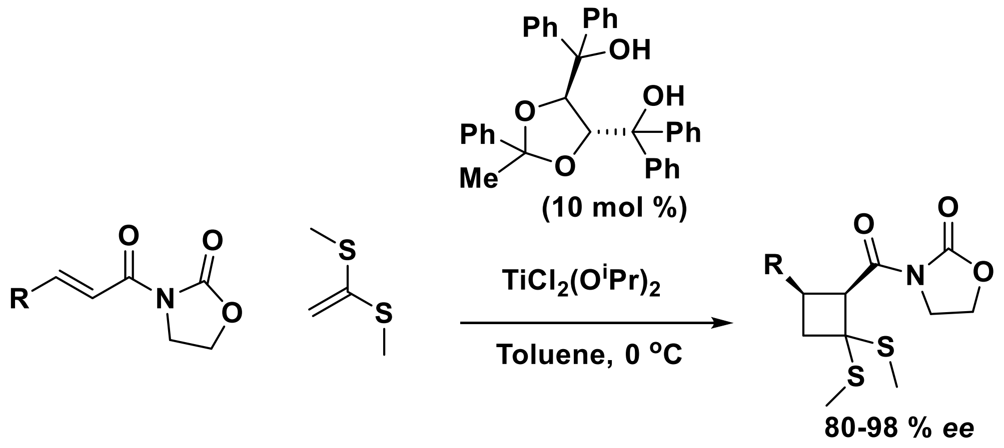
Enantioselective Desymmetrization of Cyclobutanones Enabled by Synergistic Palladium/Enamine Catalysis

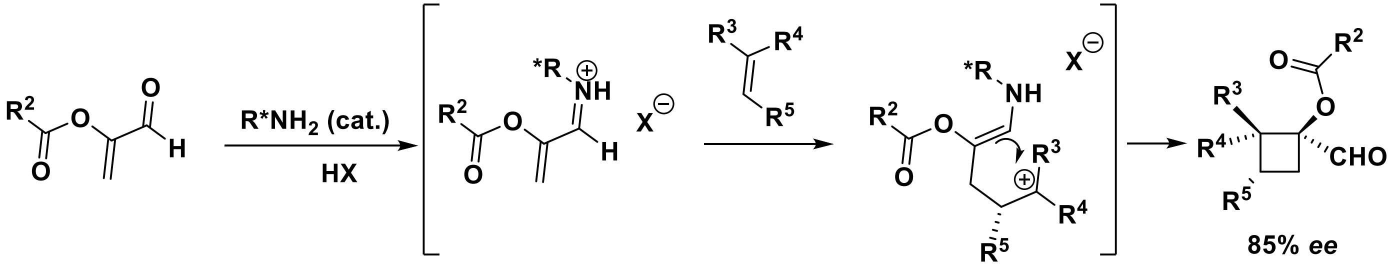
Wang, M.; Chen, J.; Chen, Z.; Zhong, C.; Lu, P.
Angew. Chem. Int. Ed. **2018**, *57*, 2707-2711

Leila Terrab
Wipf Group
Current Litterature
04/14/2018

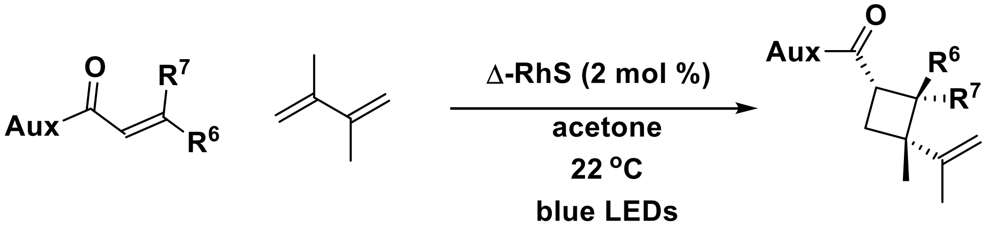
Previous enantiomeric syntheses of cyclobutanes



