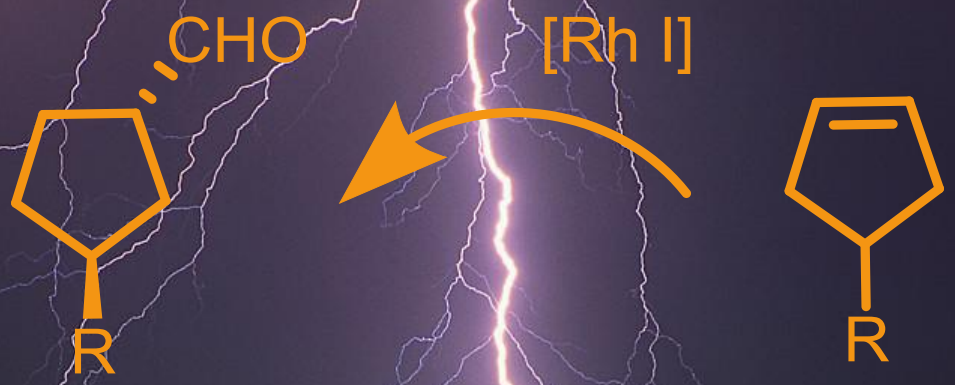
Maxime Dousset, 21/04/2016

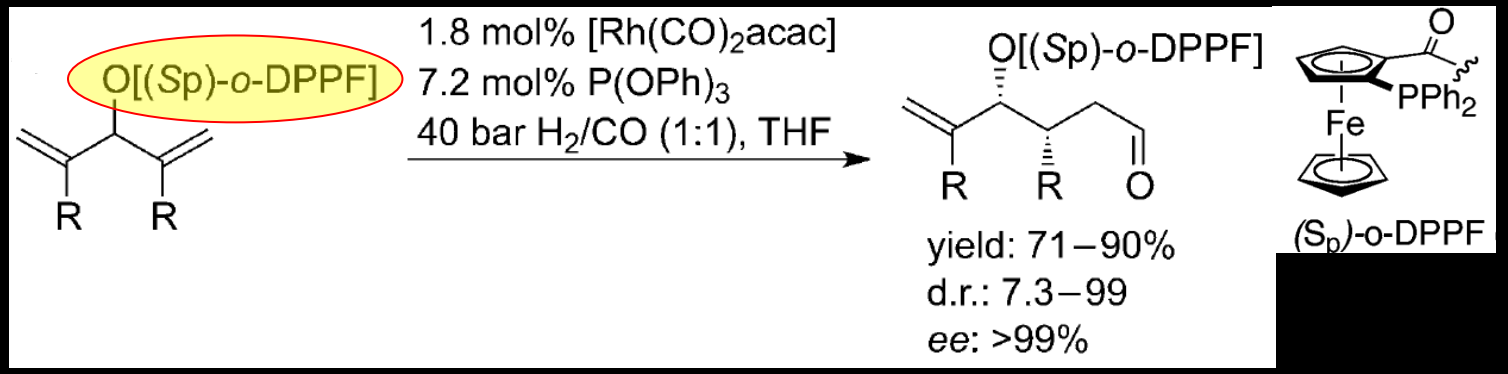


Rhodium-Catalyzed Desymmetrization by Hydroformylation of cyclopentanes : Synthesis of Chiral Carbocyclic Nucleosides

