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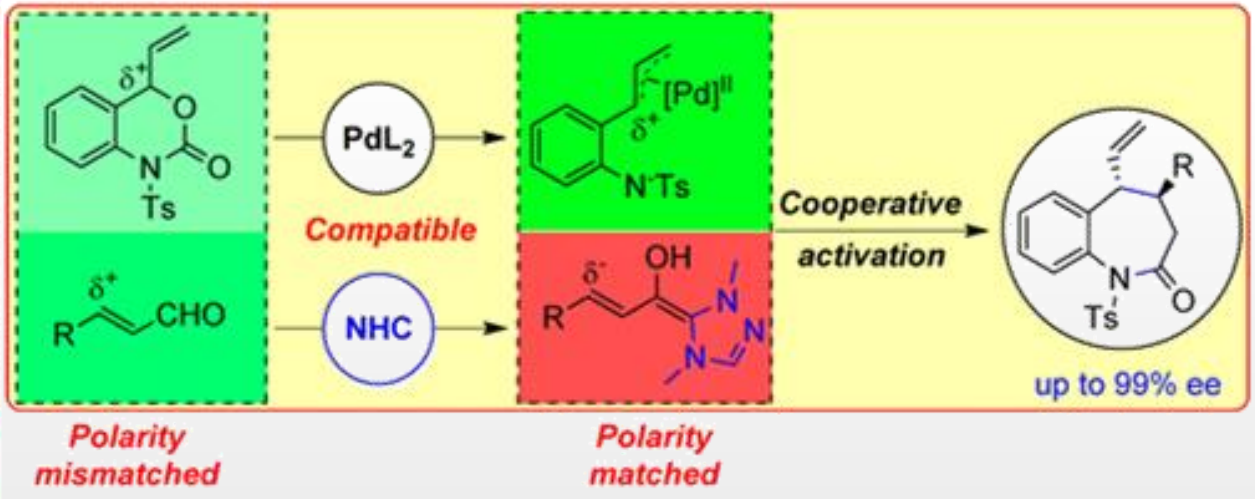
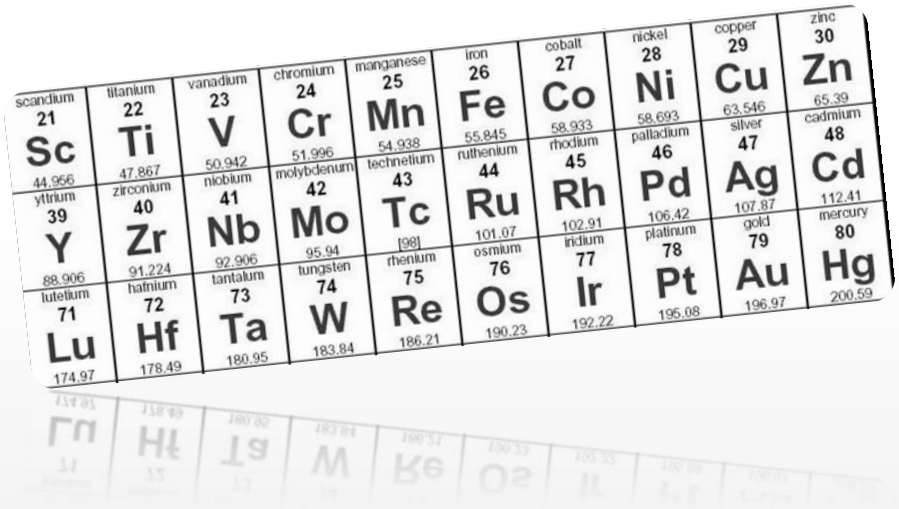
Cooperative NHC/Pd-Catalyzed Enantioselective Umpolung Annulations

C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius,
J. Am. Chem. Soc., **2016**, ASAP, DOI : 10,1021/jacs.6b04364



Dual catalysis emergence

Series of new enantioselective transformations by:



Phase-transfer catalyst

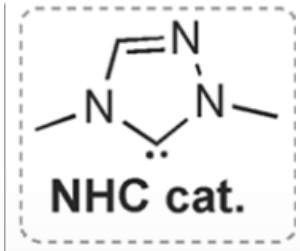
Chiral amine

Phosphoric acid catalyst

Dual catalysis emergence

NHCs are recognized to be: _ a very powerfull organocatalyst for accessing to umpolung reactivity

