Metal-enzyme catalyzes the dynamic kinetic resolution of alcohols and phenols

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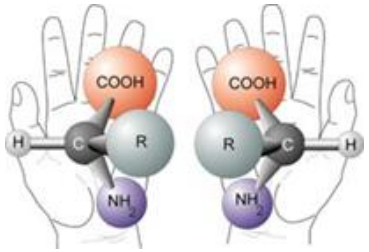
CONTENTS

CONTENTS

Part I: Introduction



Chirality

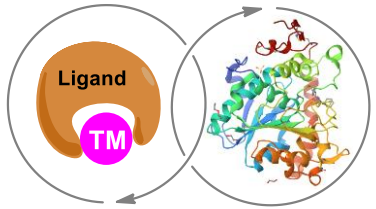
Medicine

Pesticide

Material

Transition metal catalysis + **Enzymatic catalysis** $\xrightarrow[\text{combination}]{\text{Advantages}}$ **Metal-enzyme catalysis**

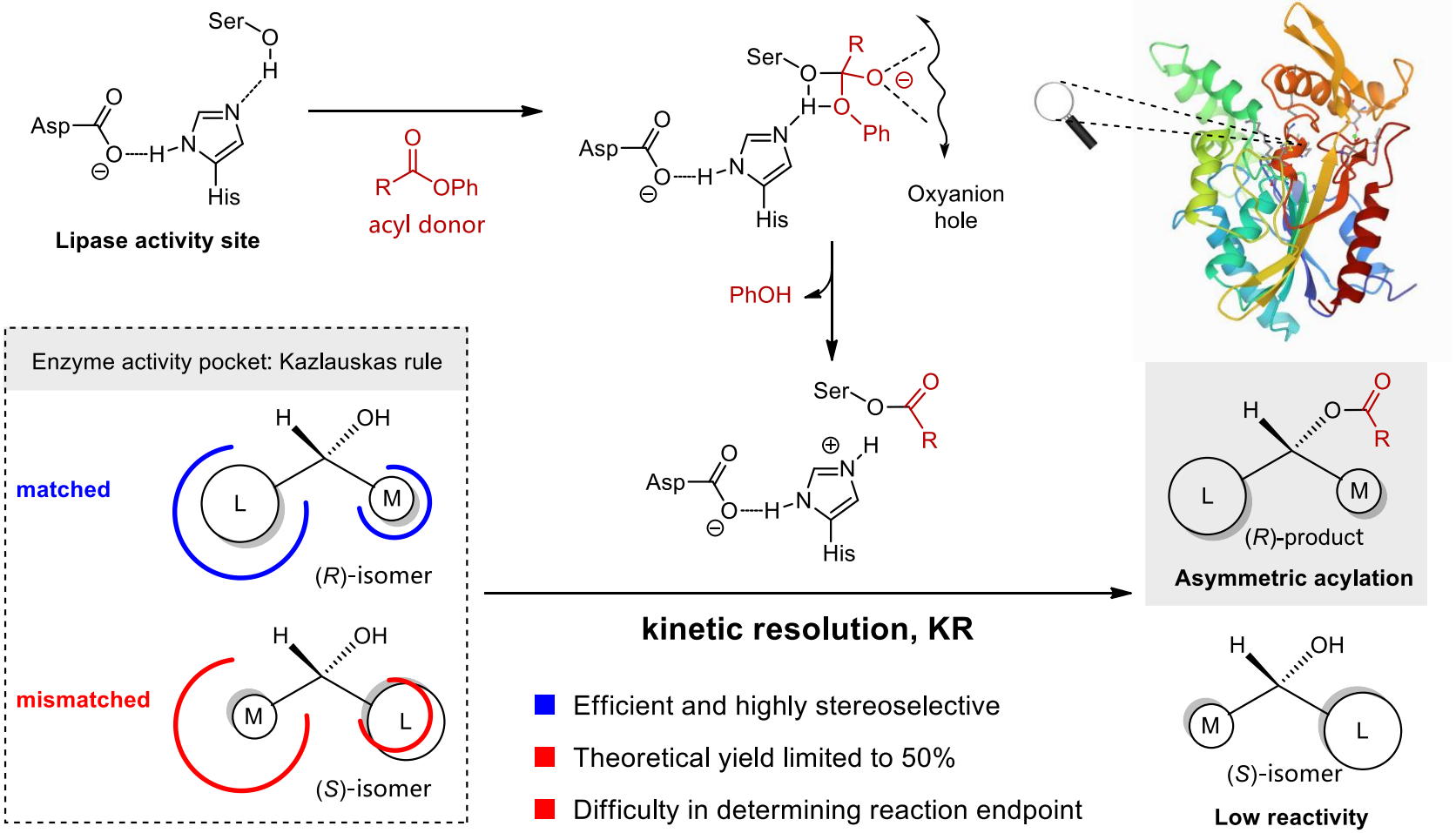
- ☑ Diverse types of metals
- ☑ Rich catalytic types
- ☑ Ligand regulation is variable
- ☑ High catalytic efficiency
- ☑ High stereoselectivity
- ☑ Mild reaction conditions