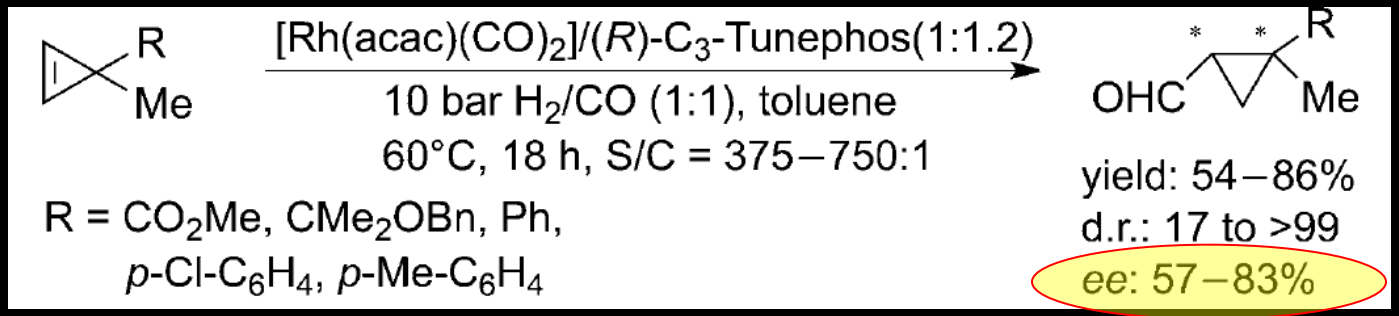
Angew. Chem. Int. Ed. **2016**. DOI: 10.1002/anie.201601478
Cai You, Biao Wei, Xiuxiu Li, Yusheng Yang, Yue Liu, Hui Lv,* and Xumu Zhang*

Background

a) Desymmetrization with Directing Group, *D. Breuninger*

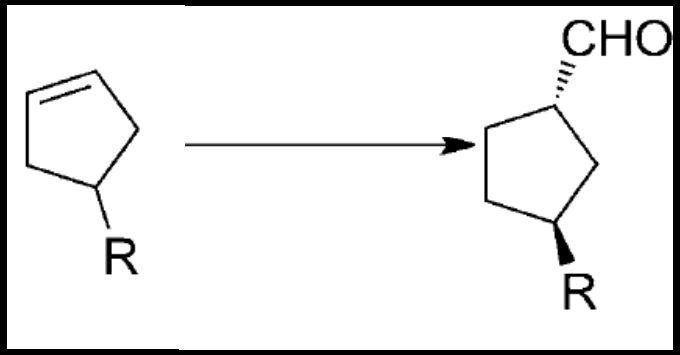


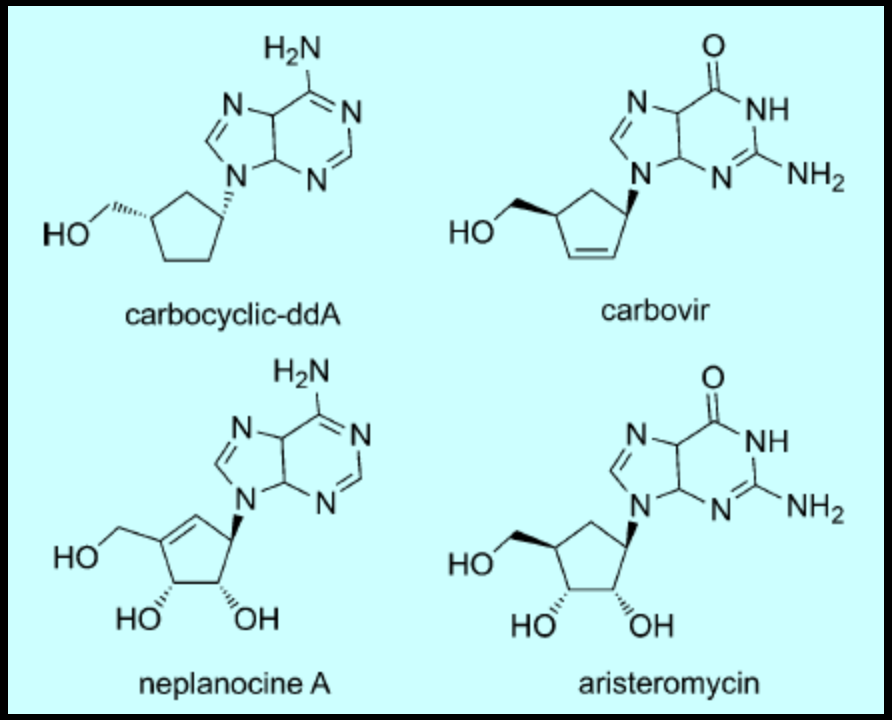
b) Desymmetrization with chiral catalyst, *M. Rubin*