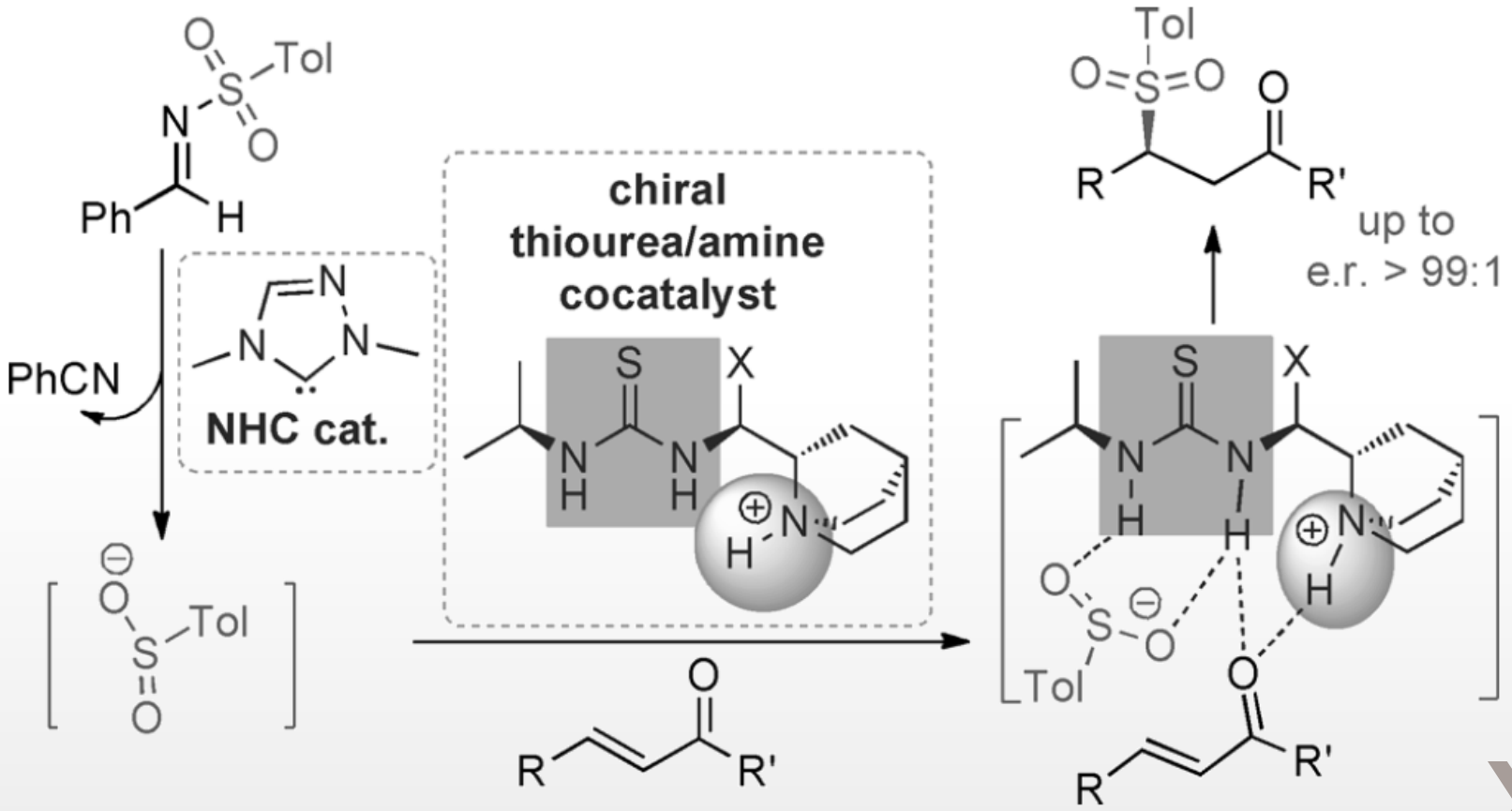
_ a good ligand for transition metal



Major challenge: *cooperative transition metal/NHC organocatalysis*

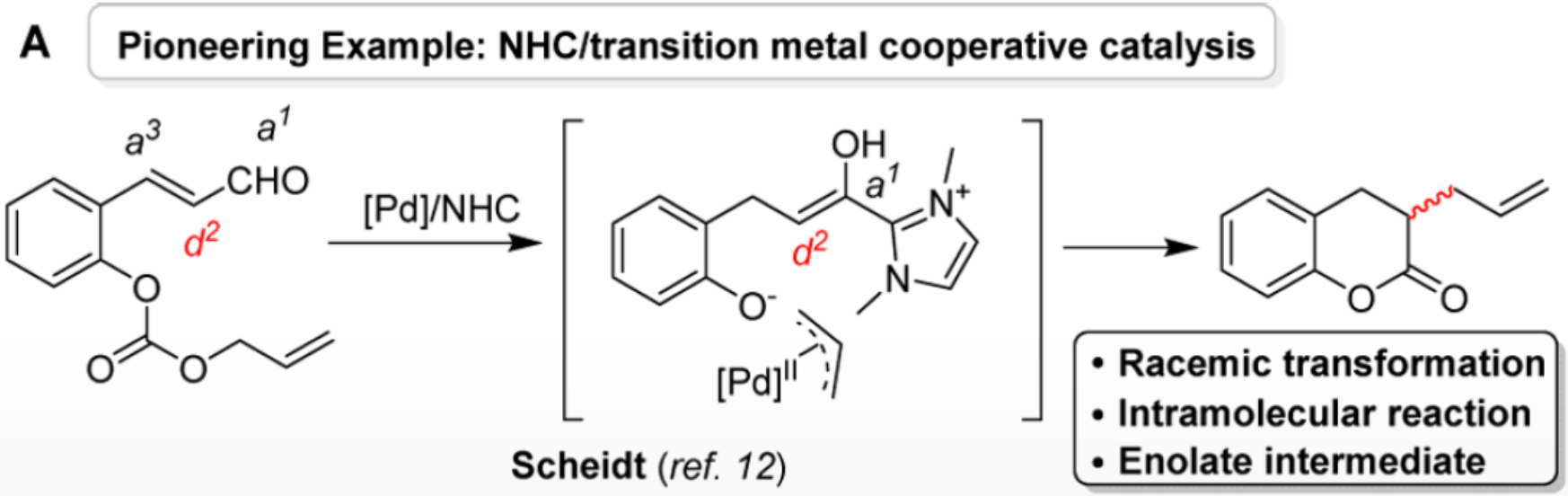
Background

Cooperative NHC/Thiourea/Tertiary amine multicatalysis
Angew. Chem. Int. Ed., **2013**, *52*, 12354



