



# DESIGN OF CHIRAL PYRIDINES AS ORGANOCATALYSTS FOR ASYMMETRIC CYCLOPROPANATION REACTION

Artis Kinens<sup>1</sup>, Edgars Suna<sup>1</sup>, Edwin Vedejs<sup>2</sup>

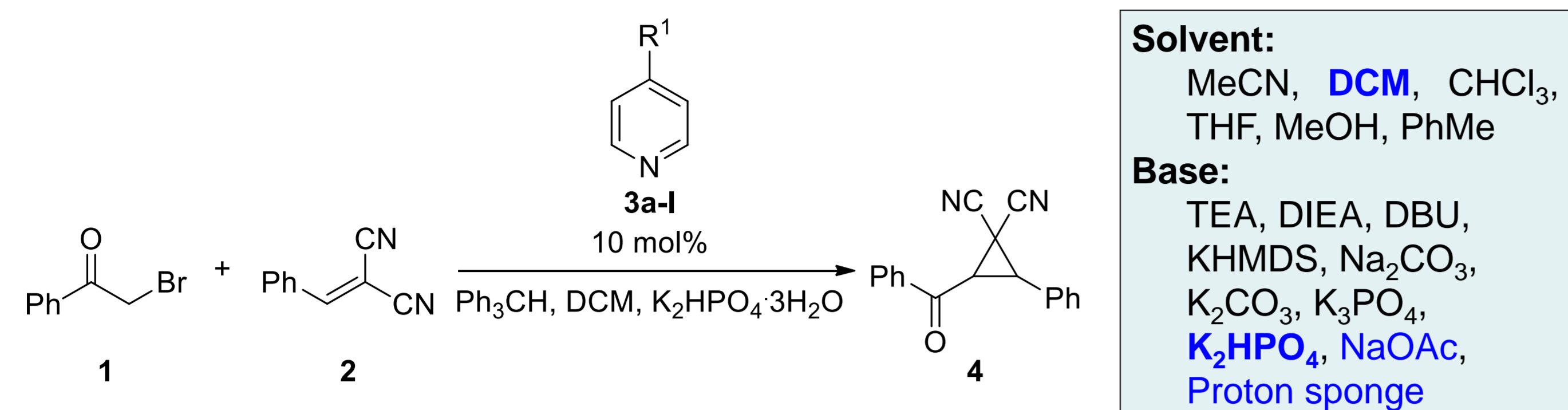
<sup>1</sup> Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga, LV-1006, Latvia