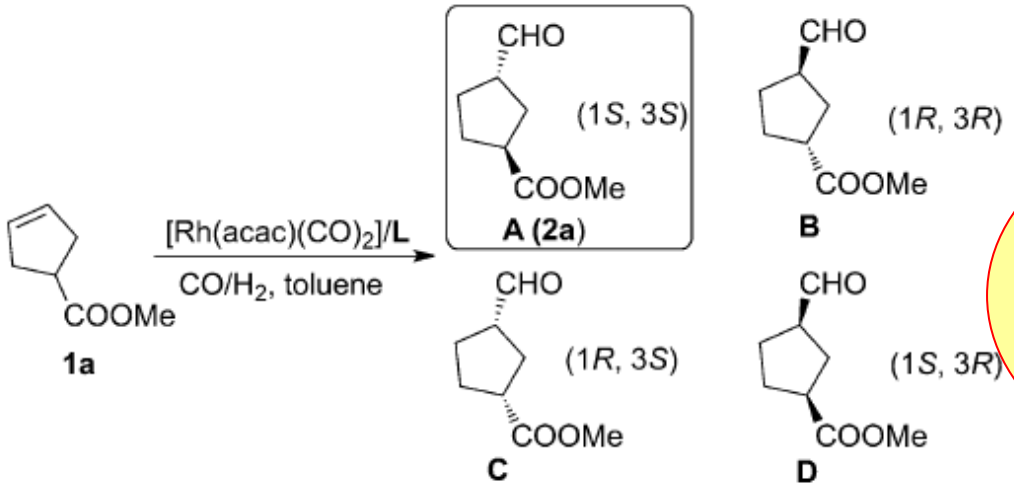
a. *J. Am. Chem. Soc*. **2004**, *126*, 10244-10245. b. *J. Am. Chem. Soc.*, **2008**, *130*, 13804–13809

With cyclopentanes



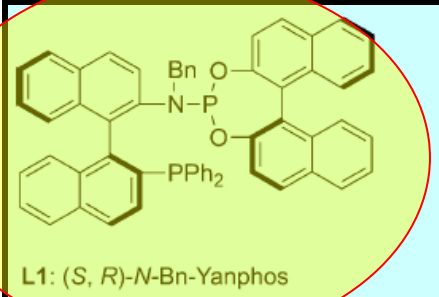


Ligand screening

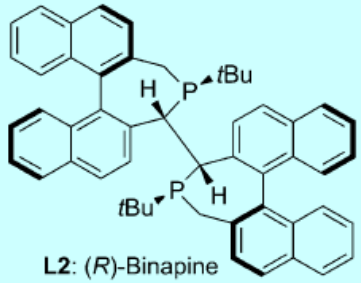


Entry	Ligand	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	**L1**	62	95:5	91 (1*S*,3*S*)
2	**L2**	2	90:10	88 (1*S*,3*S*)
3	**L3**	2	89:11	88 (1*S*,3*S*)
4	**L4**	1	88:12	92 (1*S*,3*S*)
5	**L5**	trace	–	–
6	**L6**	trace	–	–
7	**L7**	trace	–	–
8	**L8**	trace	–	–

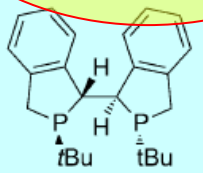
[a] Reactions were performed on a 0.5 mmol scale at 60°C in 1 mL toluene with substrate/Rh = 500:1, L/Rh = 3:1, 20 bar CO/H_2 (1:1), and a reaction time of 24 hours. [b] Determined by ^1H NMR analysis of crude