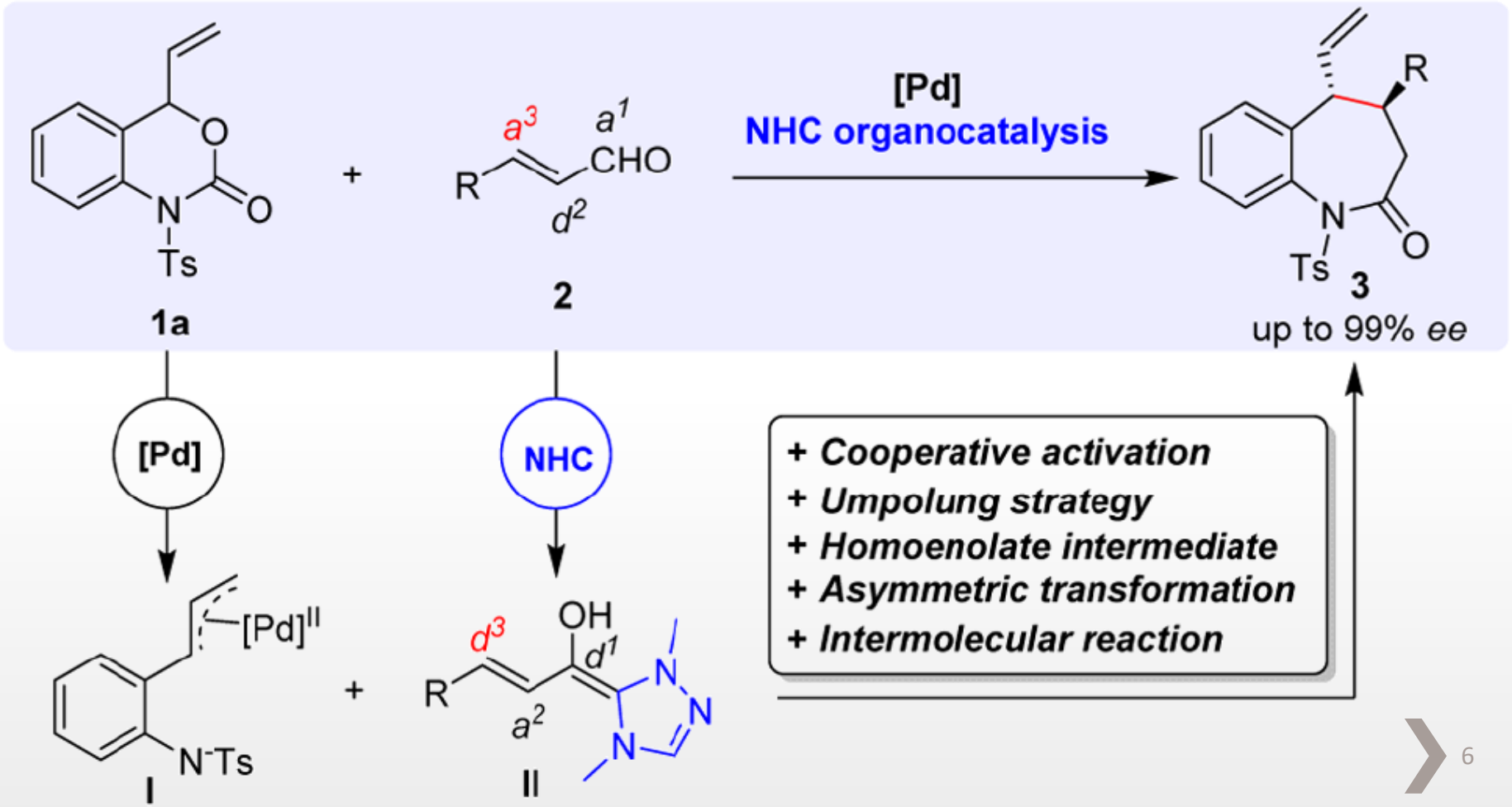
Background

Cooperative NHC/Pd dual catalysis
Chem. Sci., **2014**, *5*, 4026

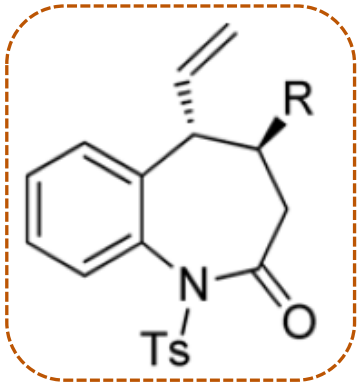


This work

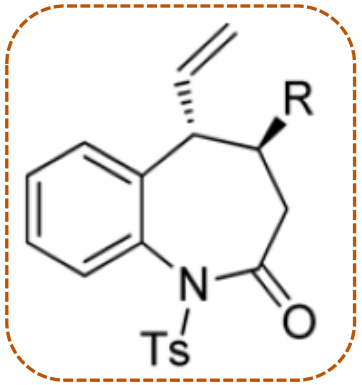
B **Cooperative enantioselective *umpolung* annulation**



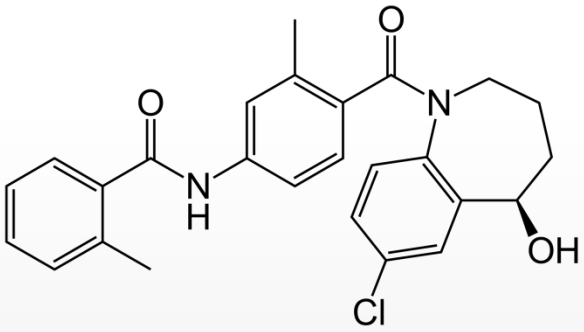
Benzazepines moiety



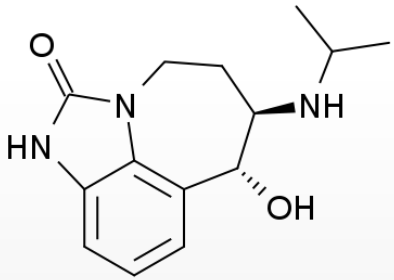
Benzazepines moiety



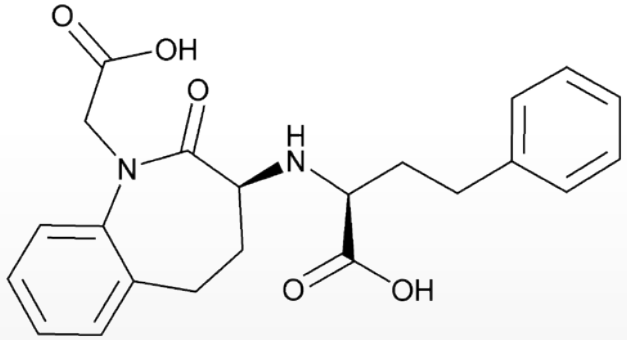
Key structural motifs in biologically active natural products and pharmaceuticals