J. Am. Chem. Soc. **1992**, *114*, 8869–8885



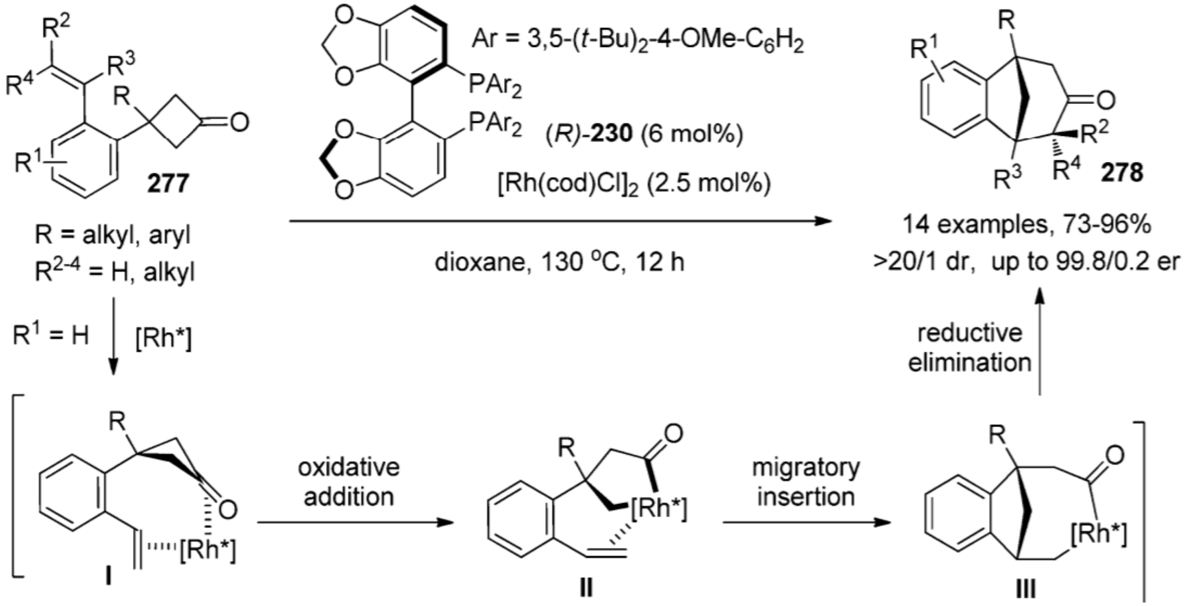
J. Am. Chem. Soc. **2007**, *129*, 8930–8931



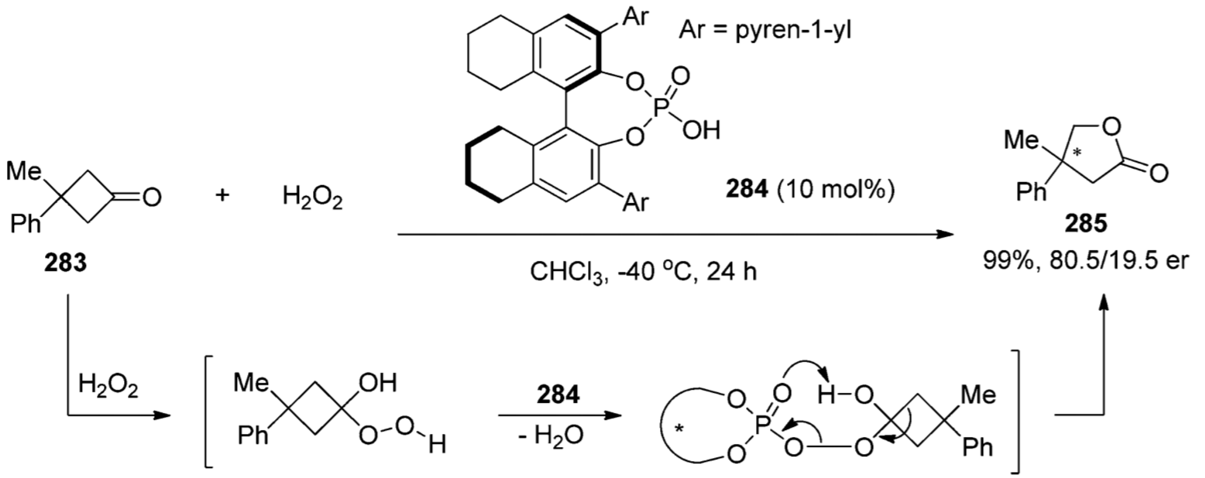
J. Am. Chem. Soc. **2017**, *139*, 9120–9123