<sup>2</sup> University of Michigan, Ann-Arbor, USA

artis@osi.lv



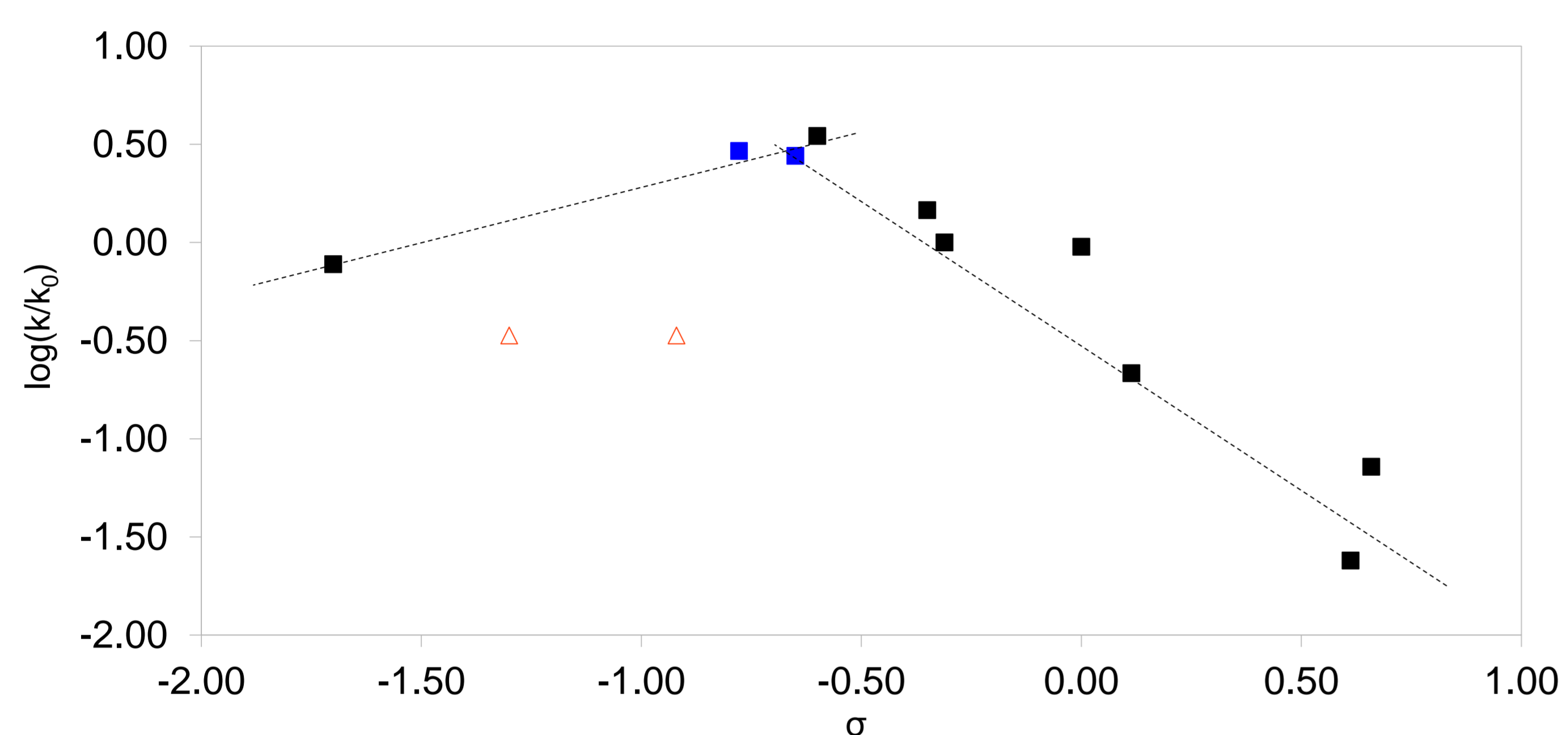
## Pyridine substituent influences catalytic activity



- a) The most suitable solvent for cyclopropanation reaction is DCM;  
 b) K<sub>2</sub>HPO<sub>4</sub>·3H<sub>2</sub>O has been chosen as base;