Synthesize more challenging molecules

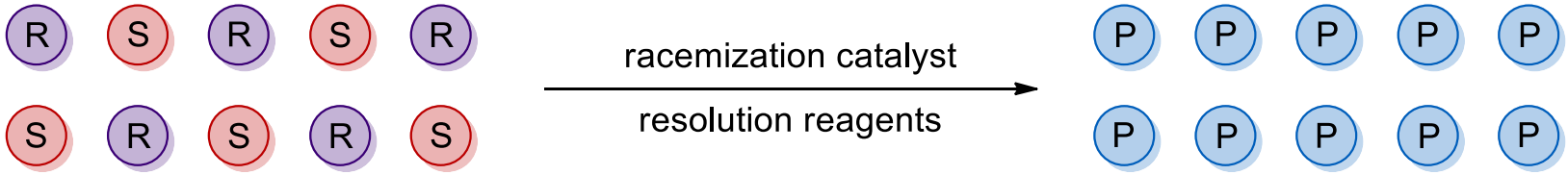
Part I: Introduction

Lipase catalyzed kinetic resolution of alcohols (kinetic resolution, KR)



Part I: Introduction

Chemoenzymatic Dynamic Kinetic Resolution (DKR):



up to 100% yield

Enzymatic catalysis

Transition metal

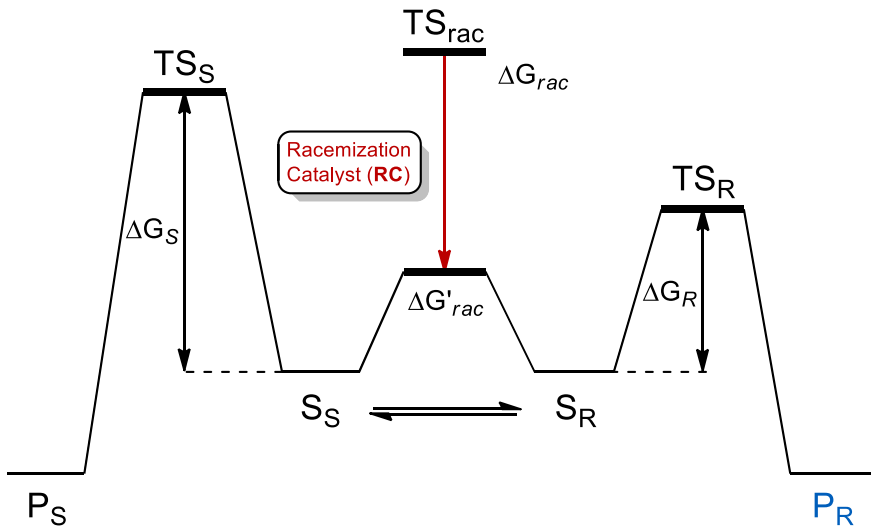
Substrate (S_R) —K_{fast}→ Product (P_R)

Racemization Catalyst (**RC**) ⇌ (K_{rac})

Substrate (S_S) ⇢K_{slow}⇢ Product (P_S)