Reactions with cyclobutanones

Rh-catalyzed Intramolecular alkene insertion of cyclobutanones:



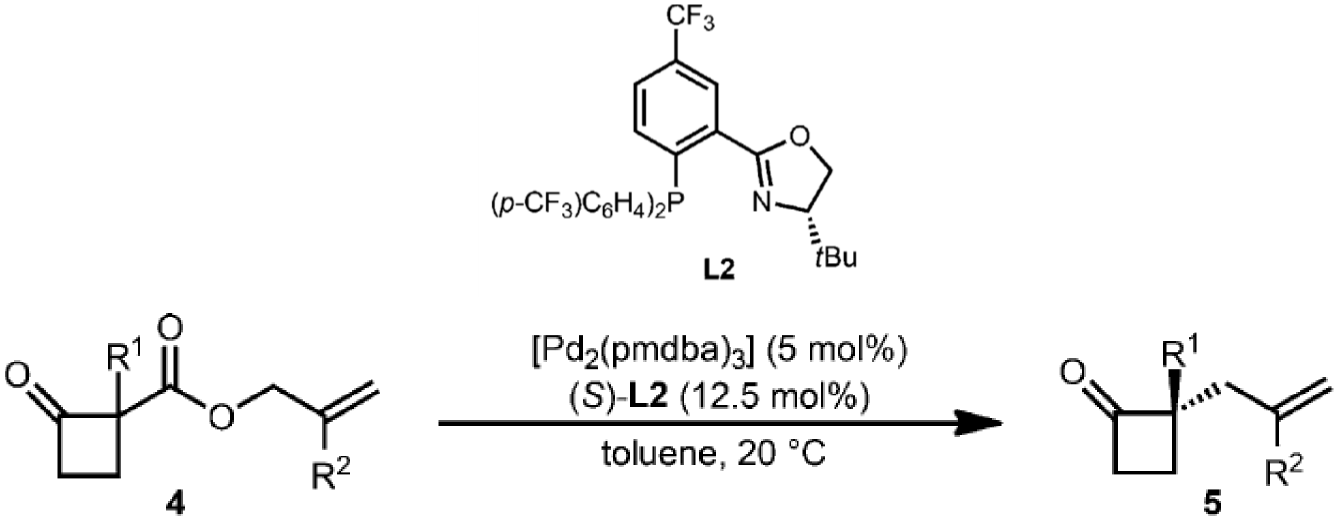
Chiral Phosphoric Acid-catalyzed enantioselective Baeyer-Villiger Oxidation



Chem. Rev. **116**, *12*, 7330-7396

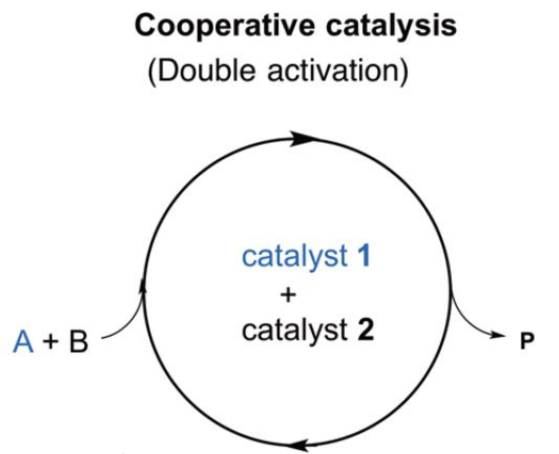
Catalytic enantioselective cyclobutanone alkylation

Stoltz group:

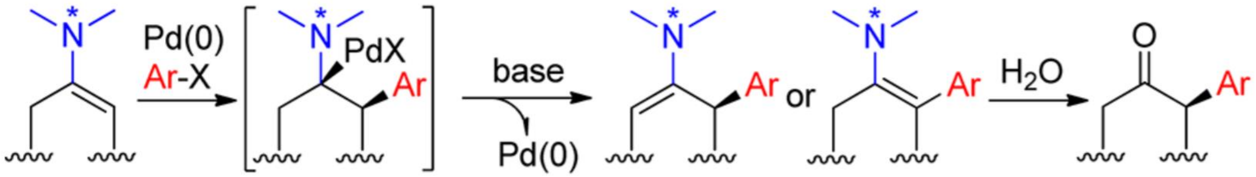


Angew. Chem. Int. Ed. **2013**, *52*, 6718-6721

α-Arylation via Pd/enamine ‘cooperative’ catalysis

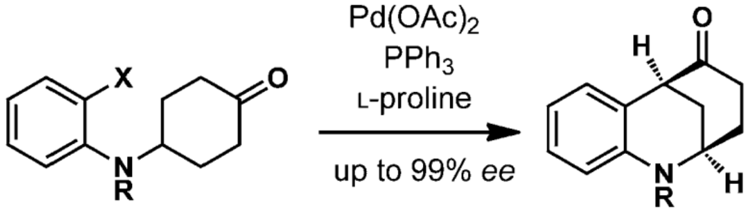


Chem. Rev. **2016**, *116*, 13512−13570



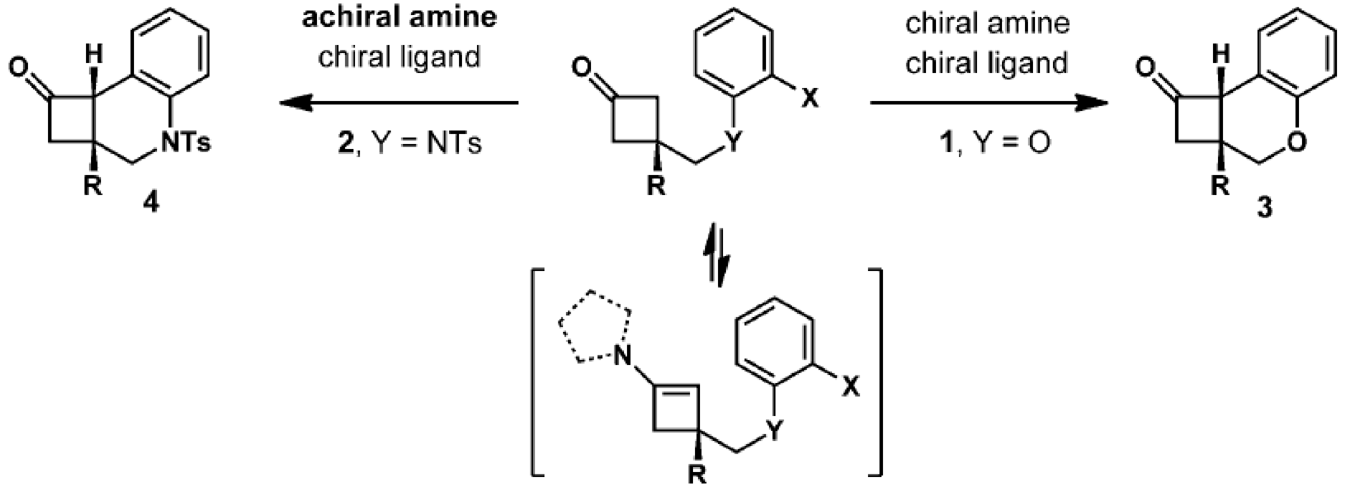
1) **Enamine formation**
2) **Heck arylation**

J. Am. Chem. Soc. ***2016***, *138*, 5198-5201



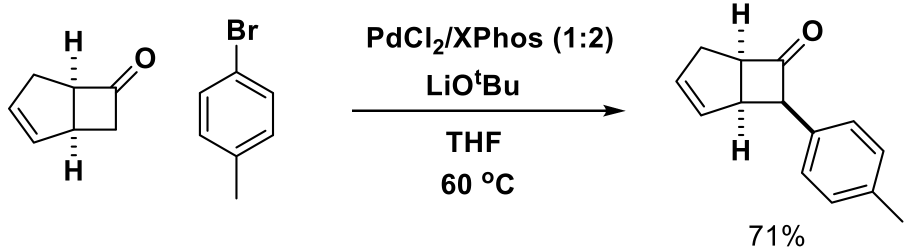
J. Am. Chem. Soc. ***2016***, *138*, 5198-5201

This paper:



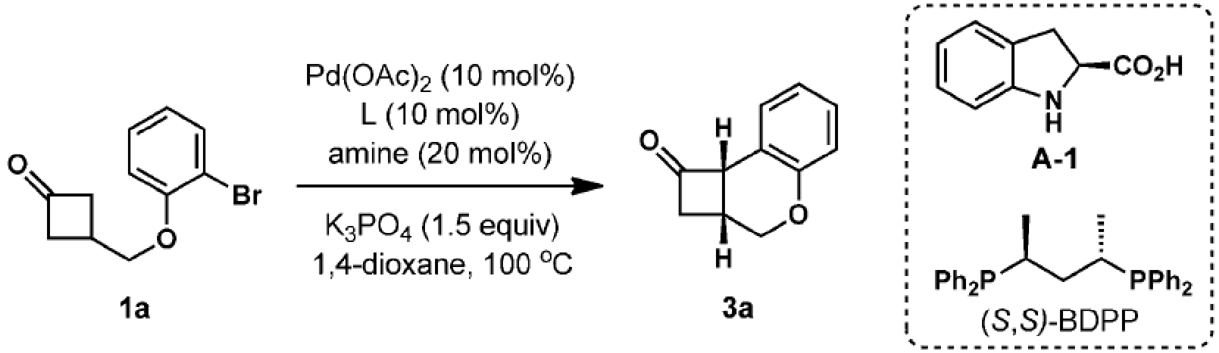
Previous α-arylation of cyclobutanones

Britton group:



Angew. Chem. Int. Ed. **2017**, *56*, 748-752.

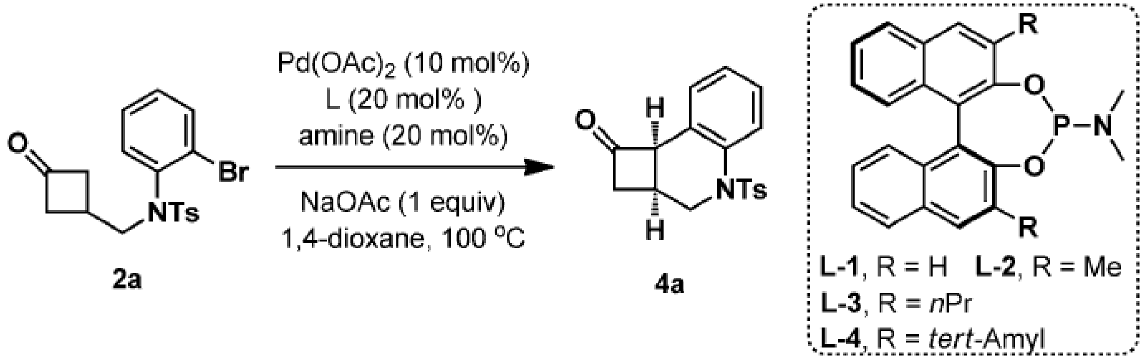
O-tethered cyclobutanone reaction optimization