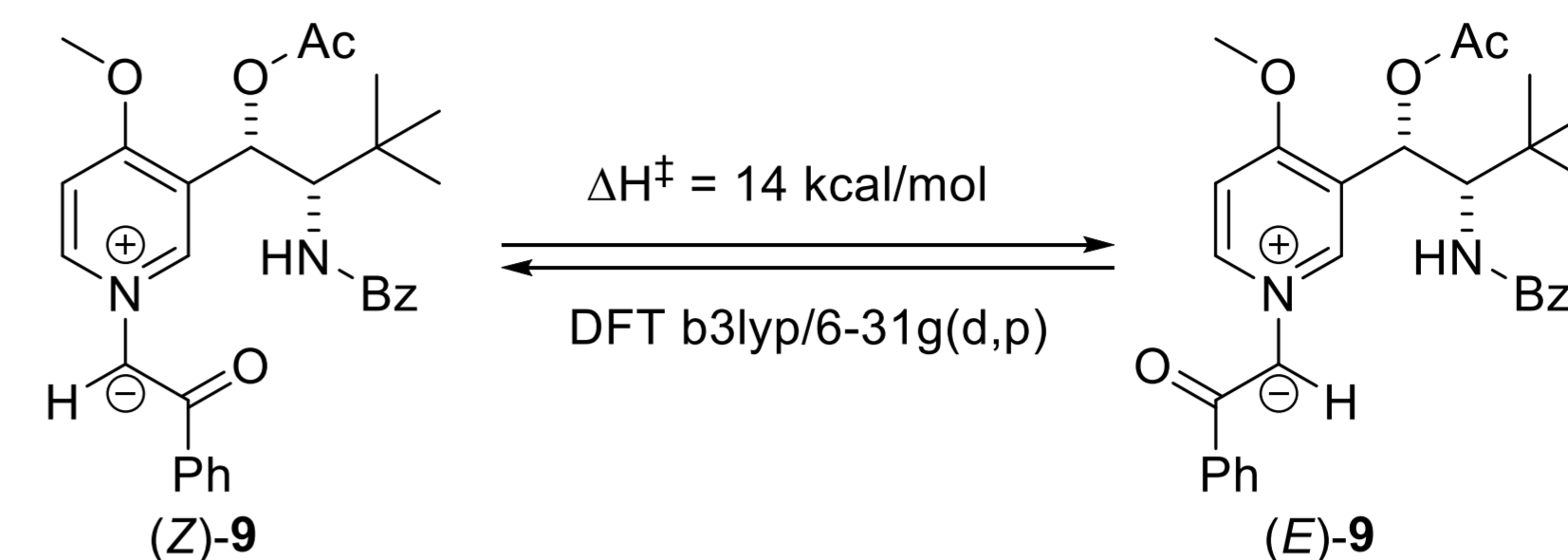
Catalyst	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l
R <sup>1</sup>	NMe <sub>2</sub>	NH <sub>2</sub>	OH	<b>OMe</b>	NMeAc	NHAc	3,4-diMe	Me	H	Cl	CF <sub>3</sub>	CN
Turnovers	2.9	2.9	1.9	<b>7.9</b>	<b>8.0</b>	7.2	5.3	3.8	5.1	1.6	0.3	0.0
Log(k/k <sub>0</sub> )	-0.11	<b>-0.47</b>	<b>-0.47</b>	0.47	0.44	0.54	0.17	0.00	-0.02	-0.67	-1.62	-1.14
σ	-1.70	<b>-1.30</b>	<b>-0.92</b>	-0.78	-0.65	-0.60	-0.35	-0.31	0.00	0.11	0.61	0.66

Hammett plot

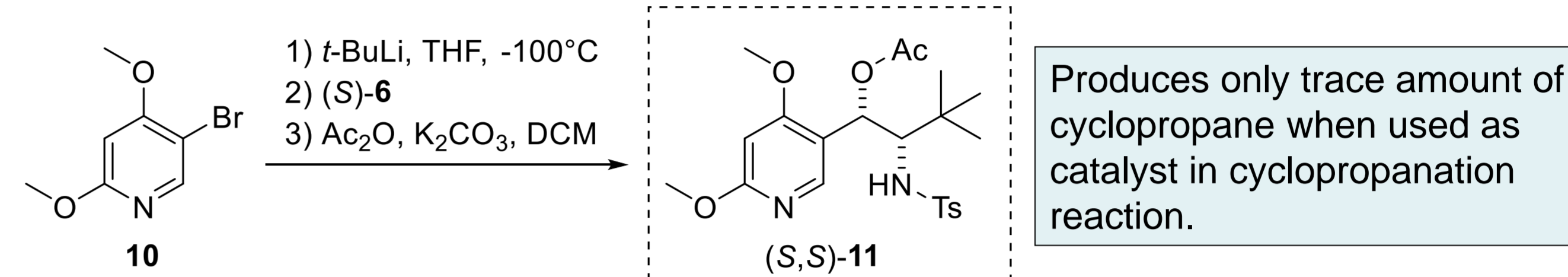


- c) Non-linear Hammett plot points to change in rate determining step or reaction mechanism;  
 d) 4-Methoxypyridine has been chosen as scaffold for development of chiral catalyst.