Tolvaptan

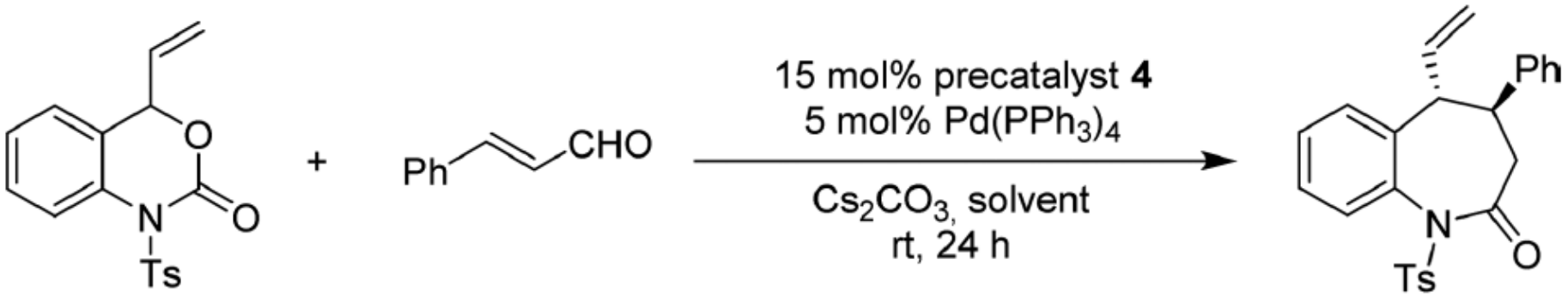


Zilpaterol

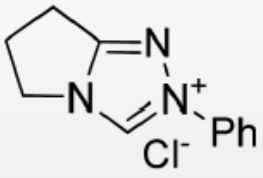


Benzanepril

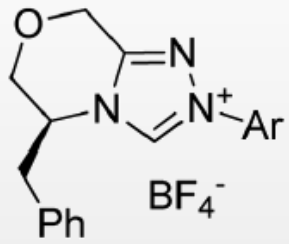
Optimization



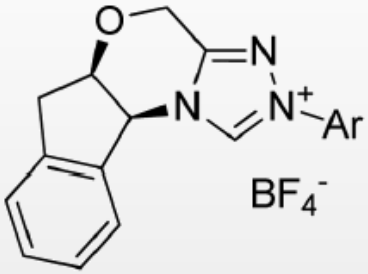
entry	precat.	solvent	yield (%)[b]	dr of **3aa**[c]	ee (%)[d]
1	**4a**	THF	nr	–	–
2	**4b**	THF	38	5:1	63
3	**4c**	THF	86	12:1	99
4	**4d**	THF	58	14:1	98



4a

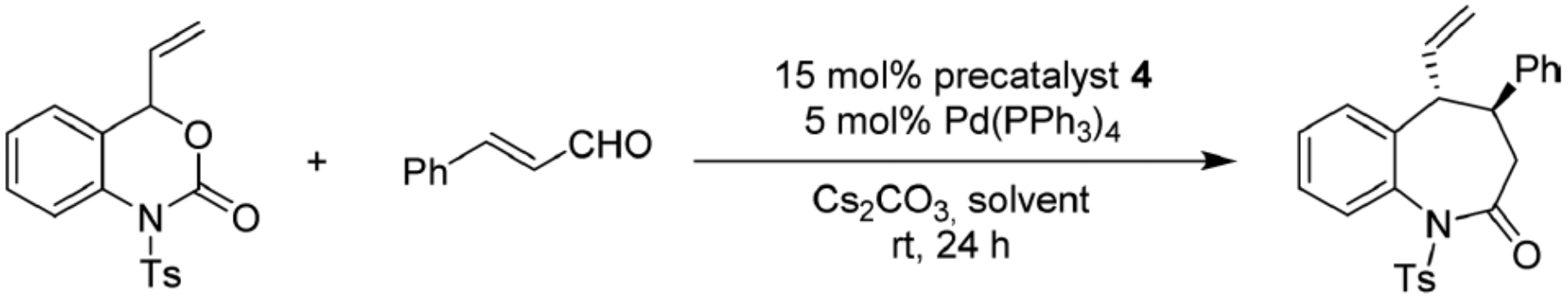


4b: Ar = 2,4,6-$Me_3C_6H_2$



4c: Ar = 2,4,6-$Me_3C_6H_2$
4d: Ar= 2,6-$Et_2C_6H_3$

Optimization



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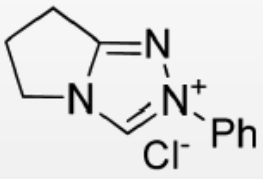
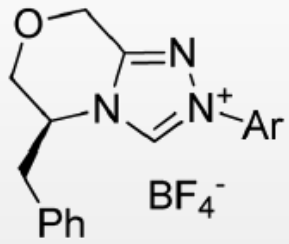


4a



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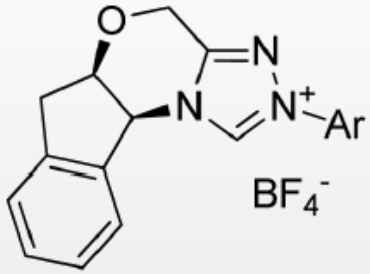
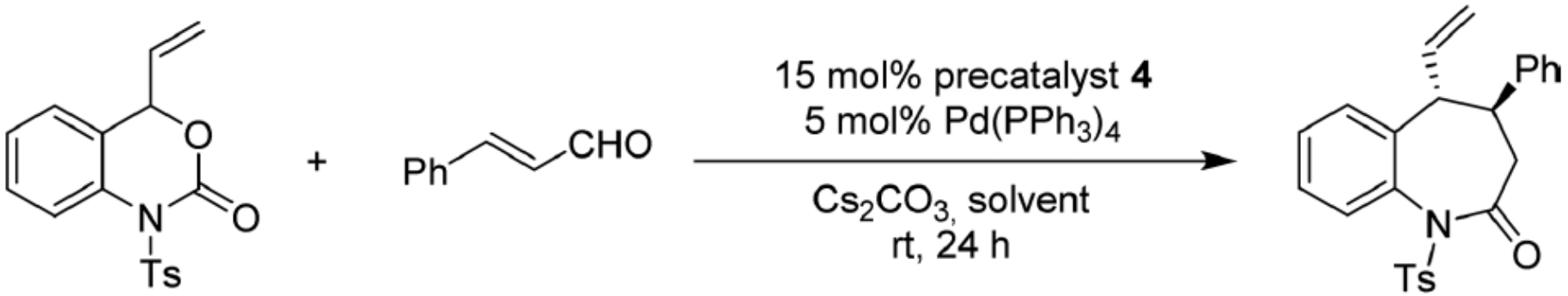