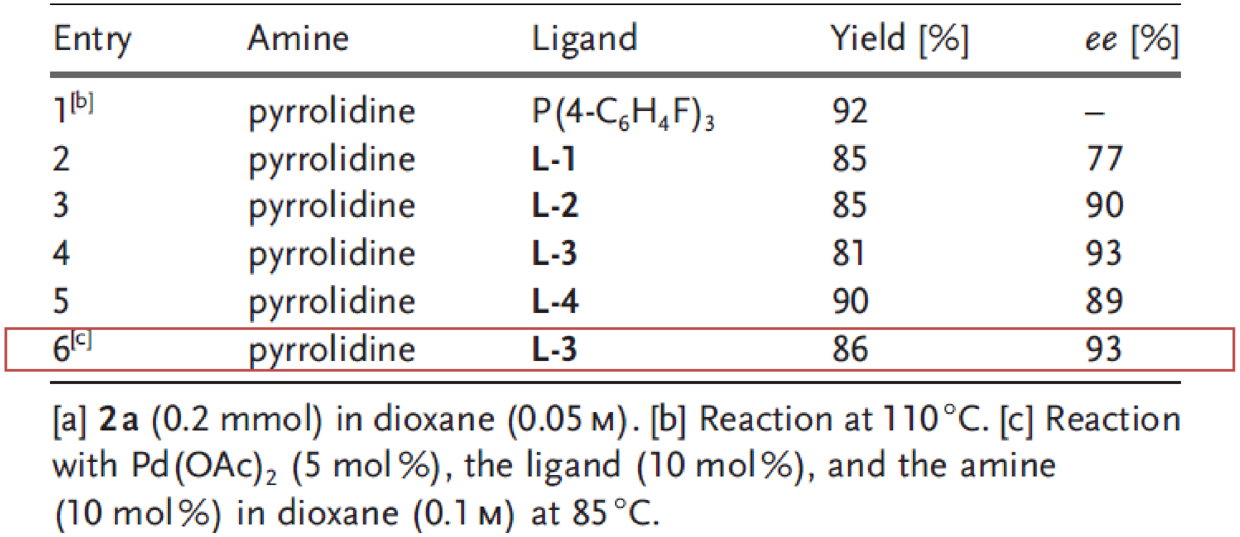


Entry	Amine	Ligand	Yield [%]	*ee* [%]
1[b]	pyrrolidine	DPEPhos	81	–
2	L-proline	DPEPhos	51	33
3	**A-1**	DPEPhos	75	47
4	**A-1**	(*S*,*S*)-BDPP	86	86
5	*ent*-**A-1**	(*S*,*S*)-BDPP	33	−70
6[c]	**A-1**	(*S*,*S*)-BDPP	72	89

[a] **1a** (0.2 mmol) in dioxane (0.05 M). [b] Reaction with NaOAc (1 equiv) as the base at 110 °C. [c] Reaction with Pd(OAc)$_2$ (5 mol%), the ligand (5 mol%), and the amine (10 mol%) in dioxane (0.1 M) at 85 °C.

N-tethered cyclobutanone reaction optimization



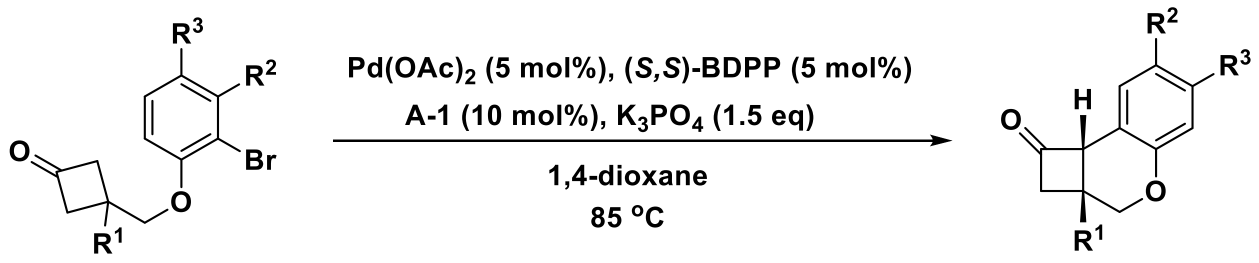


Entry	Amine	Ligand	Yield [%]	*ee* [%]
1[b]	pyrrolidine	P(4-$C_6H_4F)_3$	92	–
2	pyrrolidine	**L-1**	85	77
3	pyrrolidine	**L-2**	85	90
4	pyrrolidine	**L-3**	81	93
5	pyrrolidine	**L-4**	90	89
6[c]	pyrrolidine	**L-3**	86	93

[a] **2a** (0.2 mmol) in dioxane (0.05 м). [b] Reaction at 110 °C. [c] Reaction with Pd(OAc)$_2$ (5 mol %), the ligand (10 mol %), and the amine (10 mol %) in dioxane (0.1 м) at 85 °C.

Poor conversion observed with chiral amines

Scope of O-tether analogs

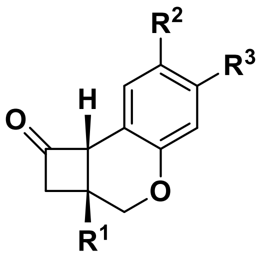


$Pd(OAc)_2$ (5 mol%), (*S,S*)-BDPP (5 mol%)

A-1 (10 mol%), K_3PO_4 (1.5 eq)