$K_{rac} > K_{fast} >> K_{slow}$

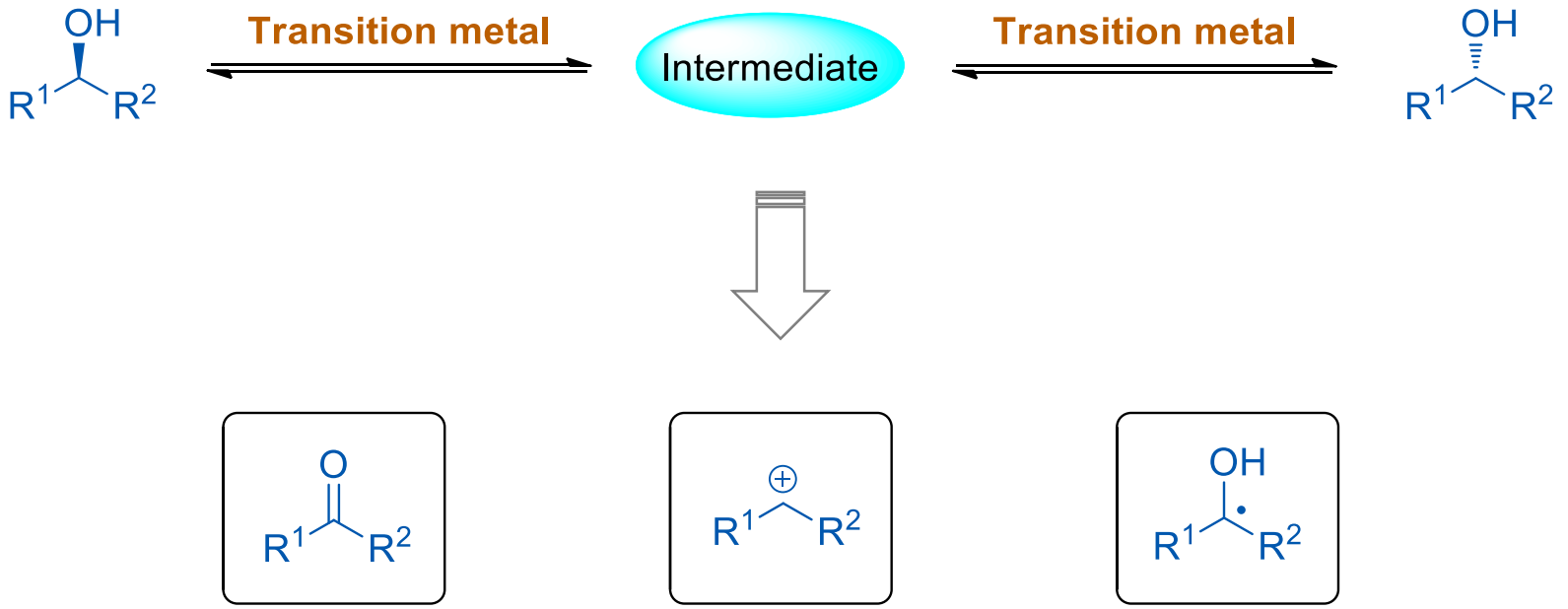
Energy barrier decreased by RC:



- **The theoretical yield is 100%;**
- **High reaction efficiency**

Part I: Introduction

Transition metal catalyzed racemization of alcohols:

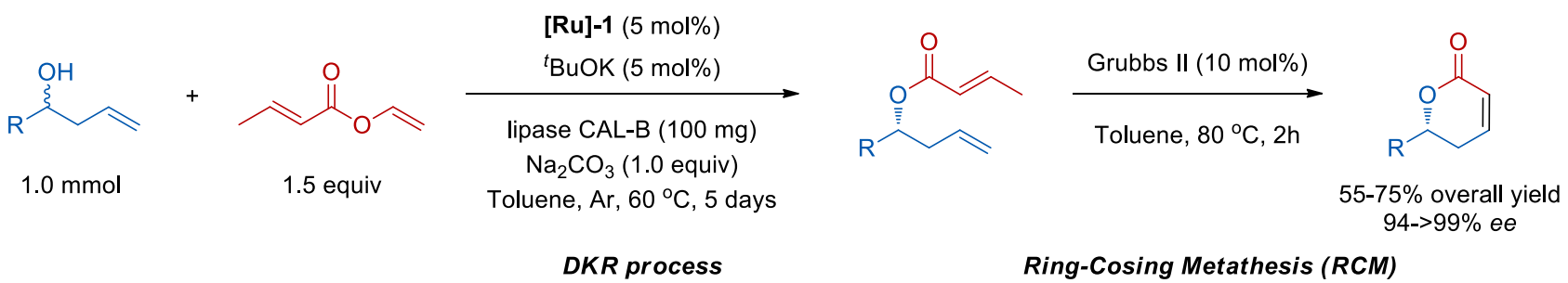


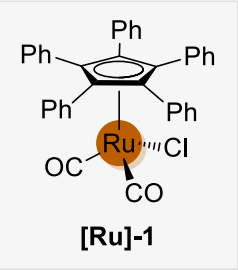
Racemization form

CONTENTS

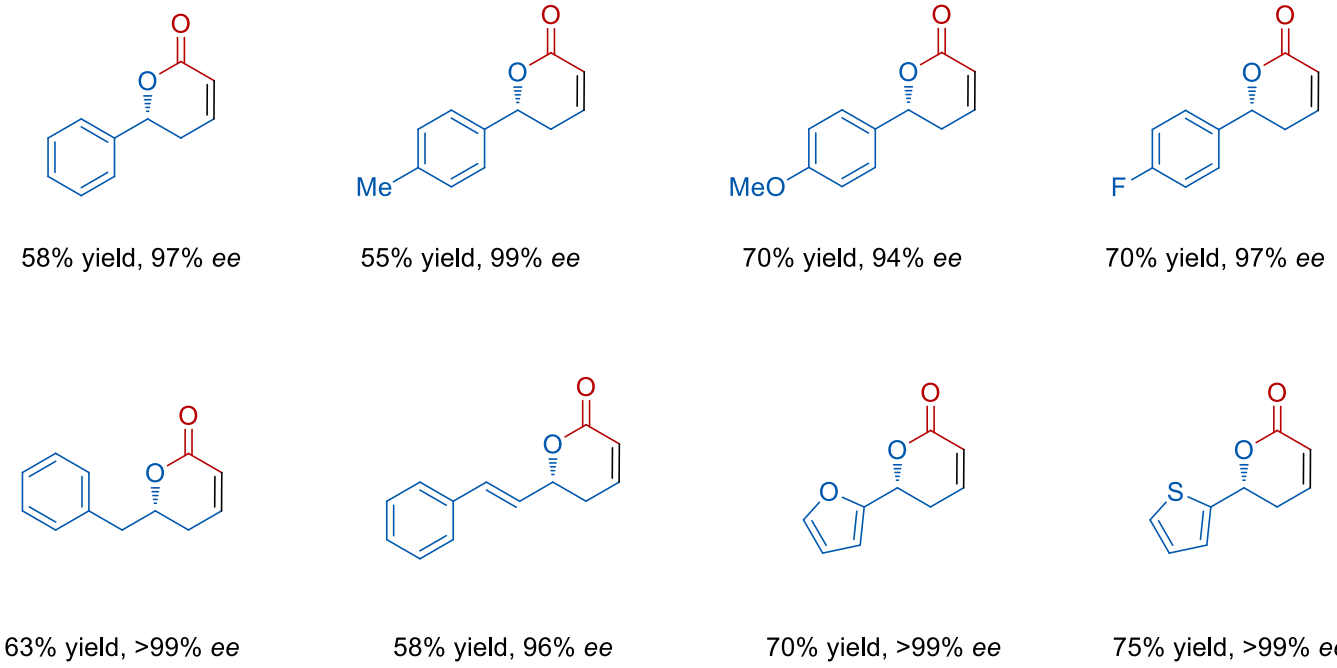
Part II: Redox racemization via ***ketone*** intermediates: *Ru catalysts*

2019, Ryszard Ostaszewski group:





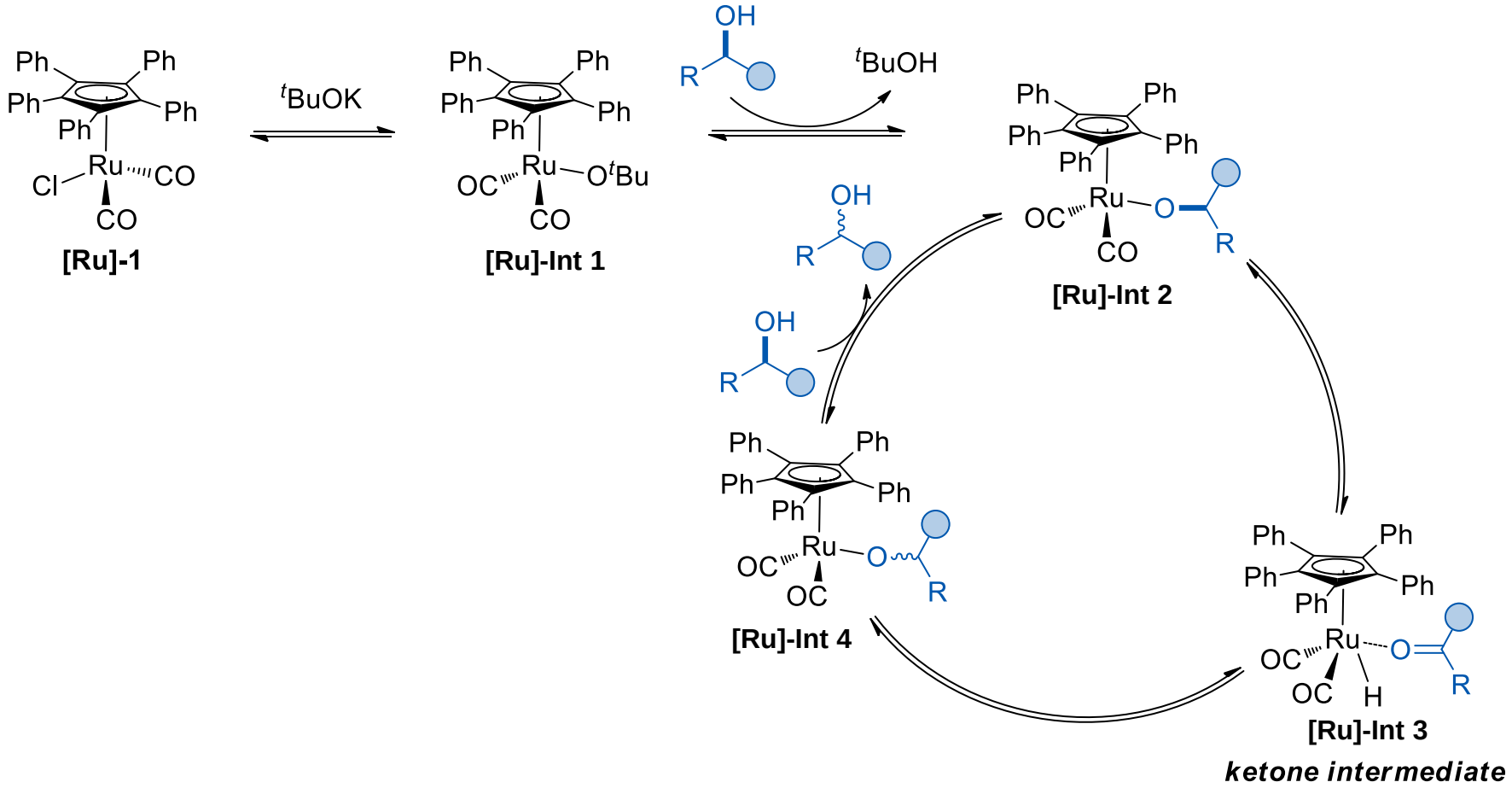
Selected substrate:



Ryszard Ostaszewski *et al*., *Eur. J. Org. Chem*. **2019**, 1653–1658

Part II: Redox racemization via ***ketone*** intermediates: *Ru catalysts*

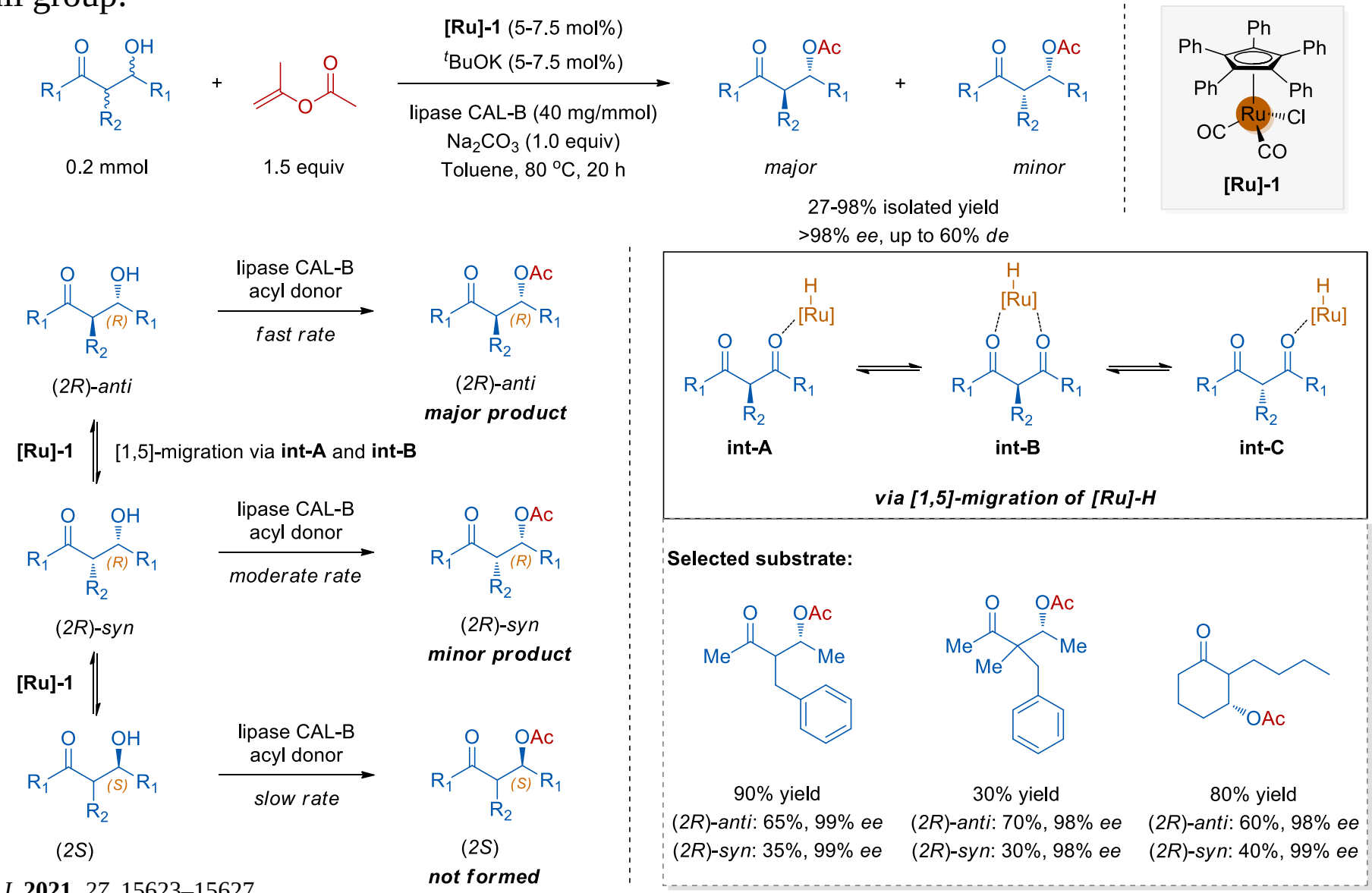
***Proposed mechanism of the racemization process*:**