4c: Ar = 2,4,6-$Me_3C_6H_2$

4d: Ar= 2,6-$Et_2C_6H_3$

Optimization



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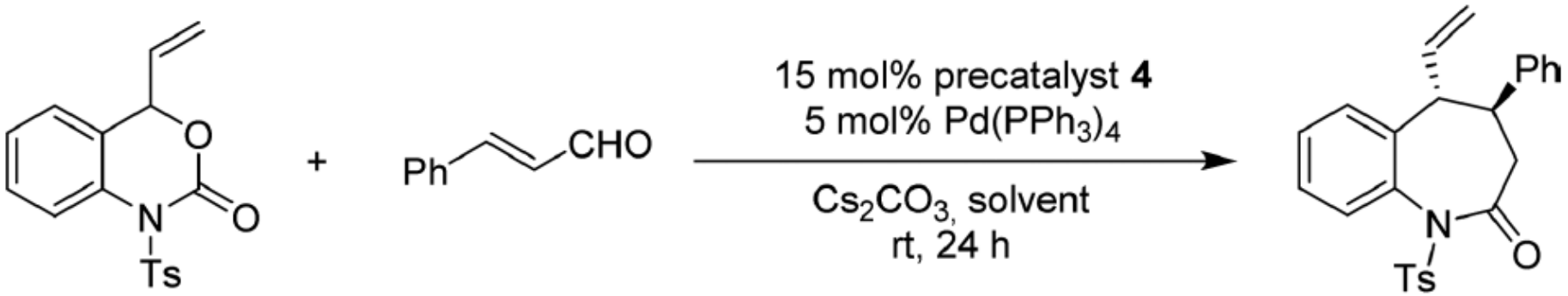
2	4b	THF	38	5:1	63
3	4c	THF	86	12:1	99
4	4d	THF	58	14:1	98
10	–	THF	nr	–	–
11[e]	**4c**	THF	nr	–	–
12[f]	**4c**	THF	nr	–	–

Optimization



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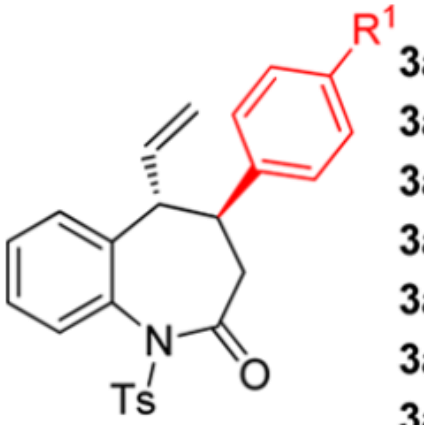
2	4b	THF	38	5:1	63
3	4c	THF	86	12:1	99
4	4d	THF	58	14:1	98
10	–	THF	nr	–	–
11[e]	4c	THF	nr	–	–
12[f]	4c	THF	nr	–	–

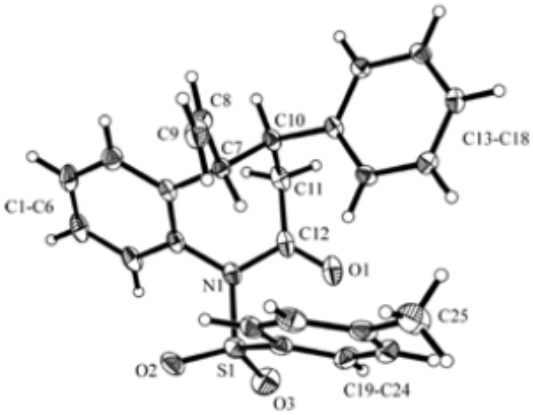
Without $Pd(PPh_3)_4$

Without Cs_2CO_3

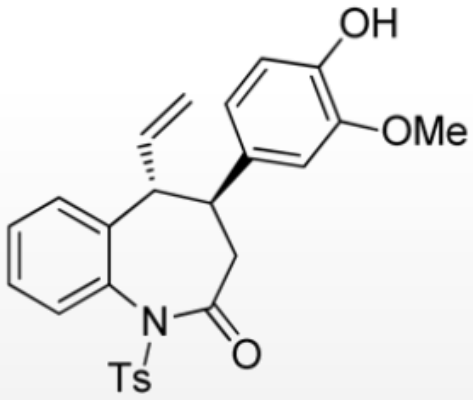
Scope of the enal *(selected examples)*



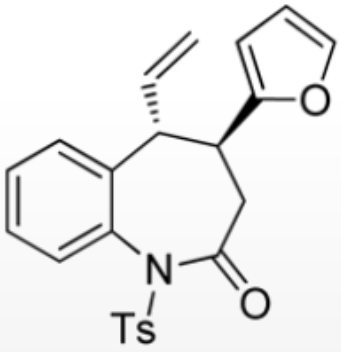
3aa R^1 = H, 86% yield, 12:1 *dr*, 99% *ee*
3ab R^1 = Me, 60% yield, 10:1 *dr*, 97% *ee*
3ac R^1 = OMe, 82% yield, 20:1 *dr*, 98% *ee*
3ad R^1 = NMe_2, 93% yield, 20:1 *dr*, 99% *ee*
3ae R^1 = Cl, 64% yield, 12:1 *dr*, 97% *ee*
3af R^1 = F, 77% yield, 20:1 *dr*, 98% *ee*
3ag R^1 = NO_2, 98% yield, 20:1 *dr*, 91% *ee*