1,4-dioxane

85 °C

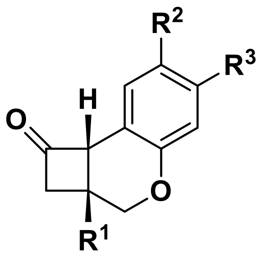


R^1, R^2 = H

R^3 = Me and OMe

72 and 88% yield

88 and 90% *ee*

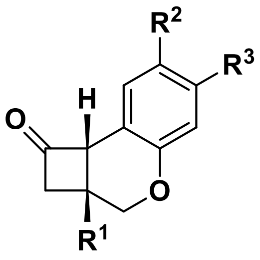


R^1, R^2 = H

R^3 = Cl, F, OCF_3

62-67% yield

84-90% *ee*

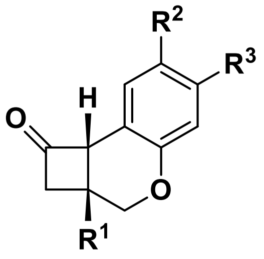


R^1 = Me and Et

R^2, R^3 = Me

86% yield

92-93% *ee*

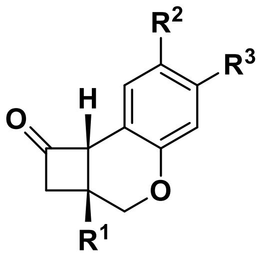


R^2 = Me, *t*Bu, OMe

R^1, R^3 = H

75-83 % yield

86-96 % *ee*



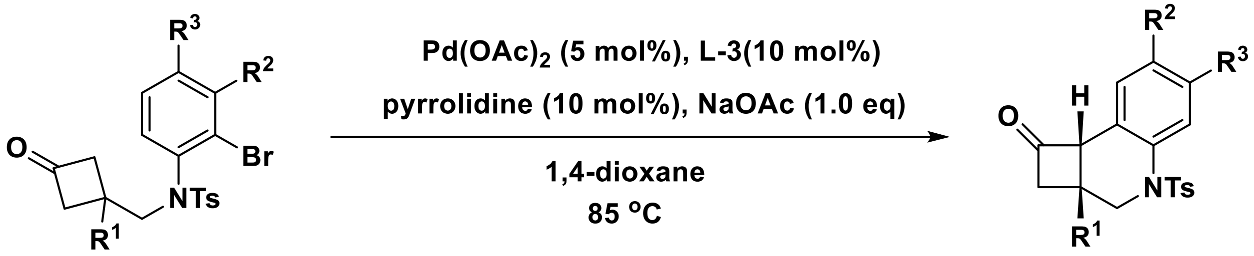
R^2 = CO_2Me and CF_3

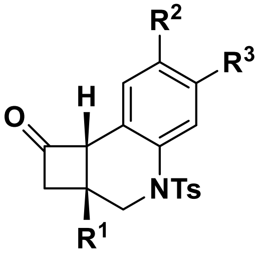
R^1, R^3 = H

56 and 80% yield

84 and 85 % *ee*

Scope of N-tether analogs



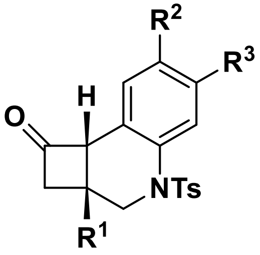


R^1, R^2 = H

R^3 = Me and OMe

88 and 59% yield

93 and 90% *ee*

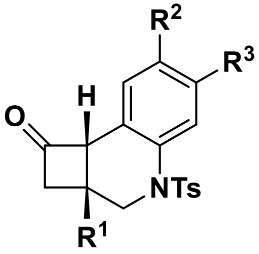


R^2 = Me, *t*Bu, OMe