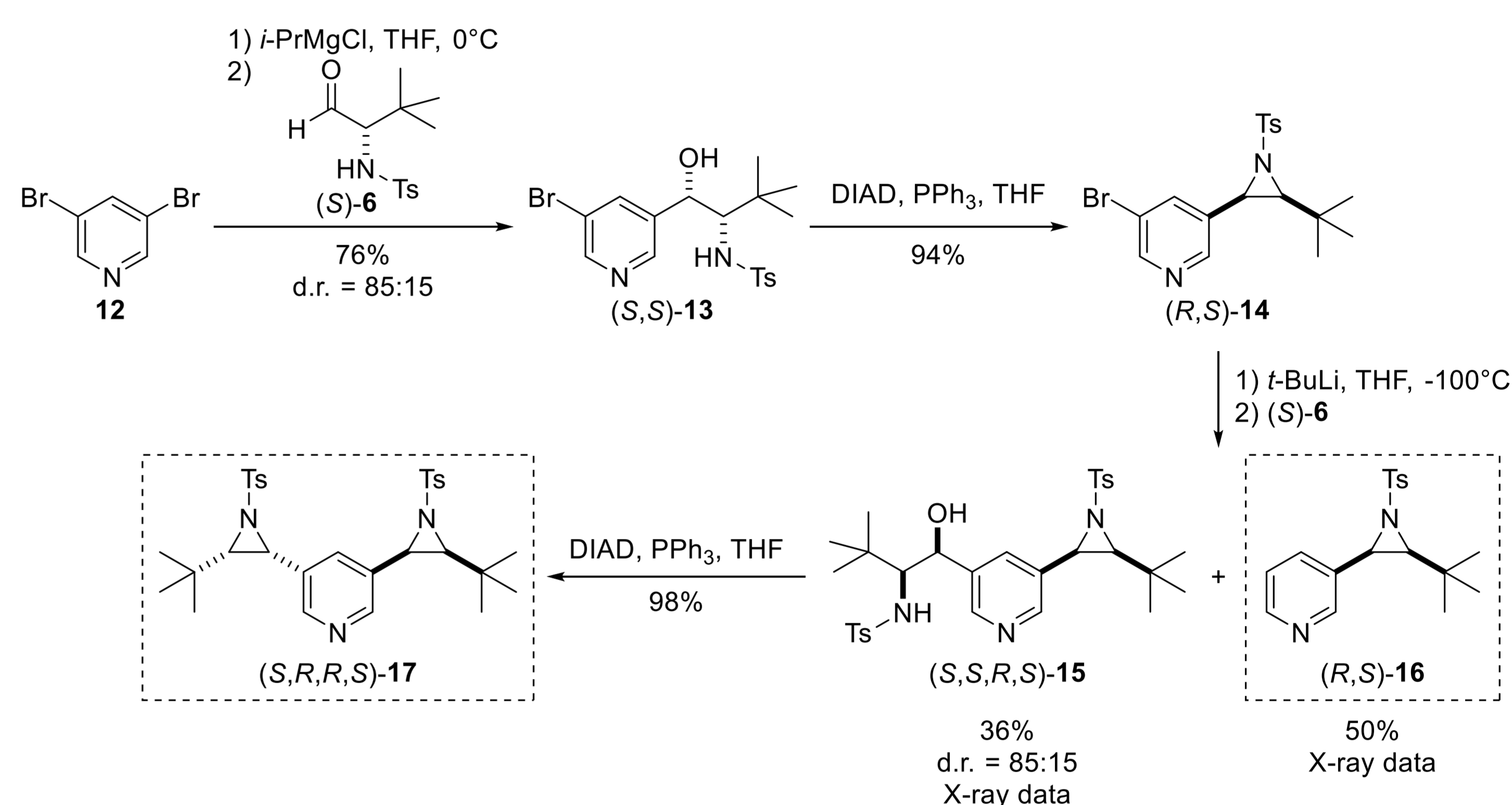
## Further development of chiral pyridine catalyst



