Deracemization/Dynamic Kinetic Resolution of Quaternary Stereocenters

Shair, M. D. et al, *Angew. Chem. Int. Ed*. **2005**, *44*,2259

Stoltz, B. M. et al, *Angew. Chem. Int. Ed*. **2005**, *44*,6924

Nakamura, E. et al, *Angew. Chem. Int. Ed*. **2005**, *44*, 7248

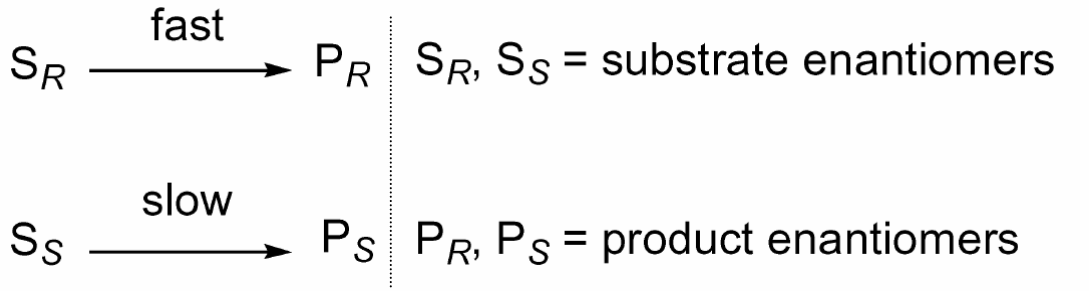
Literature Presentation

Yu Zhang

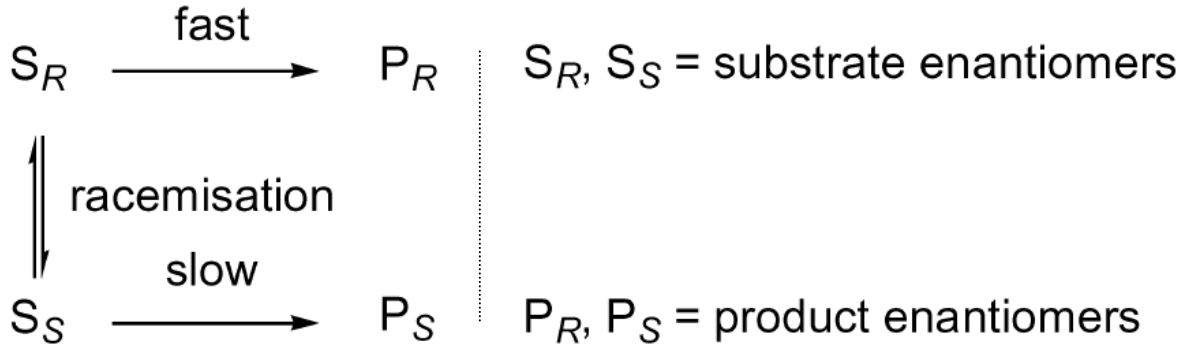
Nov. 10, 2005

Introduction to Dynamic Kinetic Resoultion (DKR)

♦Classical kinetic resolution:



♦Dynamic kinetic resolution (DKR):



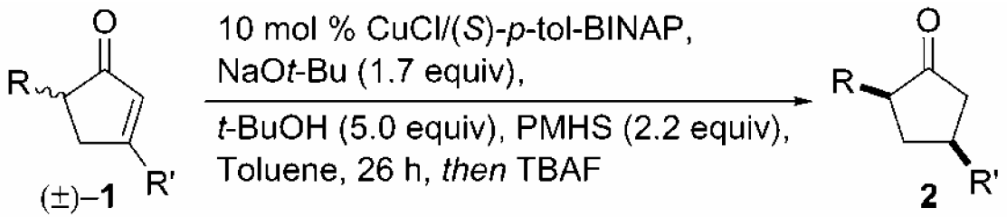
-- DKR combines the resolution step of kinetic resolution, with an in situ equilibration or racemization of the chirally labile substrate.

-- Racemization of the substrate can be performed either chemically, biocatalytically or even spontaneously; conditions must be chosen to avoid the racemization of the product.

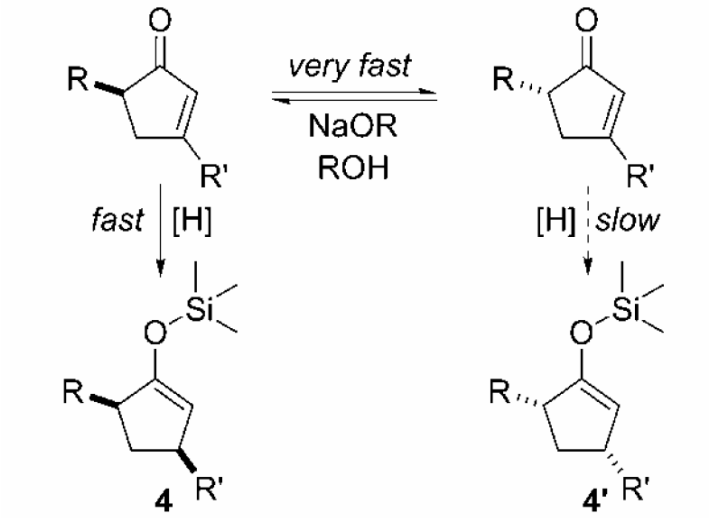
H. Pellissier, *Tetrahedron*. **2003**, *59*, 8291-8327

Example of DKR

♦DKR using proton transfer:

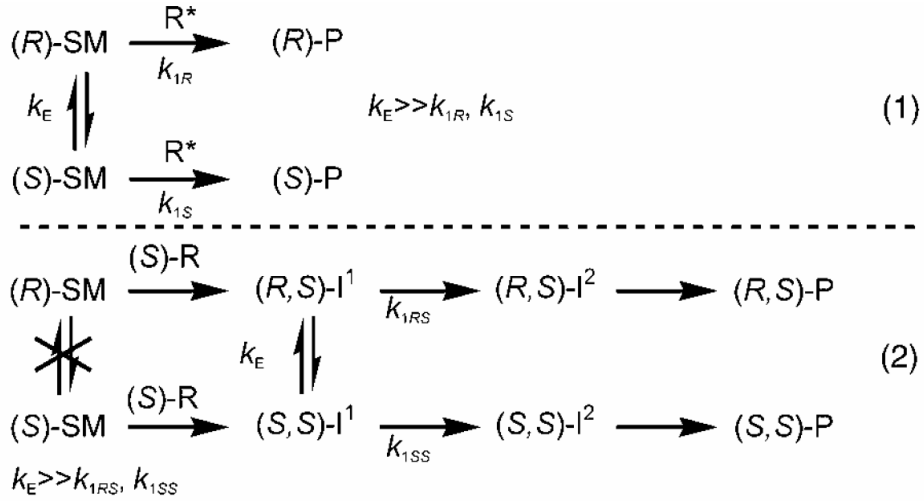


91-94% ee, 89-95% yield
>10:1 syn/anti



Buchwald et al, *JACS*. **2002**, *124*, 2892

DKR of Chiral All-Carbon Quaternary Centers

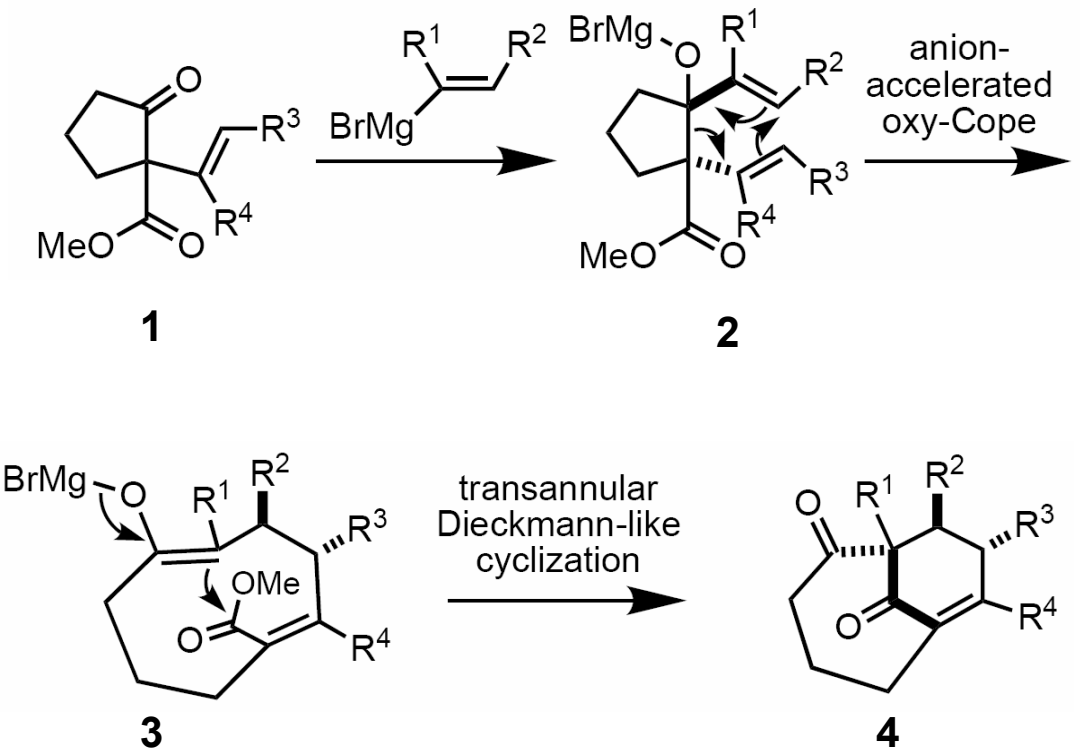


- Dynamic kinetic resolution with enantiomerization of the SM. Eq. (1).
- Dynamic kinetic resolution with epimerization in the second step (Eq. (2)). I^1=first intermediate, I^2=second intermediate, P=product.

Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

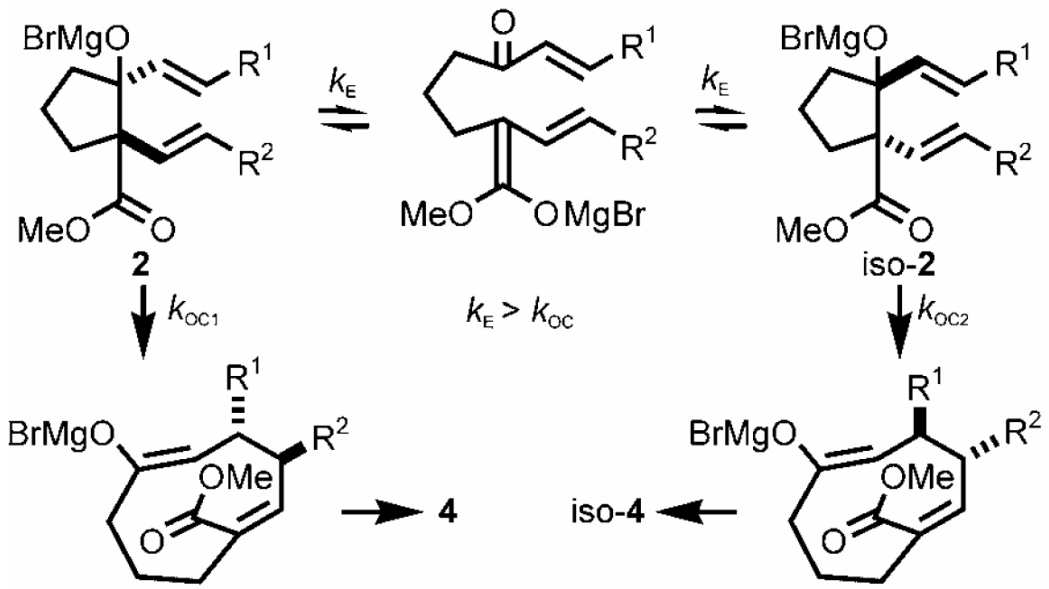
DKR of Chiral All-Carbon Quaternary Centers

♦ A cascade reaction for the synthesis of polycyclic bridgehead enone compounds. (Shair, *Ang*, **2000**, *39*, 2714)



Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

DKR of Chiral All-Carbon Quaternary Centers

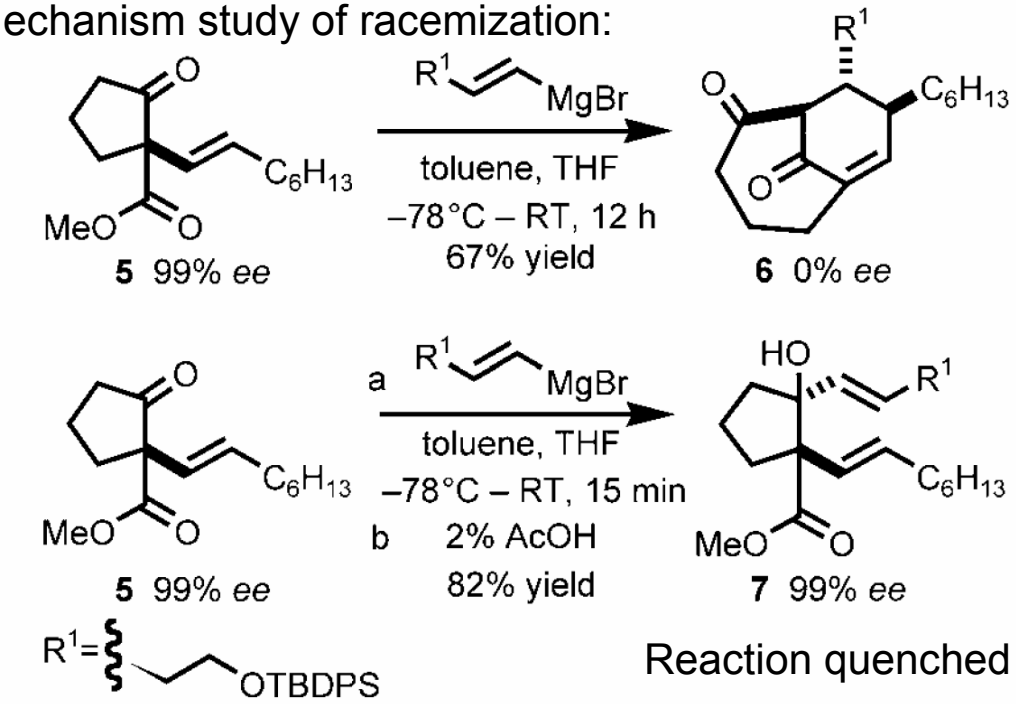


- Possibility of **2** to undergo retro-aldo/aldol equilibrium?
- Retro-aldo or Dieckmann reaction – Which one is faster?

Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

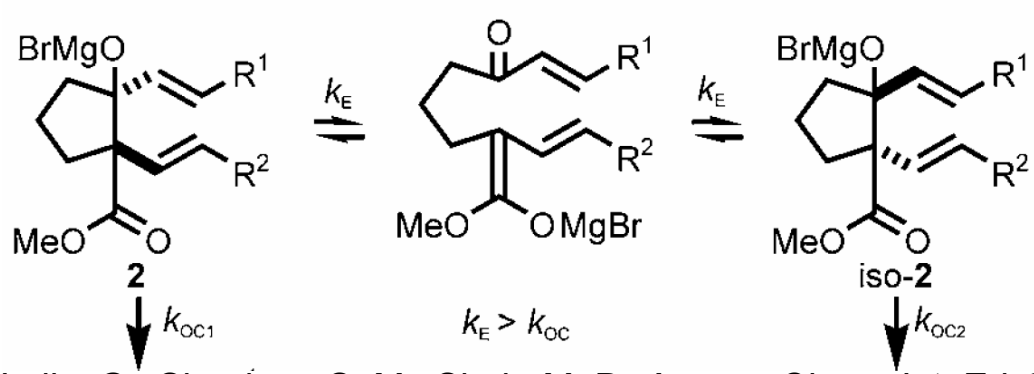
DKR of Chiral All-Carbon Quaternary Centers

- Mechanism study of racemization:



Reaction quenched by AcOH at 0°C.

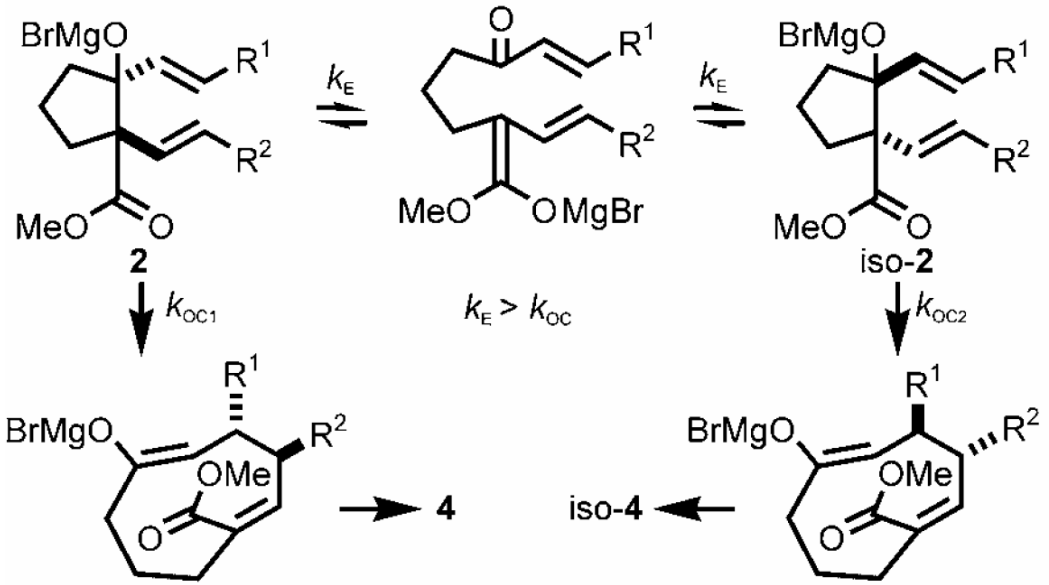
- Result: $K_E >> K_{OC}$



Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

DKR of Chiral All-Carbon Quaternary Centers

♦ Racemization of cascade reaction:



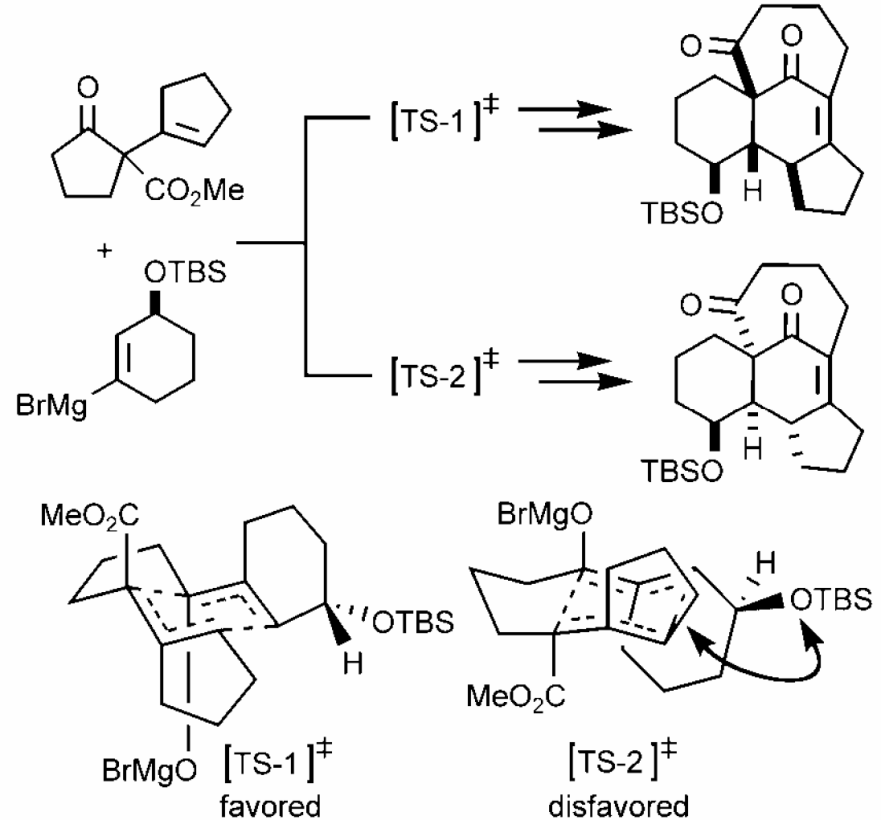
-- Retro-aldol/aldol much faster than anionic oxy-Cope(AOC);

-- AOC involves highly organized TS, control relative rate of K_{OC1} and K_{OC2} possible?

Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

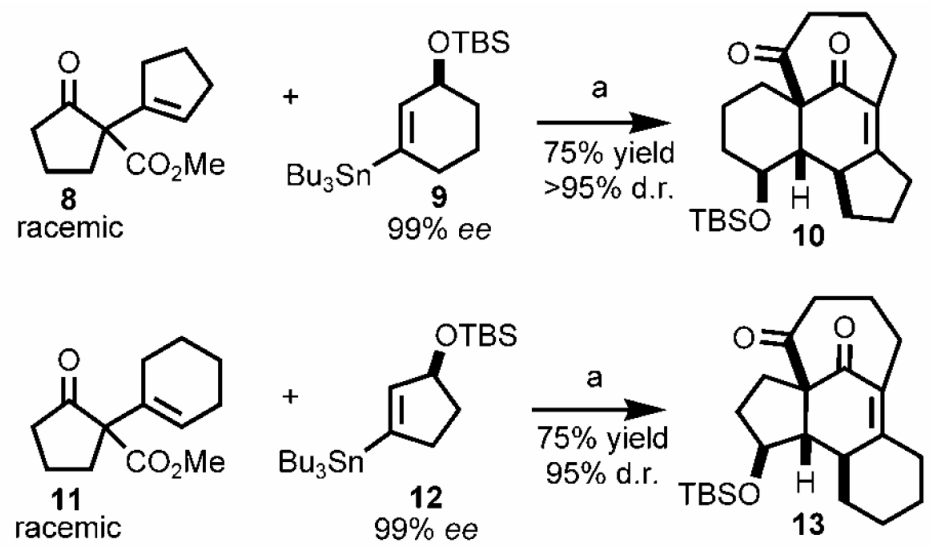
DKR of Chiral All-Carbon Quaternary Centers

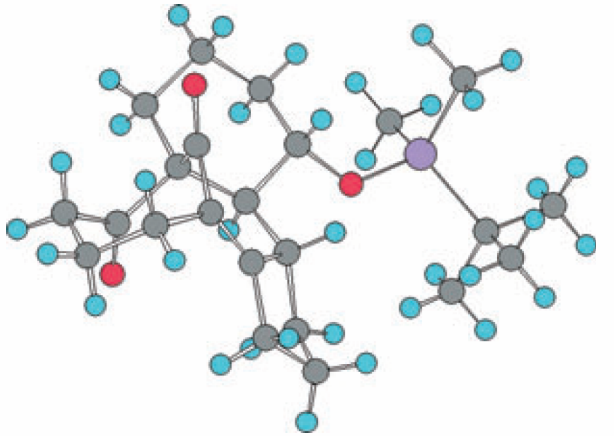
♦ Proposed DKR of the polycyclic products:



Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

DKR of Chiral All-Carbon Quaternary Centers

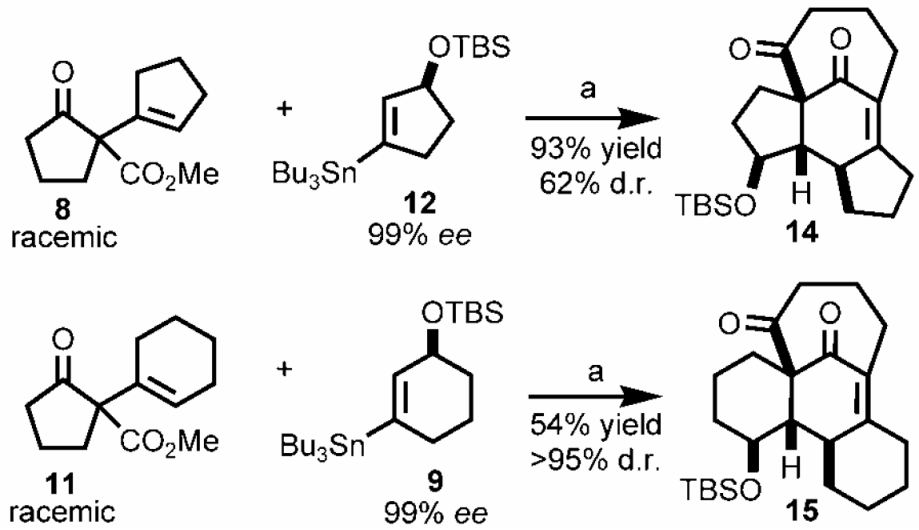




a) *n*BuLi, THF, -78^{o}C,; $MgBr_2$, Et_2O/benzene, O^{o}C; THF/toluene, 23^{o}C, 18 h.

Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

DKR of Chiral All-Carbon Quaternary Centers

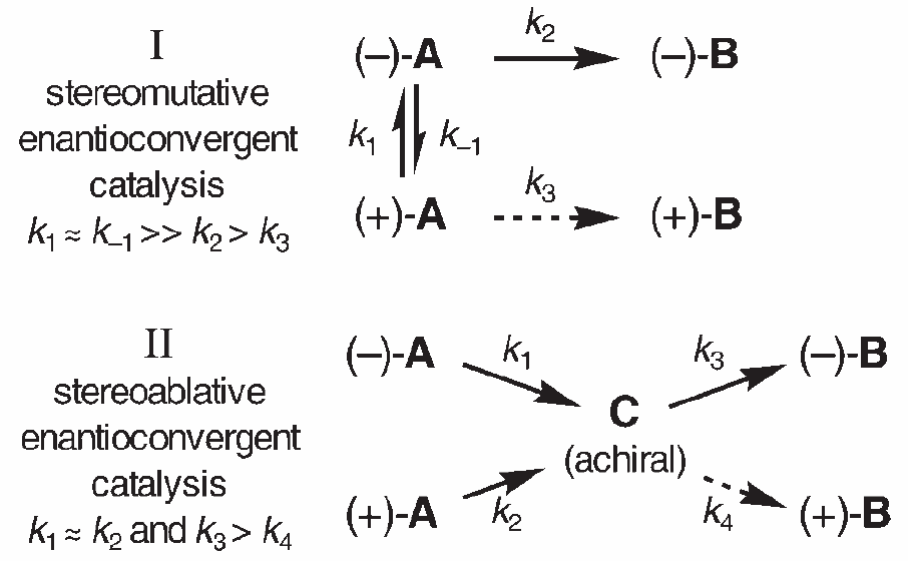


a) *n*BuLi, THF, -78^{o}C,; $MgBr_2$, Et_2O/benzene, O^{o}C; THF/toluene, 23^{o}C, 18 h.

Xu, K.; Lalic, G., Sheehan, S. M.; Shair, M. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 2259

Deracemization of Quaternary Centers - Introduction

♦ Stereomutative versus stereoablative enantioconvergent catalysis.

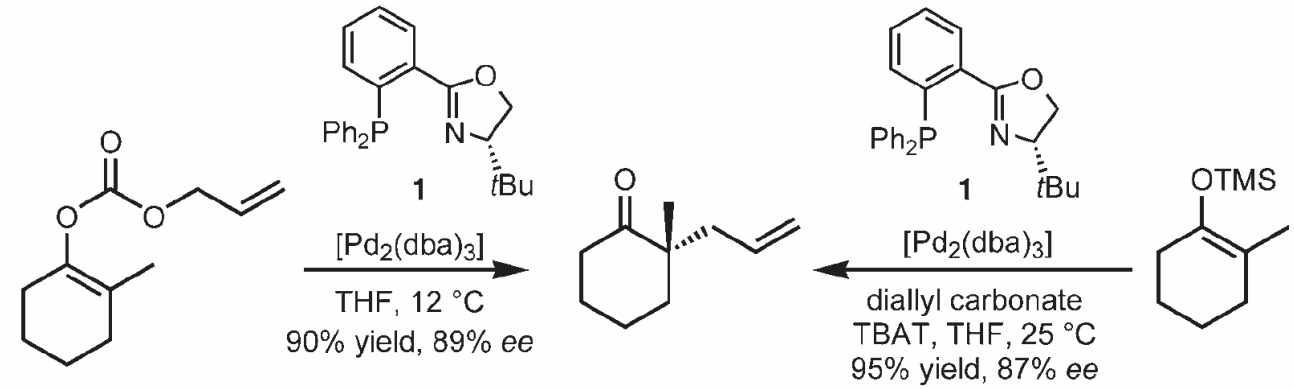


-- The term “stereoablative” describes the conversion of a chiral molecule to an achiral molecule.

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M, *Angew. Chem. Int. Ed*. **2005**, *44*, 6924

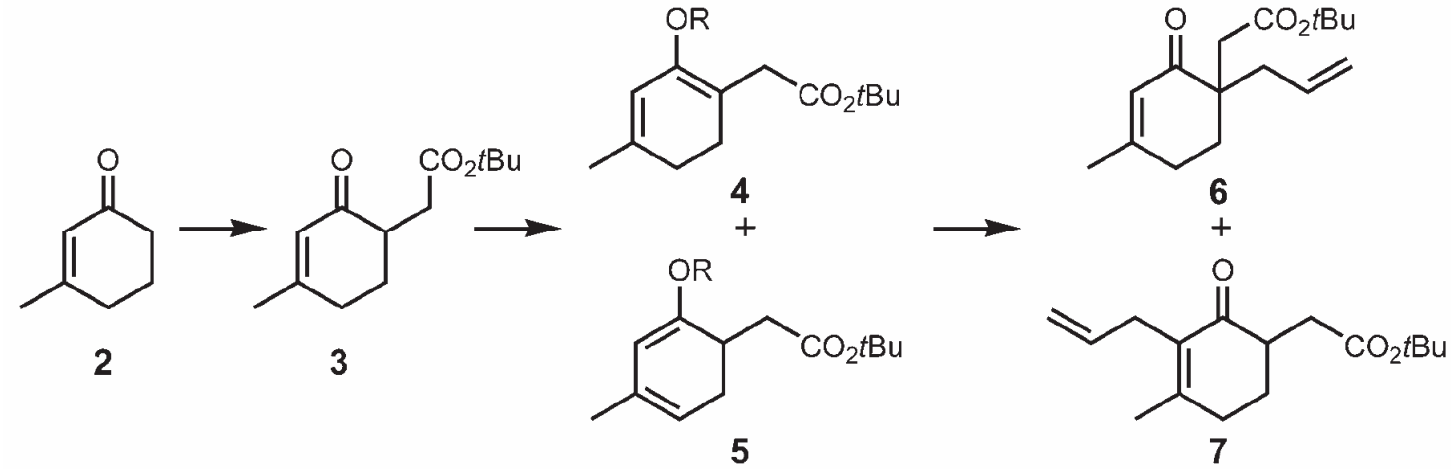
Deracemization of Quaternary Centers - Introduction

♦ Enantioselective Tsuji Allylations:



Stoltz. *JACS*, **2004**, *126*, 15044

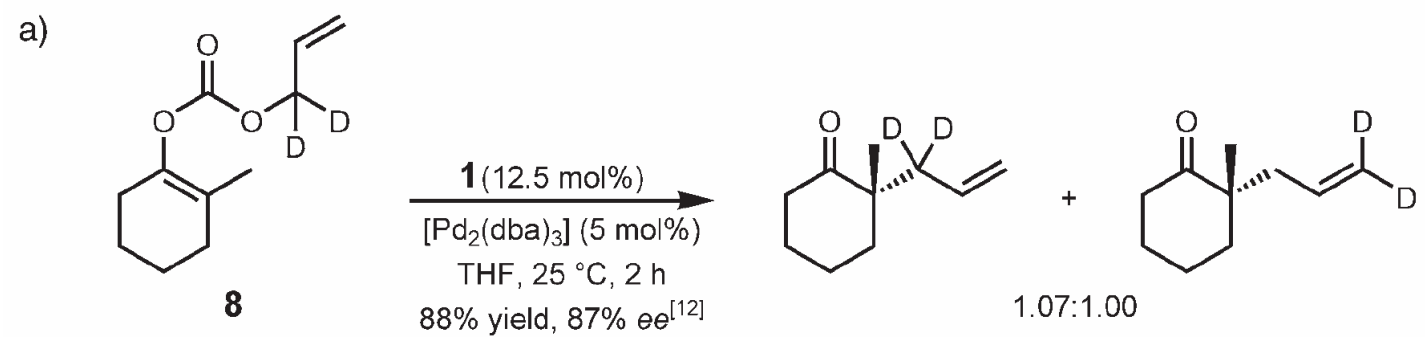
♦ However, enolization not selective for the synthesis of **4** (R = CO_2allyl or TMS):