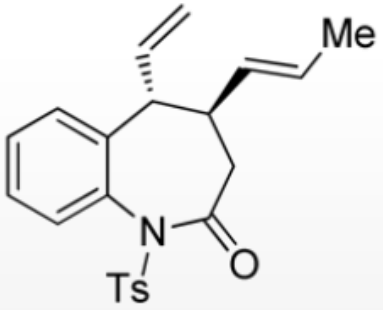
X-ray structure of 3aa



3aj 69% yield
15:1 *dr*, 98% *ee*

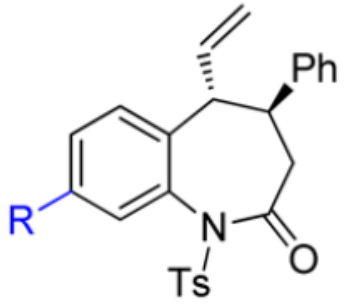


3ak 80% yield
10:1 *dr*, 98% *ee*

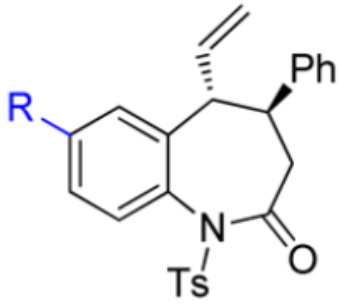


3al 79% yield
6:1 *dr*, 92% *ee*[b]

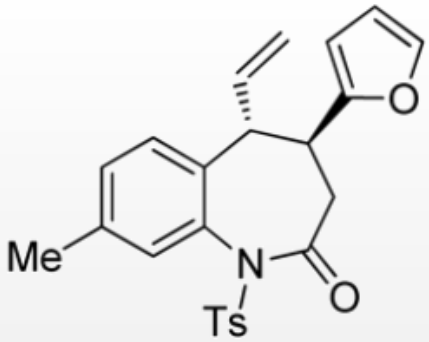
Scope of the benzoxazinanone *(selected examples)*



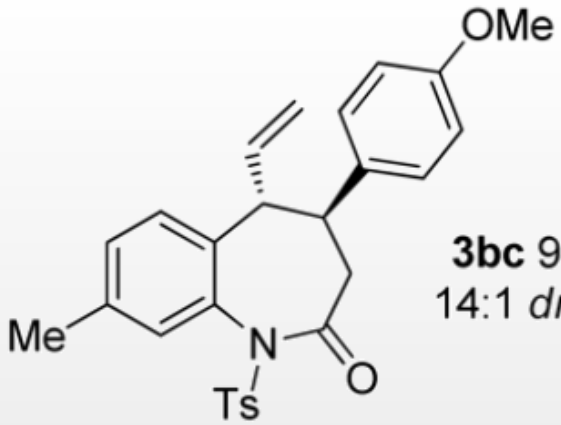
3ba R = Me, 88% yield, 14:1 *dr*, 99% *ee*
3ca R = Cl, 61% yield,12:1 *dr*, 92% *ee*
3da R = F, 61% yield, 9:1 *dr*, 93% *ee*
3ea R = Br, 55% yield,10:1 *dr*, 93% *ee*
3fa R = CF_3, 44% yield, 8:1 *dr*, 90% *ee*[b]



3ga R = Me, 80% yield, 20:1 *dr*, 99% *ee*
3ha R = Cl, 68% yield, 14:1 *dr*, 97% *ee*
3ia R = F, 77% yield, 14:1 *dr*, 98% *ee*
3ja R = Br, 73% yield,13:1 *dr*, 98% *ee*
3ka R = OMe, 87% yield, 9:1 *dr*, 99% *ee*