R^1, R^3 = H

80 and 74 % yield

92-93% *ee*

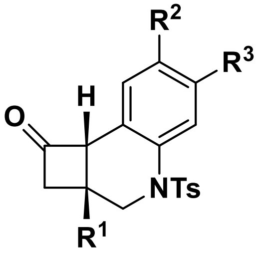


R^1, R^2 = H

R^3 = CF$_3$, F, Cl

68, 82, and 90% yield

92-93% *ee*

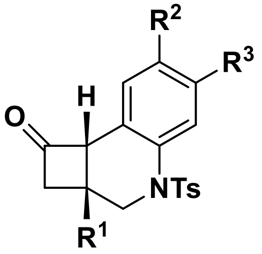


R^2 = F, CO$_2$Me, and Cl

R^1, R^3 = H

54, 76, and 98% yield

86, 93, and 86% *ee*



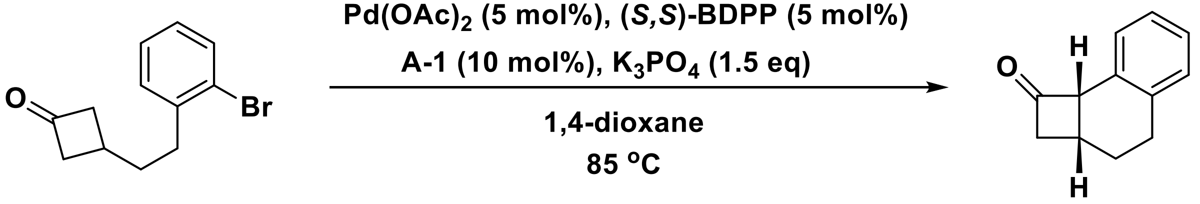
R^1 = Me

R^2, R^3 = Me

85% yield

92% *ee*

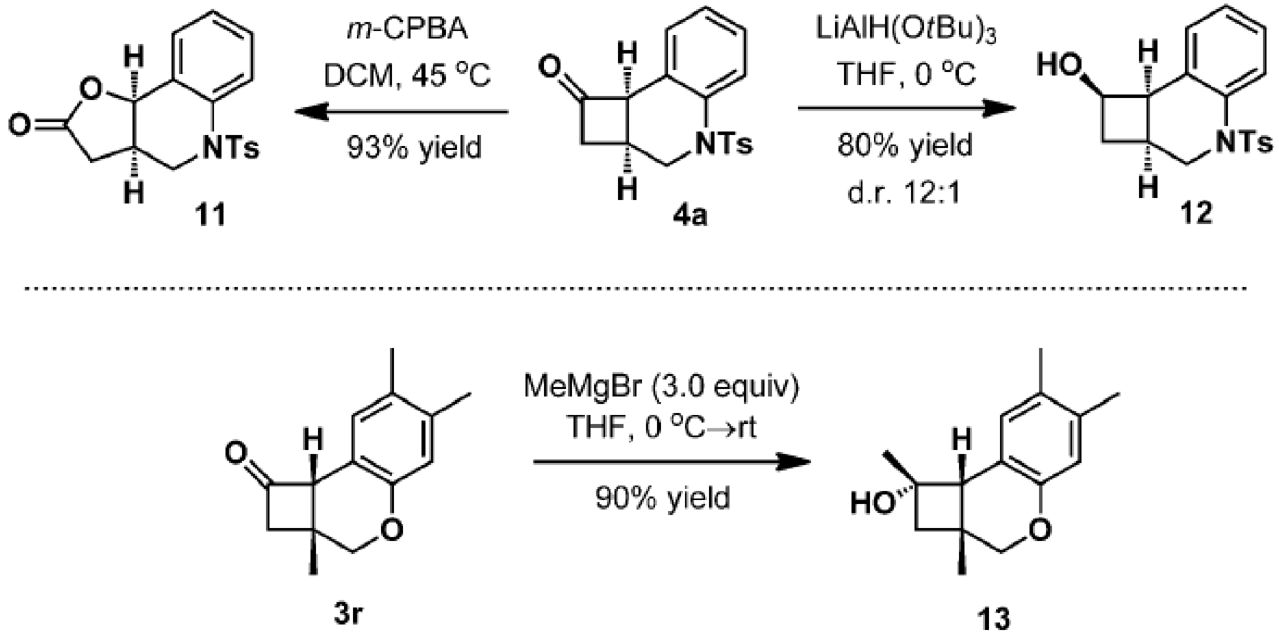
Carbon chain instead of heteroatom tether



$Pd(OAc)_2$ (5 mol%), (*S,S*)-BDPP (5 mol%)
A-1 (10 mol%), K_3PO_4 (1.5 eq)
1,4-dioxane
85 ^{o}C

67 % yield, 85% *ee*

Further Transformations of Cyclobutanones



Conclusion

Use of cooperative Pd/amine catalysis in the intramolecular α- arylation of cyclobutanones

α- Arylation approach similar to the Britton group: used cyclohexanones