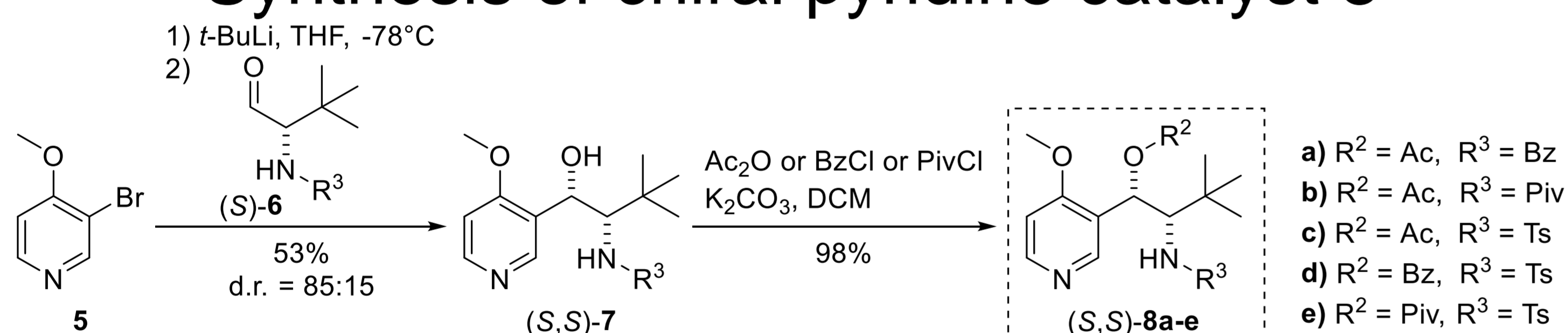
- a) Moderate cyclopropanation enantioselectivity might be a result of a relatively small rotational barrier about pyridine ylide bond;



- b) Substituent *ortho* to pyridine nitrogen decreases dramatically catalyst's activity;



## Synthesis of chiral pyridine catalyst 8



- a) *ortho*-Lithiation of pyridine 5 followed by acylation with acetic anhydride produced catalysts (S,S)-8a-e with >90% ee.  
 b) Relative stereochemistry of (S,S)-8a was determined by X-ray analysis;