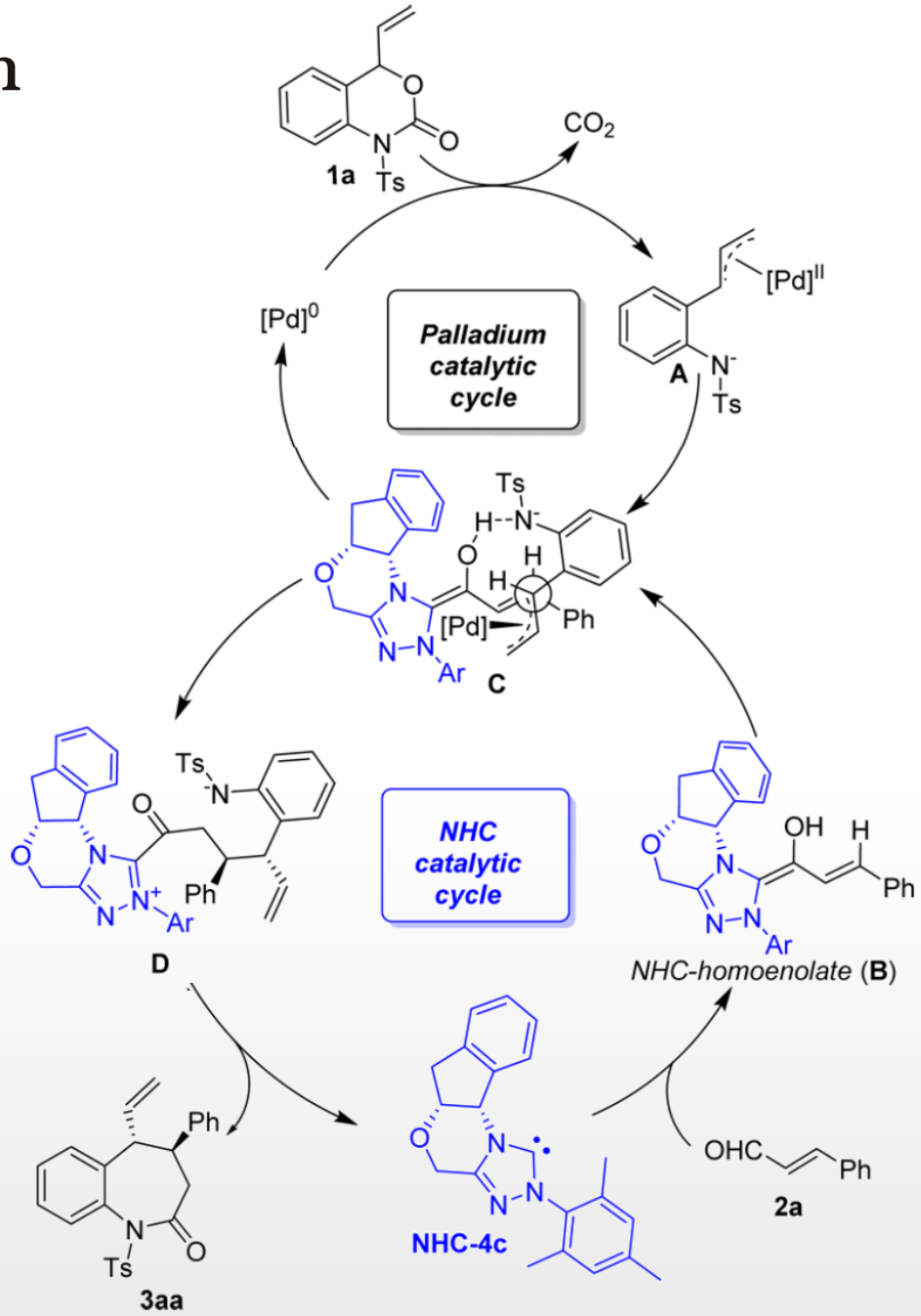


3bk 90% yield
12:1 *dr*, 99% *ee*

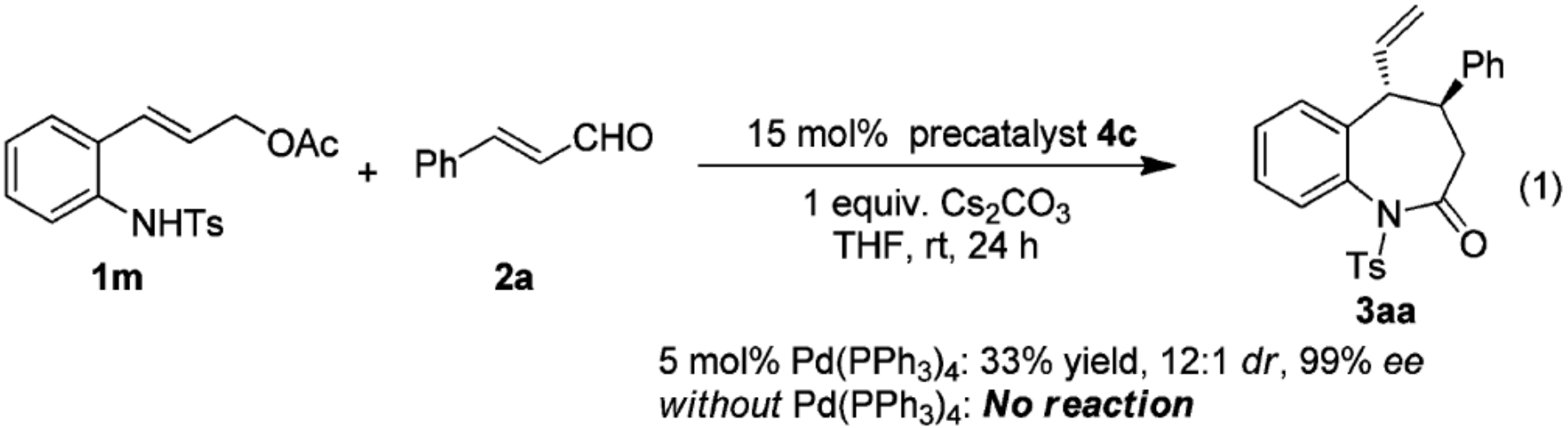


3bc 94% yield
14:1 *dr*, 99% *ee*

Mechanism


1a
Ts
CO2
[Pd]II
A
[Pd]0
Palladium catalytic cycle
Ts
H
O
H
H
[Pd]
Ph
N
N
Ar
C
NHC catalytic cycle
OH
H
Ph
NHC-homoenolate (B)
D
Ts
Ph
NHC-4c
OHC
Ph
2a
Ph
Ts
3aa

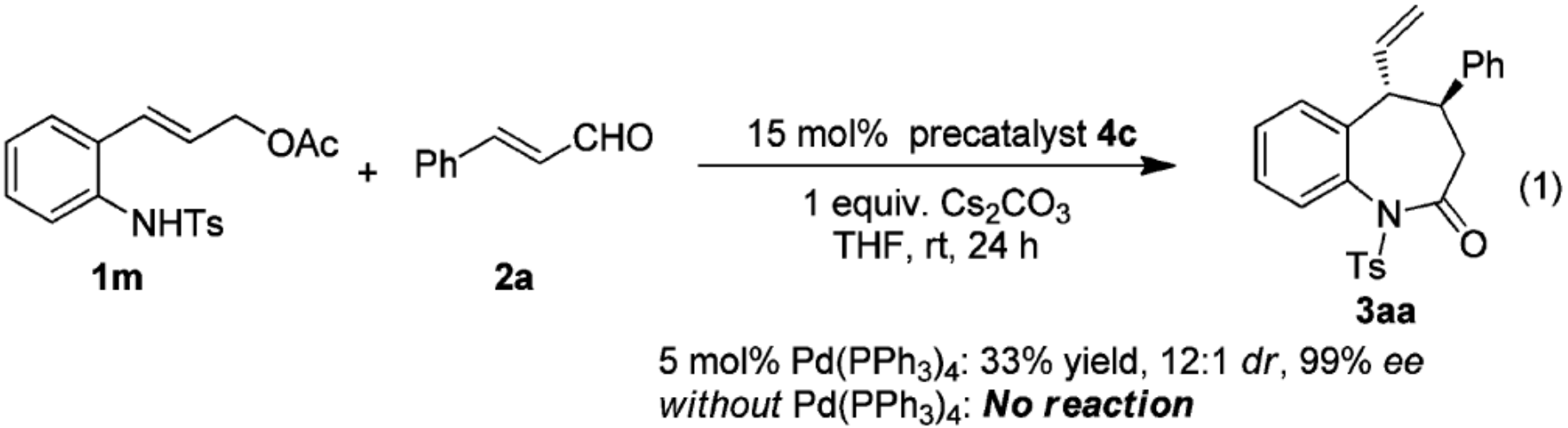
Control experiments



5 mol% $Pd(PPh_3)_4$: 33% yield, 12:1 *dr*, 99% *ee*
without $Pd(PPh_3)_4$: ***No reaction***