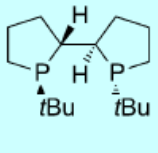
L1: (*S*, *R*)-*N*-Bn-Yanphos



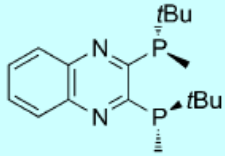
L2: (*R*)-Binapine



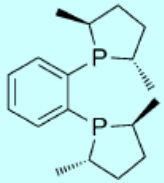
L3: (*Rc*, *Sp*)-Duanphos



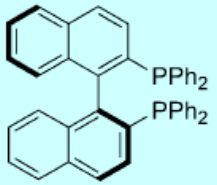
L4: Tangphos



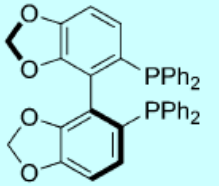
L5: (*R*)-QuinoxP*



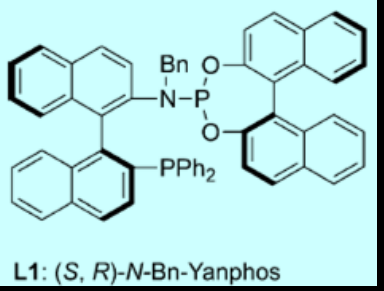
L6: (*S*,*S*)-Me-DuPhos



L7: (*S*)-BINAP

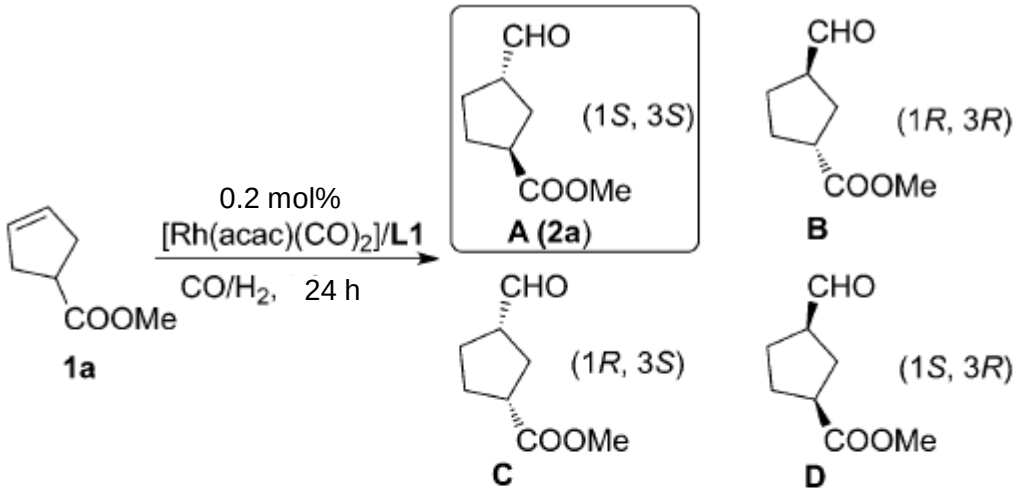


L8: (*S*)-SegPhos



L1: (*S*, *R*)-*N*-Bn-Yanphos