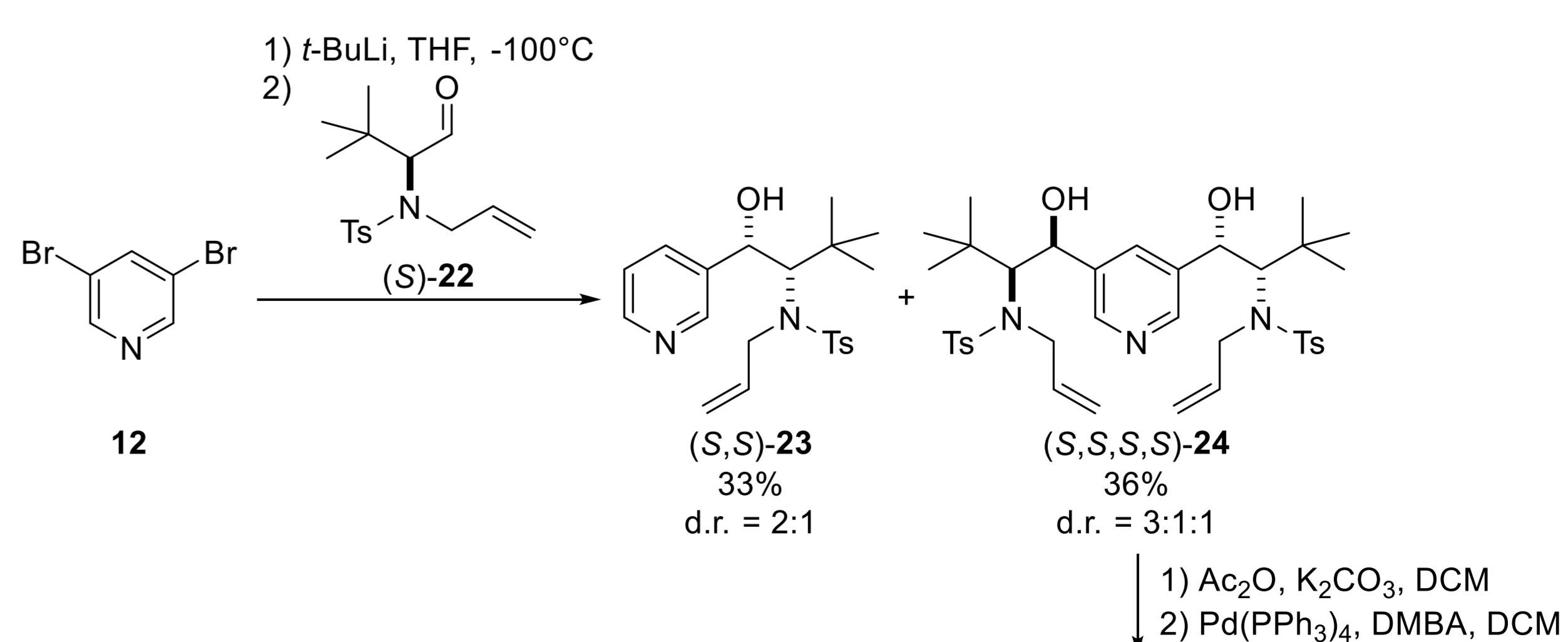
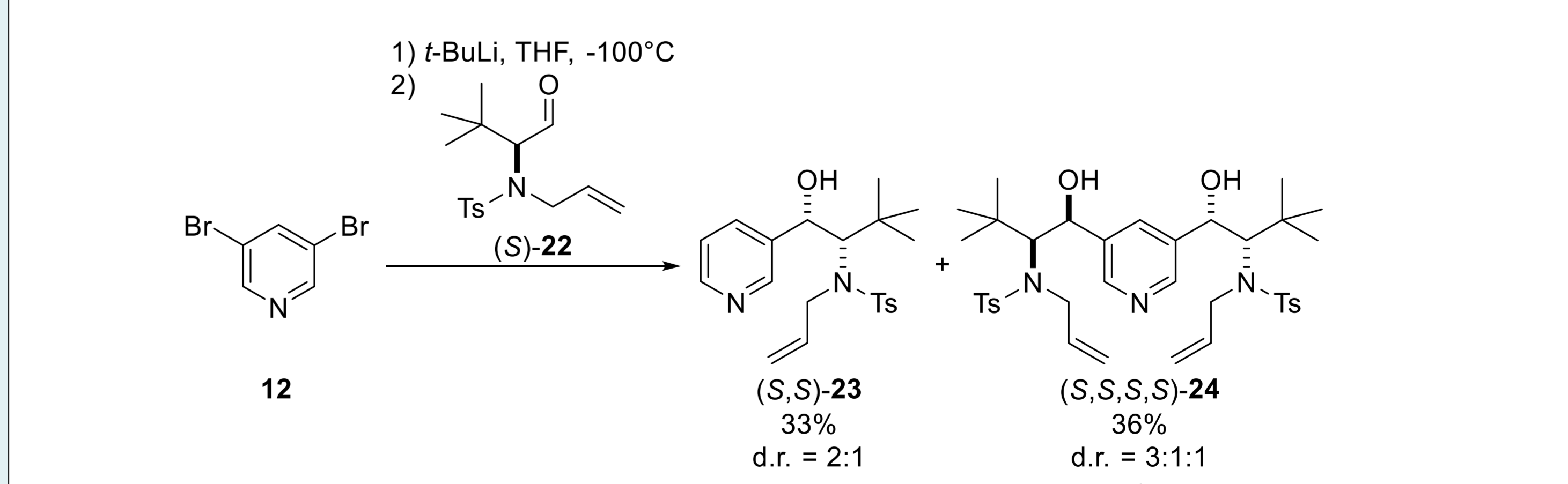
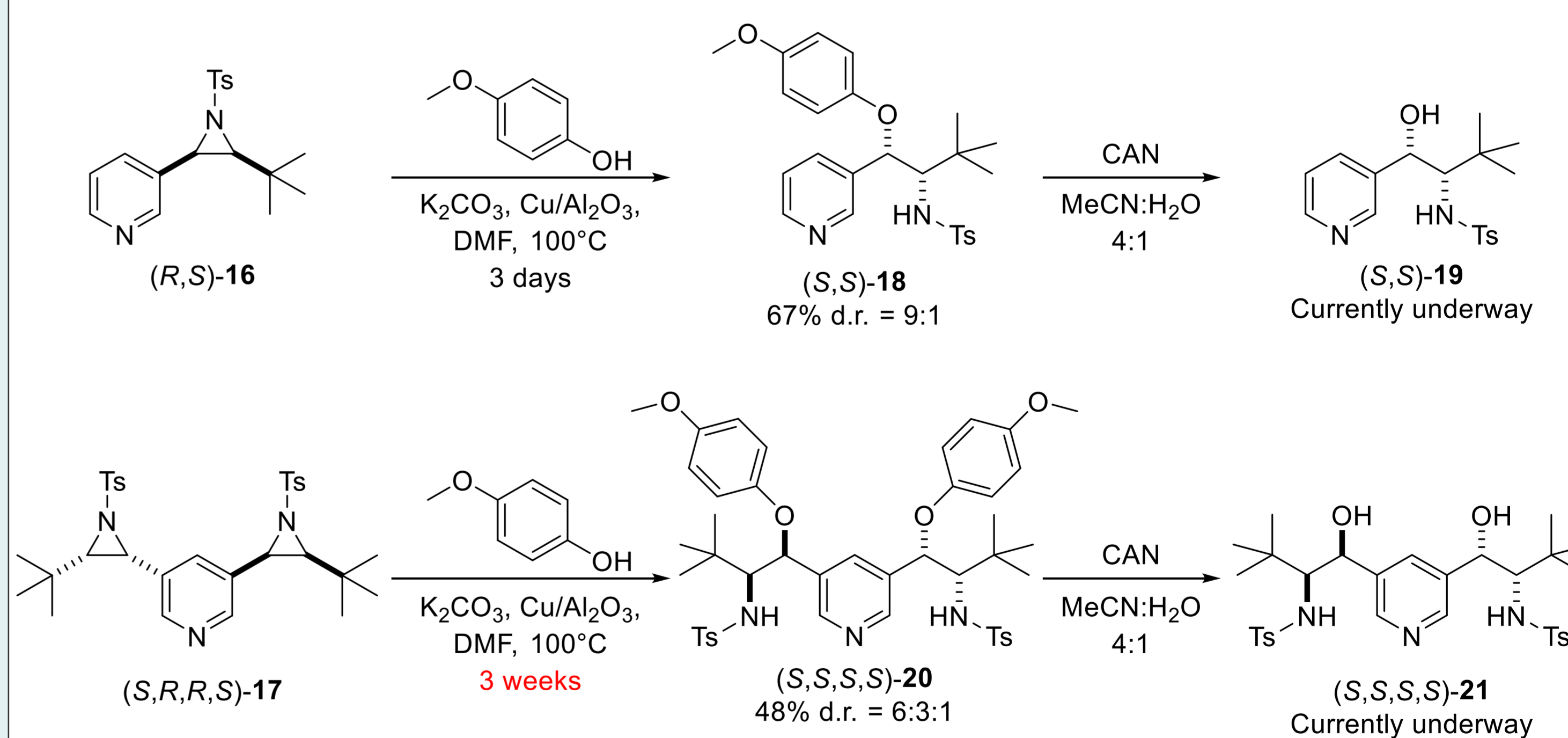
## Results of asymmetric cyclopropanation

Catalyst	4a	4b	4c	4d	4e	4f	4g
1 (R,S)-8a	-23	-20	-19	-18	-2	-12	
2 (S,S)-8a	31	17	18	17	11	13	-19
3 (S,S)-8b	34	18	16	28	29	<b>49</b>	1
4 (S,S)-8c	<b>34</b>	<b>38</b>	<b>32</b>	<b>31</b>	14	5	<b>-20</b>
5 (S,S)-8d	8	<b>49</b>				12	
6 (S,S)-8e	-13	34				14	

- a) Chiral benzylic center of the catalyst determines absolute configuration of cyclopropane;  
 b) The highest enantioselectivity (49% ee) was obtained with sterically large R<sup>3</sup> substituent (Piv, Ts);

Catalyst	4a	4b	4d	4f
1 (R,S)-16	9	-2	-8	-1
2 (S,R,R,S)-17	17	-6	1	-6

c) Chiral aziridine ring-containing organocatalysts gives low enantioselectivities in cyclopropanation reaction;



- d) Separation of C-2 symmetric pyridine (S,S,S,S)-25 diastereomers is ongoing to address the issue of ylide bond geometry.