- **Cooperative activation mode in the annulation is operative**

Control experiments



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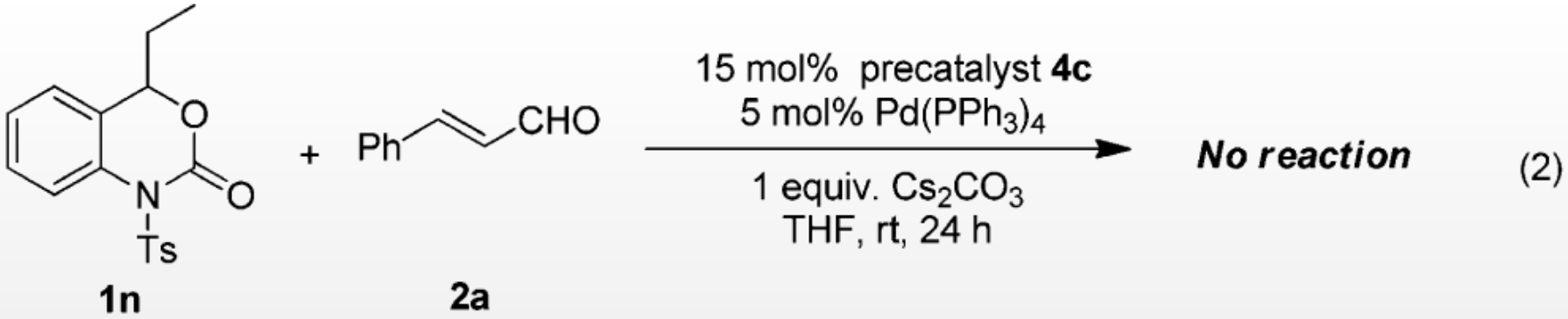
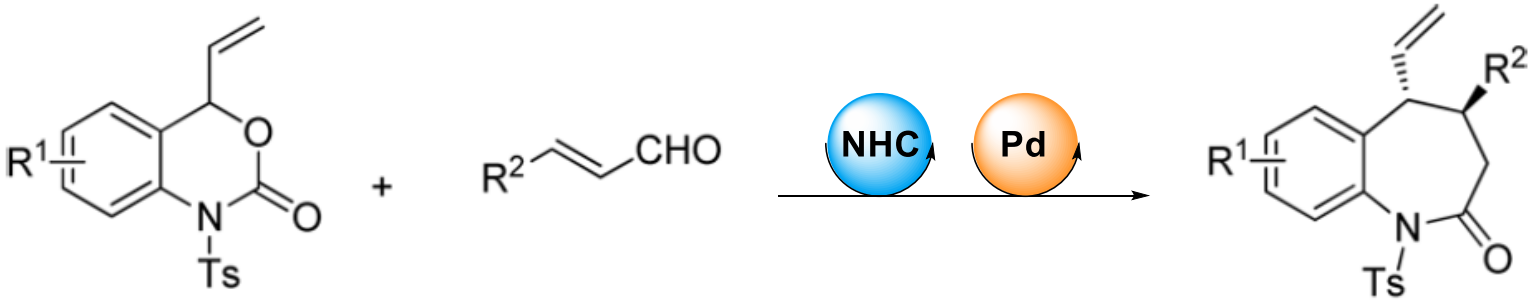


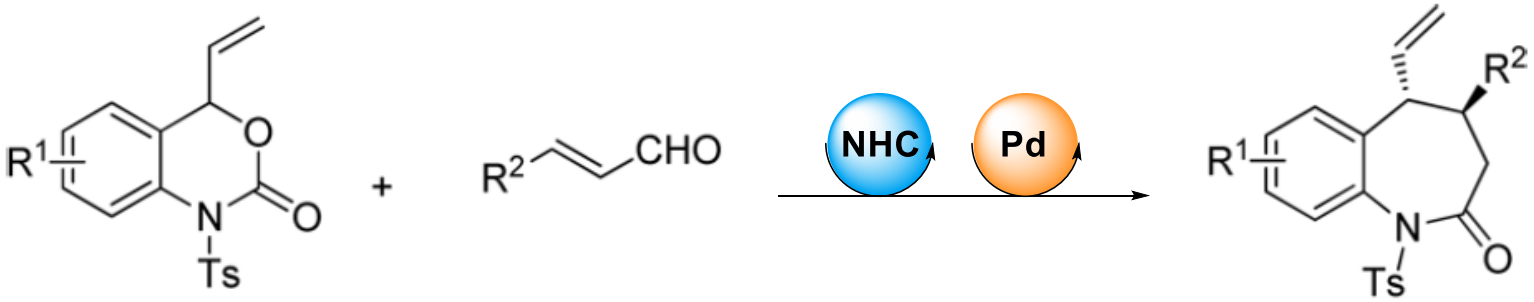
- **Benzoxazinone inable to form π-allyl palladium species**

Conclusion



- **Combination of transition metal/NHC catalysis in cooperative process**
- **Asymmetric induction by chiral NHC organocatalyst**
- **General method, high enantioselectivities**

Conclusion



- **Combination of transition metal/NHC catalysis in cooperative process**
- **Asymmetric induction by chiral NHC organocatalyst**
- **General method, high enantioselectivities**

Thank you for your attention