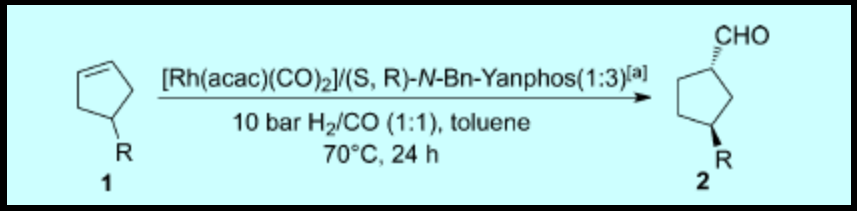
Conditions screening

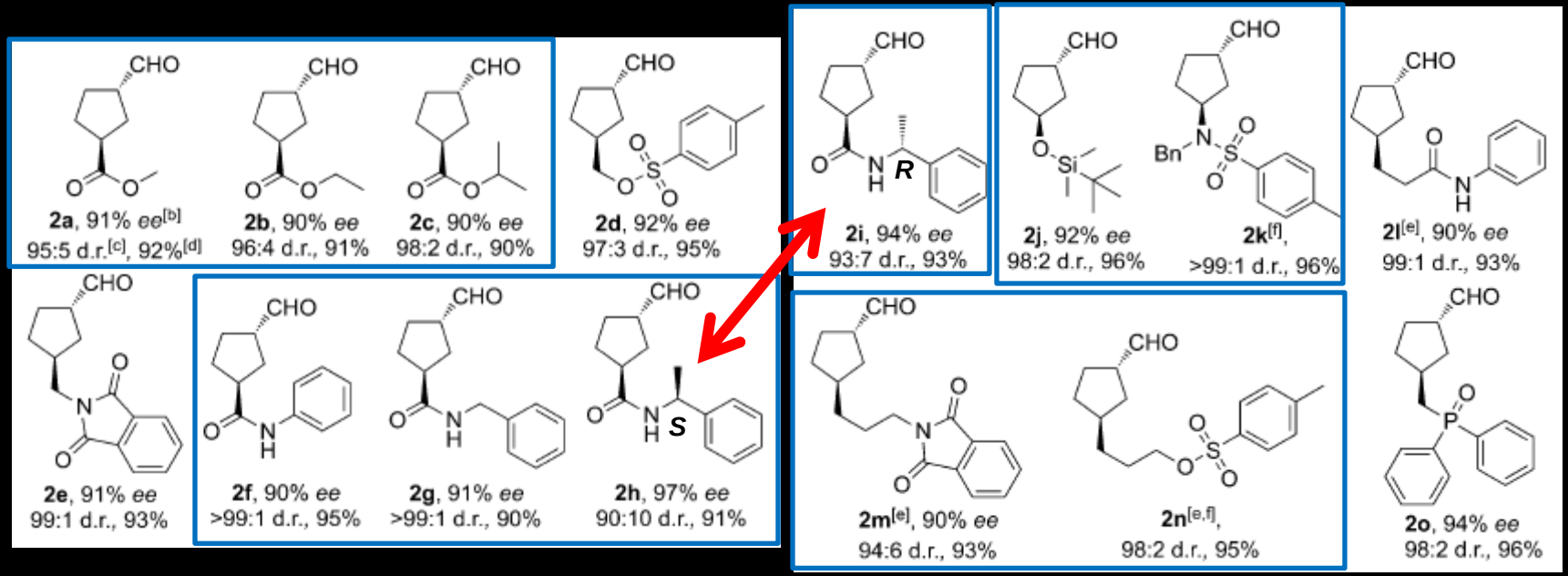


Entry	Solvent	*T* [°C]	CO/H_2 [bar]	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	toluene	60	10:10	62	95:5	91
2	toluene	70	10:10	91	95:5	91
3	toluene	80	10:10	99	95:5	90
4	CH_2Cl_2	70	10:10	20	93:7	92
5	THF	70	10:10	12	93:7	91
6	EtOAc	70	10:10	16	77:23	90
7	CH_3CN	70	10:10	16	94:6	92
8	toluene	70	5:5	99	95:5	91
9	toluene	70	20:20	13	95:5	92
10[d]	toluene	70	5:5	88	95:5	91