Ryszard Ostaszewski *et al*., *Eur. J. Org. Chem*. **2019**, 1653–1658

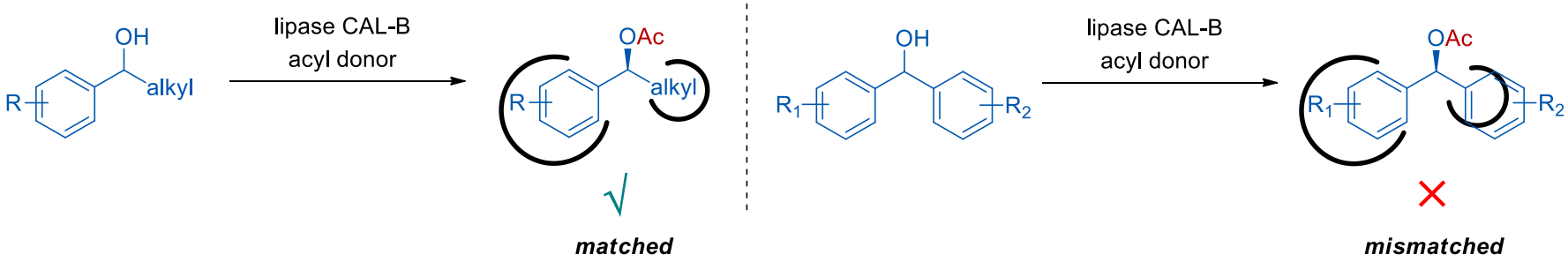
Part II: Redox racemization via ***ketone*** intermediates: *Ru catalysts*

2021, Bäckvall group:

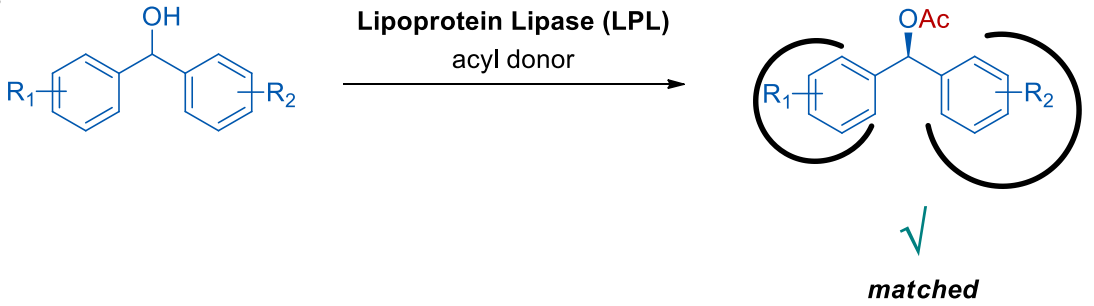


J. E. Bäckvall *et al*., *Chem. Eur. J.* **2021**, *27*, 15623–15627

Part II: Redox racemization via ***ketone*** intermediates: *Ru catalysts*



2015, J. W. Park and M. J. Kim group:



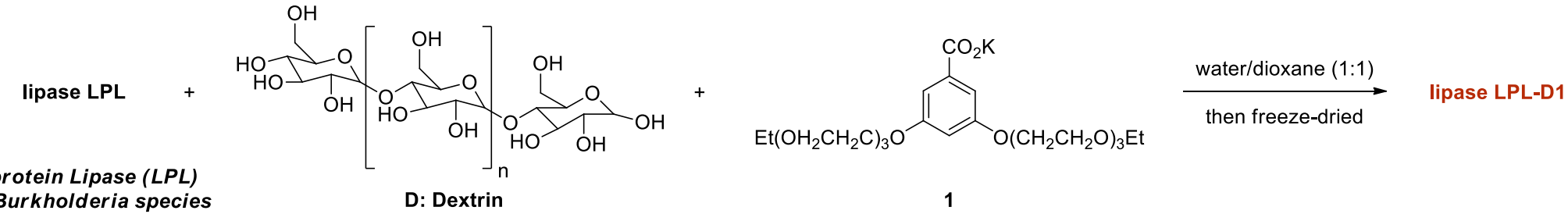
entry	lipase	ROH	solvent	k_{cat} (s^{-1})
1	LPL	H_2O	phosphate buffer	2.8×10^{2}
2	LPL	$PhCH(CH_3)OH$	toluene	1.7×10^{-2}
3	LPL-D**1**	H_2O	phosphate buffer	5.7×10^{2}
4	LPL-D**1**	$PhCH(CH_3)OH$	toluene	5.5×10