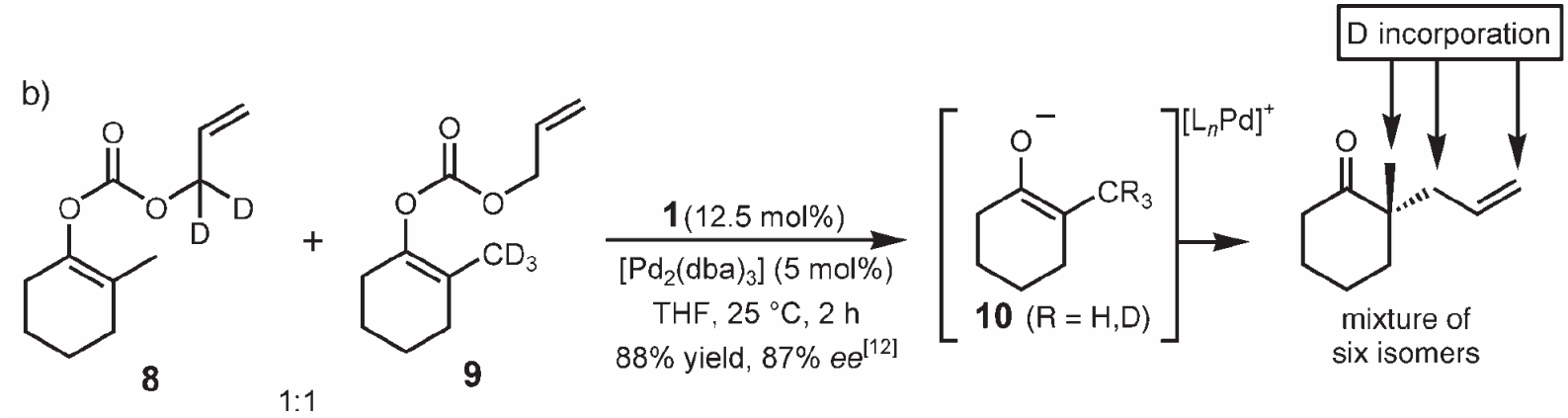
Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M, *Angew. Chem. Int. Ed*. **2005**, *44*, 6924

Deuterium-labeling experiments

♦ Deuterium-labeling experiment with **8**:



♦ Crossover experiment with **8** and **9**:

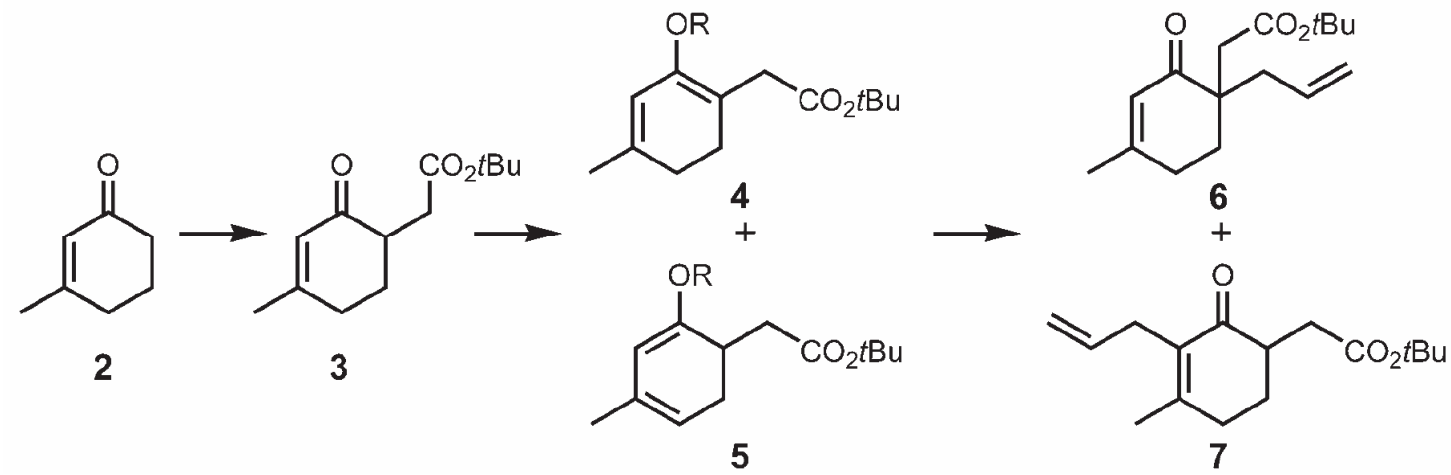


-- A discrete achiral ketone enolate **10** must exist.

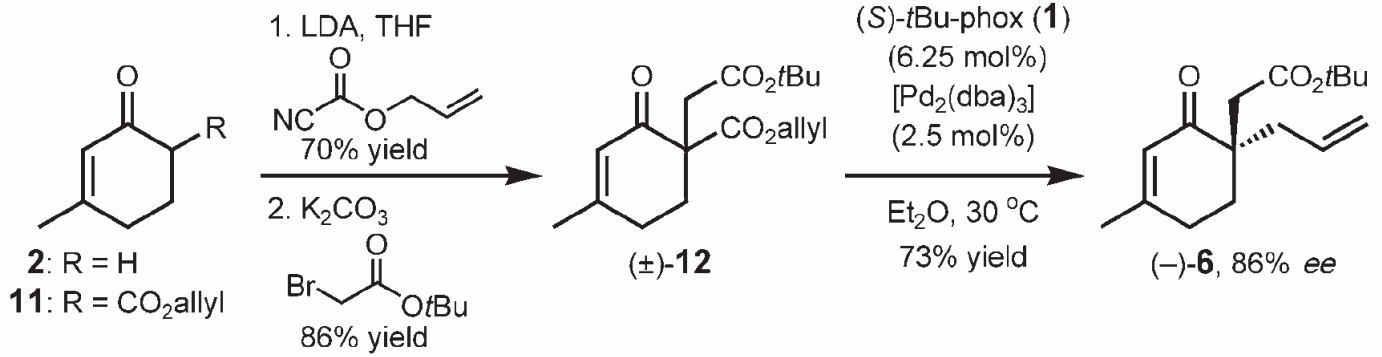
Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M, *Angew. Chem. Int. Ed*. **2005**, *44*, 6924

β-Ketoester synthesis and decarboxylative allylation

♦ Nonselective synthesis of **6**



♦ Enantioselective synthesis of **6** via decarboxylative allylation.

