construction of larger rings

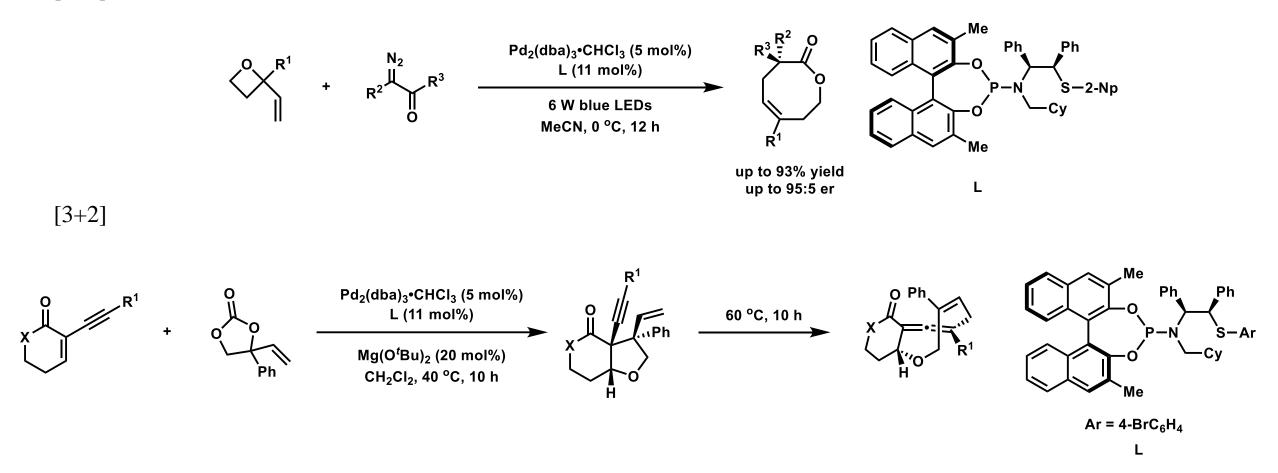


Y. Zhao, et al. *Nat. Chem.* 2020, *12*, 860-868.
Y. Zhao, et al. *Angew. Chem. Int. Ed.* 2021, *60*, 12775-12780.
X. Li, et al. *ACS Catal.* 2021, *11*, 2684-2690.

3. Outlook



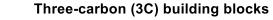
[6+2]

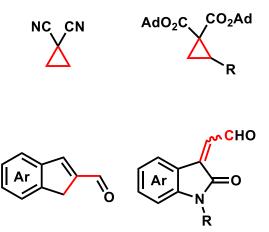


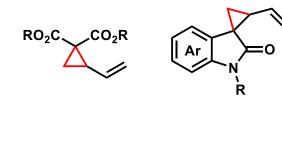
W. Xiao, et al. *Sci. China. Chem.* 2020, 65, 2437-2443.
W. Xiao, et al. *Angew. Chem. Int. Ed.* 2022, 61, e202117215.