About 3000 times compared to entry 2

M. J. Kim *et al.*, *ACS Catal.*, **2015**, *5*, 683−689

Part II: Redox racemization via *ketone* intermediates: *Ru catalysts*

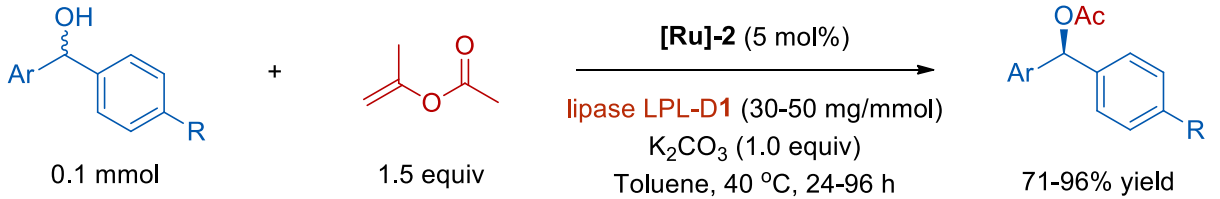
Preparation of lipase LPL-D1:

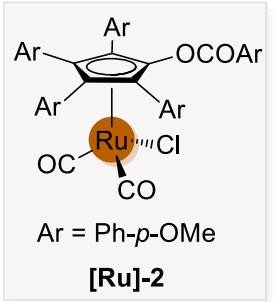


Lipoprotein Lipase (LPL) from Burkholderia species

D: Dextrin

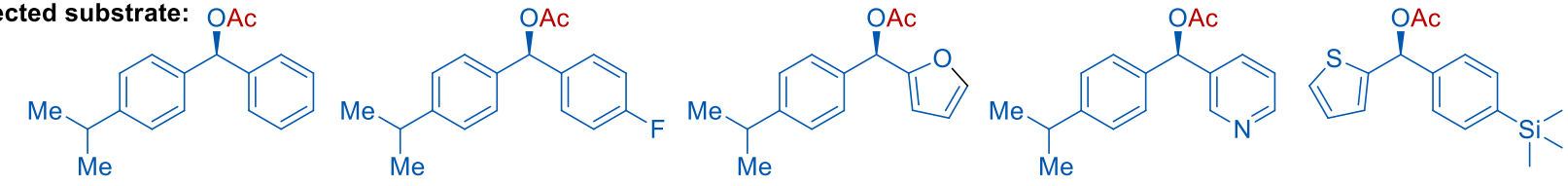
1

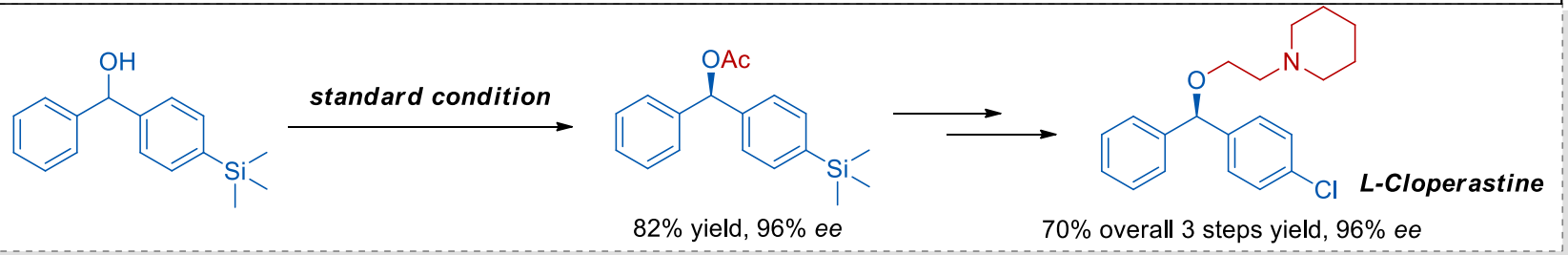




more reactivity

Selected substrate:

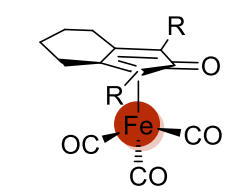




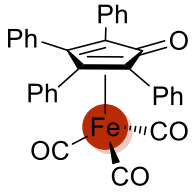
M. J. Kim *et al.*, *ACS Catal.*, **2015**, *5*, 683−689