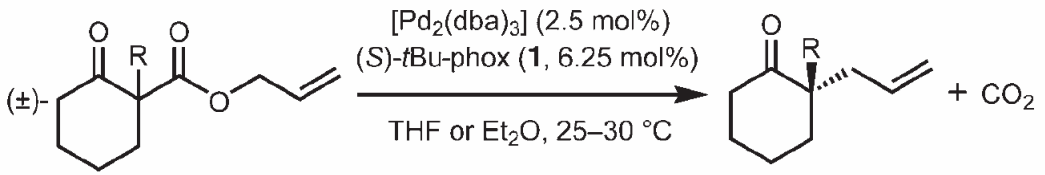


-- Above process solved the nonselective enolization of **3**;
-- **12** was racemic throughout the reaction.

Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M, *Angew. Chem. Int. Ed*. **2005**, *44*, 6924

Catalytic enantioconvergent decarboxylation allylation

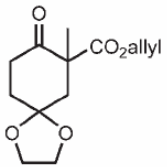
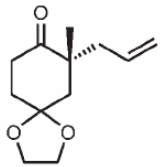
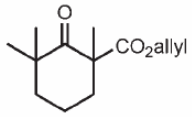
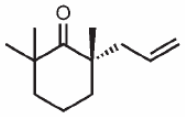
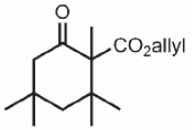
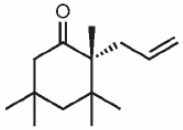
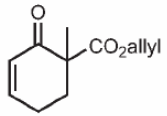
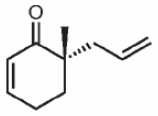
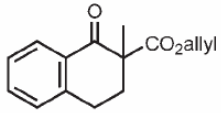
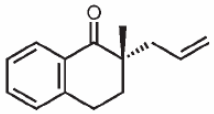
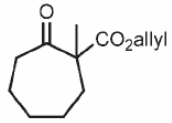
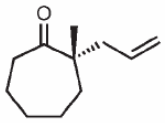
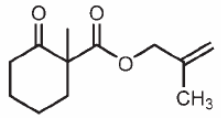
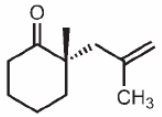
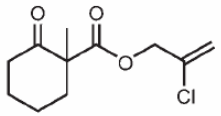
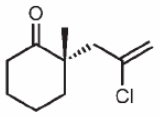
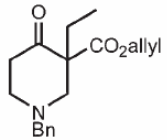
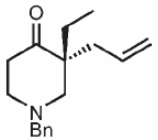
♦Enantioconvergent decarboxylation allylation of 2-carboxyallylcyclohexanones.



Entry	R	Solvent	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	CH_3	THF	25	7.5	85	88
2	CH_3	Et_2O	25	4.75	89	88
3	prenyl	Et_2O	30	6	97	91
4	CH_2CH_2CN	Et_2O	25	6.5	97	88
5[c]	$CH_2CH_2CO_2Et$	Et_2O	25	6	96	90
6	$CH_2C_6H_5$	THF	25	0.5	99	85
7	$CH_2(4\text{-}CH_3OC_6H_4)$	THF	25	10	80	86
8	$CH_2(4\text{-}CF_3C_6H_4)$	THF	25	0.5	99	82
9[c]	$CH_2OTBDPS$	THF	25	5	86	81
10	F	Et_2O	30	3.5	80	91

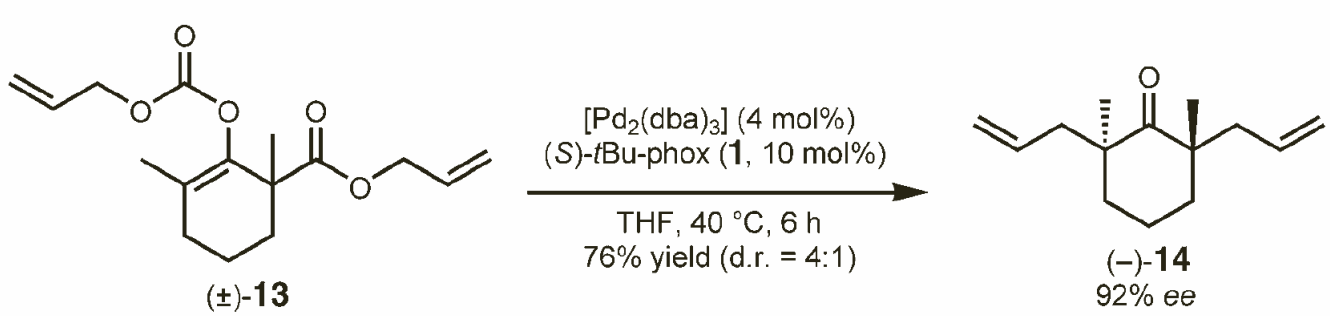
Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M, *Angew. Chem. Int. Ed*. **2005**, *44*, 6924

Catalytic enantioconvergent decarboxylation allylation

Entry	Substrate	Product	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]
1			25	1.5	94	85
2[c]			25	24	94	86
3			30	9	89	90
4			25	5	90	85
5[d,e]			30	4	77	90
6[d]			25	10	97	92
7			25	9.5	83	87
8[d]			35	6.5	87	92
9[d,e]			35	2.5	87	91
10			25	2.5	91	92

Catalytic enantioconvergent decarboxylation allylation

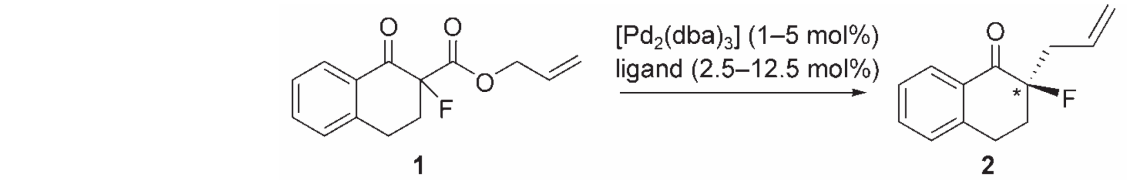
- The enantioselective allylation cascade generating two quaternary carbon stereocenters:

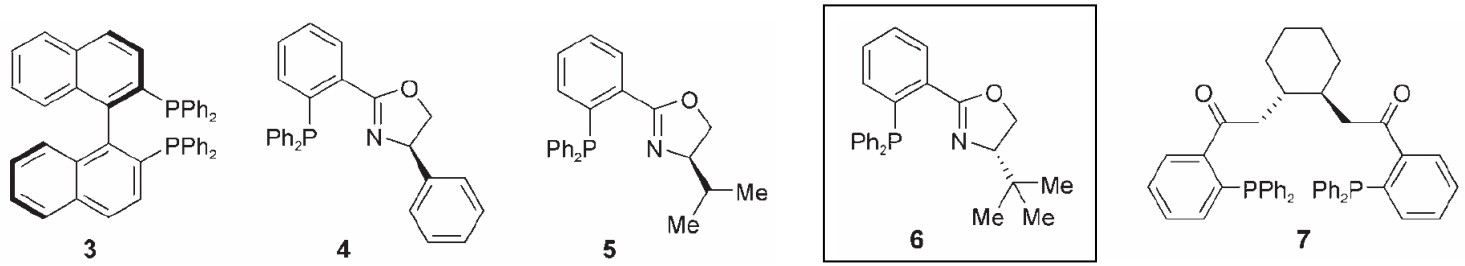


(±)-**13**

(–)-**14**
92% *ee*

Catalytic enantioselective decarboxylation

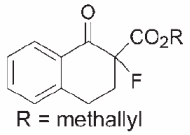
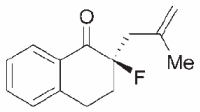
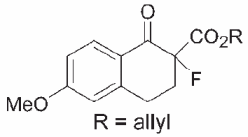
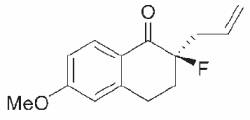
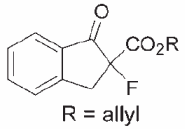
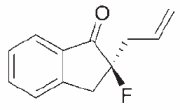
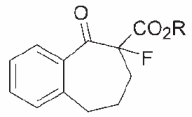
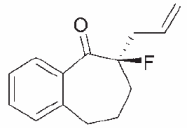


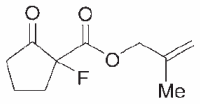
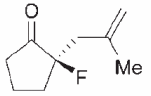
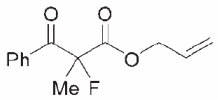
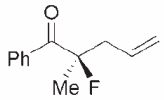
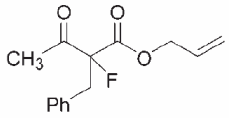
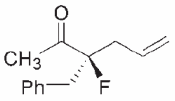
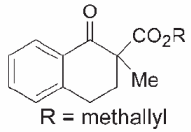
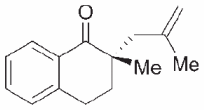
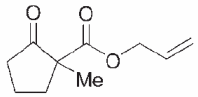
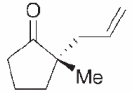
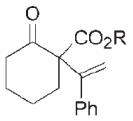
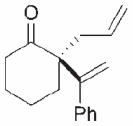


Entry	Ligand	*t* [h]	Solvent	$[Pd_2(dba)_3]$[b] [mol%]	Yield [%][c]	*ee* [%][d]
1	none	24	THF	5	0	–
2	**3**	5	THF	5	83	11
3	**4**	3	THF	5	91	11
4	**5**	3	THF	5	94	83
5	**6**	3	THF	5	95	96
6	**6**	4	THF	2.5	95	96
7	**6**	10	THF	1	93	94[e]
8	**6**	4	Et_2O	5	93	96
9	**6**	5	CH_2Cl_2	5	89	25
10	**6**	4	THF	2.5	94	96[f]
11	**7**	10	THF	5	9	n.d.[g]

M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem. Int. Ed*. **2005**, *44*, 7248

Catalytic enantioselective decarboxylation

Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	**1**	**2**	95	96
2[d]	 R = methallyl		96	99
3			95	97
4	 R = allyl		92	96
5	 R = allyl		94	91
6	 R = allyl		94	93

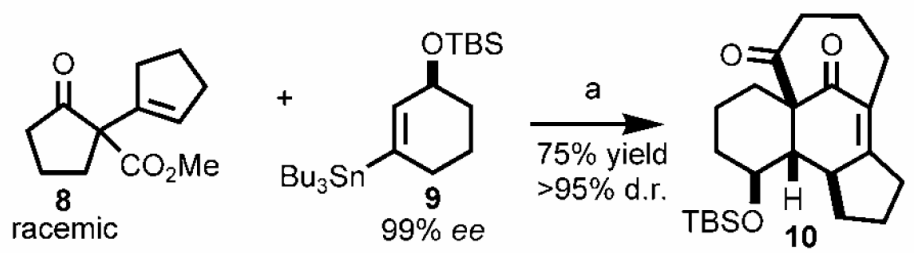
Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
7			82[e]	85
8			89	51
9			91	55
10	 R = methallyl		94	95
11			87[e]	84
12			89	39

All reactions were performed with a 0.05m substrate concentration in THF for 4–10 h at 22–25°C in the presence of $[Pd_2(dba)_3]$ (2.5 mol%) and ligand **6** (6.25 mol%).

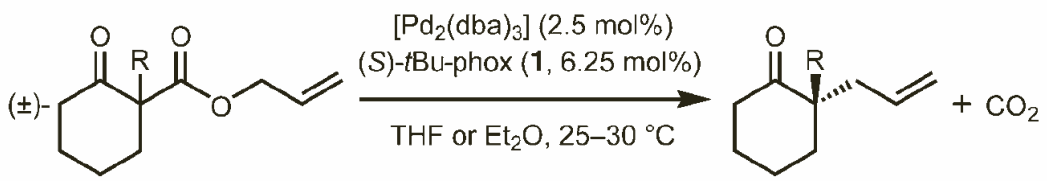
M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem. Int. Ed*. **2005**, *44*, 7248

Conclusion

- Shair:



- Stoltz, Nakamura:



♦ Careful consideration – detailed mechanism study – valuable reaction.