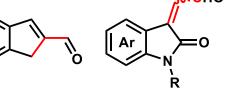
Three-atom building block



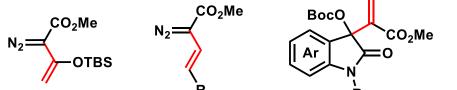


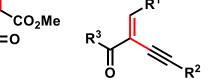


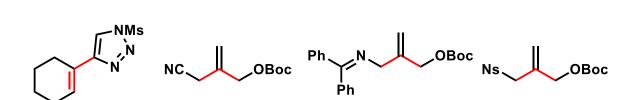




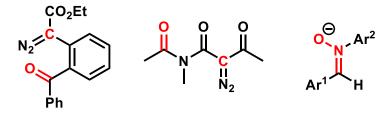




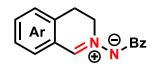


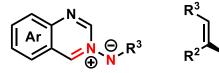


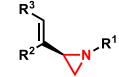
Oxa-three-atom building blocks



Aza-three-atom building blocks





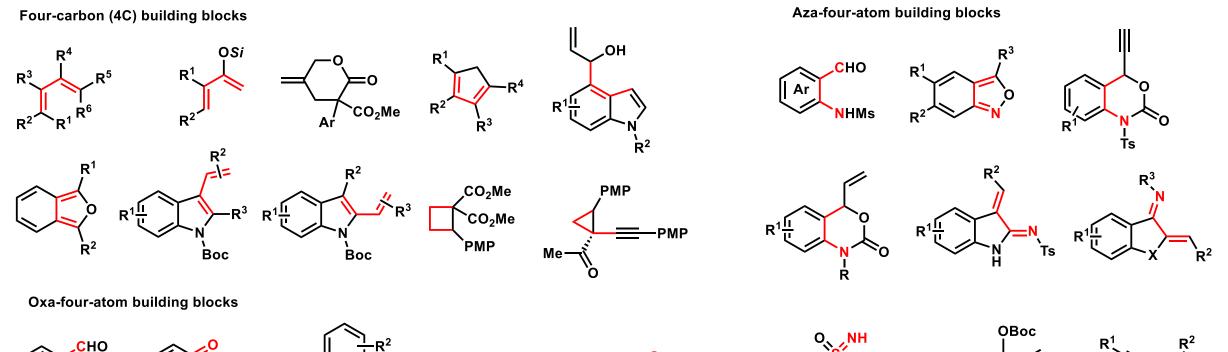


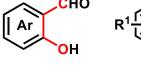
ÇO₂Et CO₂Et

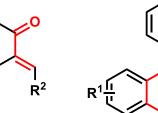


Four-atom building block

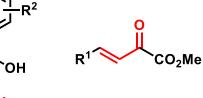


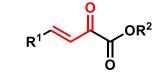


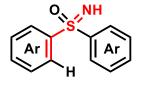




OH









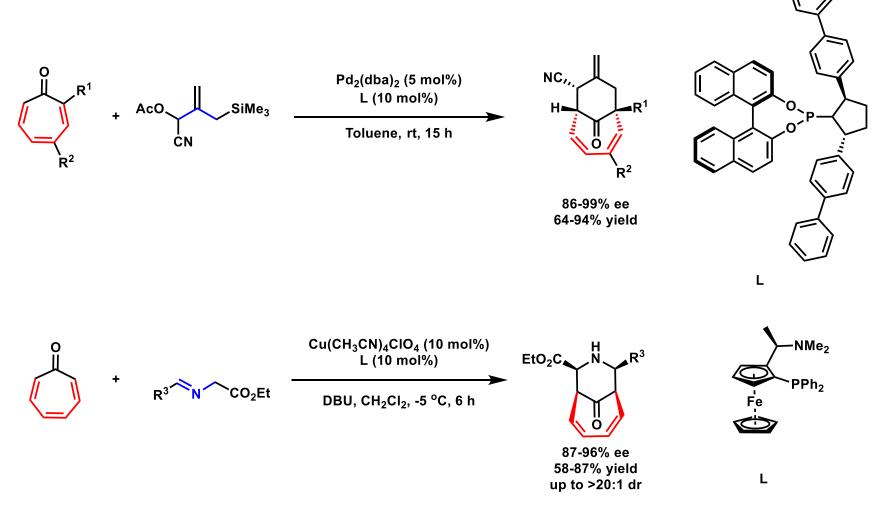
Thanks for your kind attention

3. Outlook



Three-atom building block/four-atom building block used in the construction of larger rings

[6+3]



B. M. Trost, et al. Org. Lett. 2009, 11, 3782-3785.
H. Guo, et al. J. Am. Chem. Soc. 2014, 136, 2625-2629.

3. Outlook



Three-atom building block/four-atom building block used in the construction of larger rings

[6+3] PPh₂ $Cu(CH_3CN)_4BF_4$ (5 mol%) L (5 mol%) CO₂Me `NHMe + R^{1} CO₂Me °, 1NH Fe NEt₃ (15 mol%), CH₂Cl₂ -10 °C, 18-24 h up to 90% yield L R = Aryl, Alkyl, up to 99% ee Heteroaryl up to 20:1 dr CF₃ $Cu(CH_3CN)_4BF_4$ (3 mol%) Br 0、____Ph L (3 mol%) MeO₂C NEt₃ (15 mol%), CH₂Cl₂ 'NH₂ F₃C + R² `CO₂Me F₃C NHPPh₂ H -40 °C, 18-24 h R² Ĥ Br ĊF₃ up to 88% yield up to 98% ee L up to 20:1 dr

C. Wang, et al. J. Am. Chem. Soc. 2014, 136, 4075-4080.
C. Wang, et al. J. Am. Chem. Soc. 2014, 136, 8685-8692.

Stereochemistry explanation