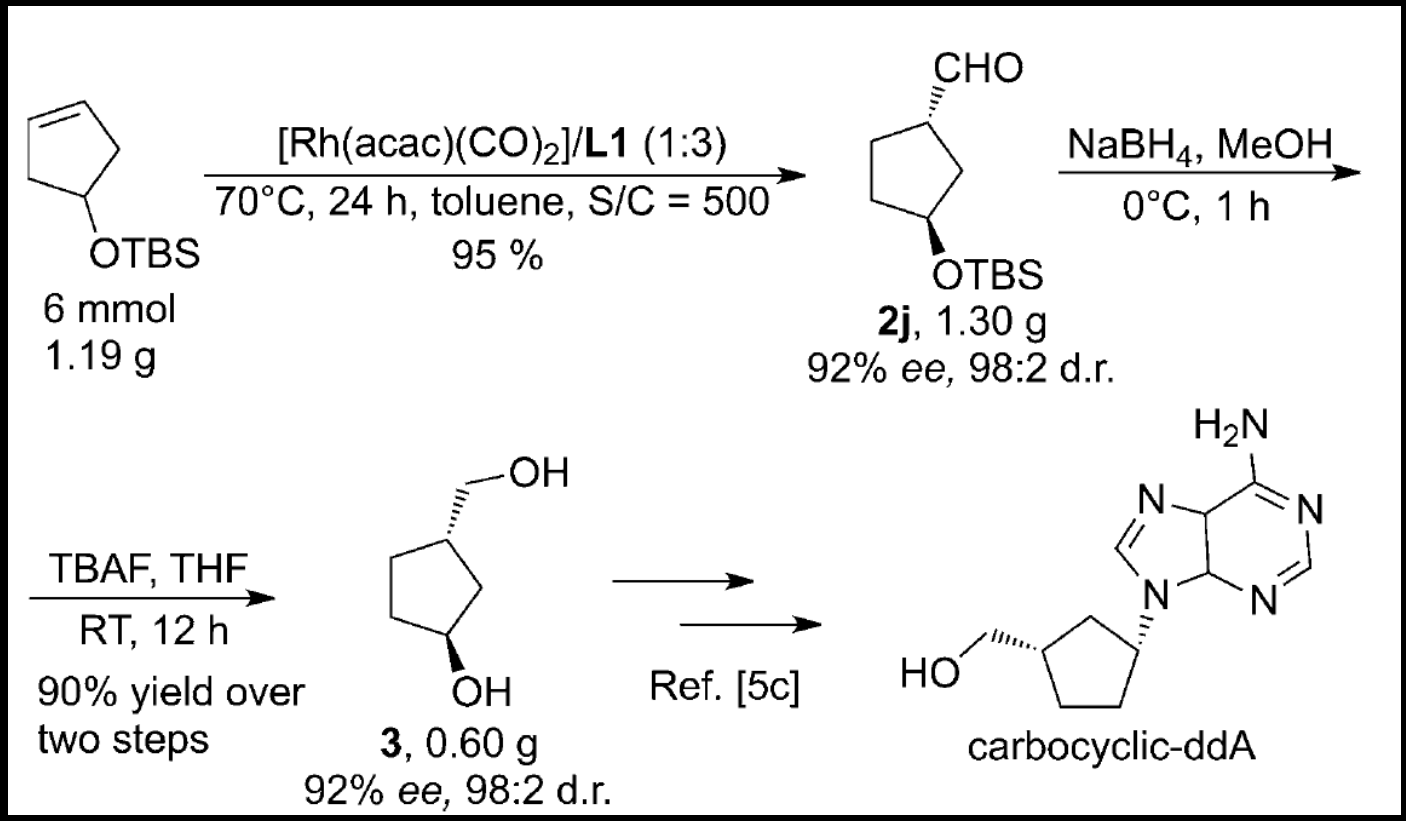
0.05 mol% Rh

Scope of the reaction



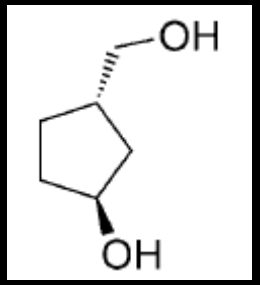


Synthetic application

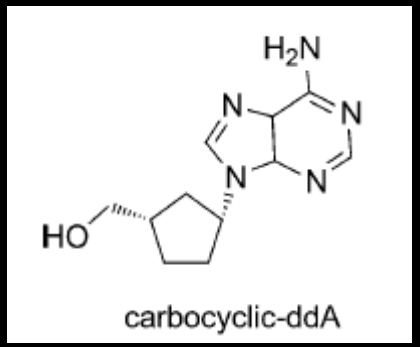


In summary

- ✓ Powerful asymmetric hydroformylation on cyclopentanes
- ✓ Easy to set up
- ✓ Number of steps reduced and improved yield



- ✓ Quickly access to the chiral carbocyclic nucleosides



Synthetic application