Part II: Redox racemization via ***ketone*** intermediates: *Fe catalysts*

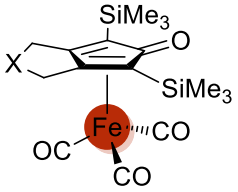
2016, Magnus Rueping group:



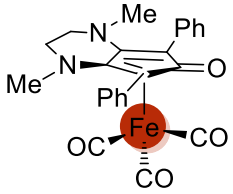
[Fe]-1, R = $SiMe_3$
[Fe]-2, R = Si^tBuMe_3



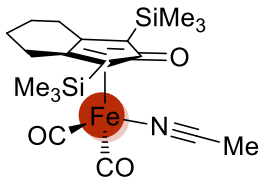
[Fe]-3



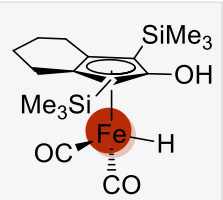
[Fe]-4, X = O
[Fe]-5, X = NTs



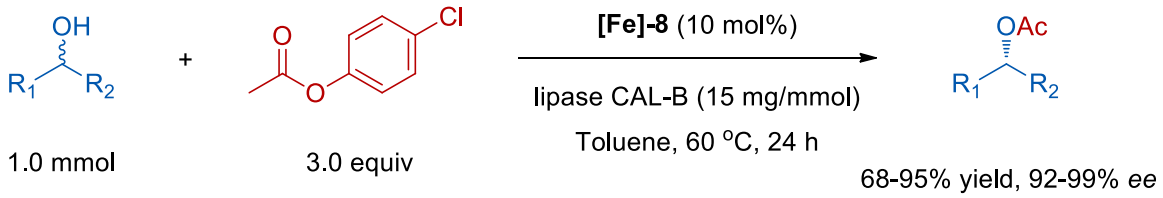
[Fe]-6



[Fe]-7

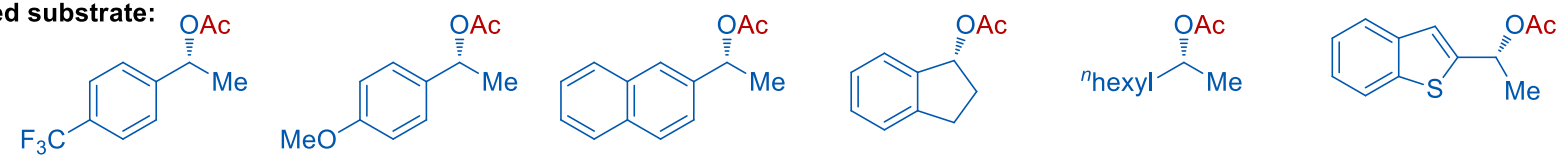


[Fe]-8



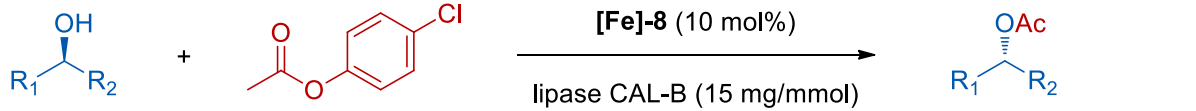
1.0 mmol　　3.0 equiv　　68-95% yield, 92-99% *ee*

Selected substrate:



92% yield, 99% *ee*　86% yield, 95% *ee*　91% yield, 95% *ee*　95% yield, 95% *ee*　82% yield, 92% *ee*　95% yield, 99% *ee*

Inversion experiment:

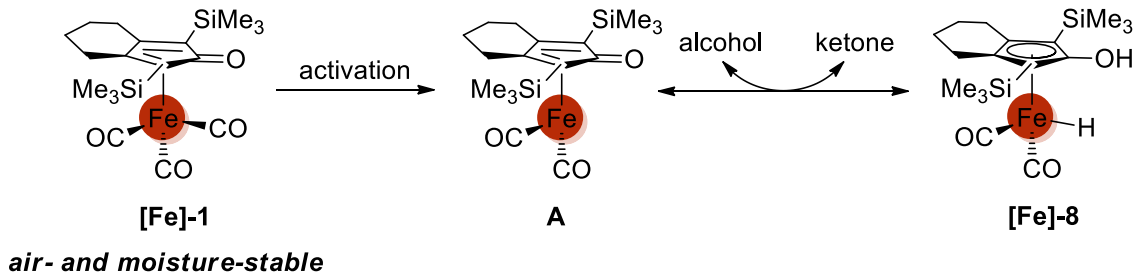


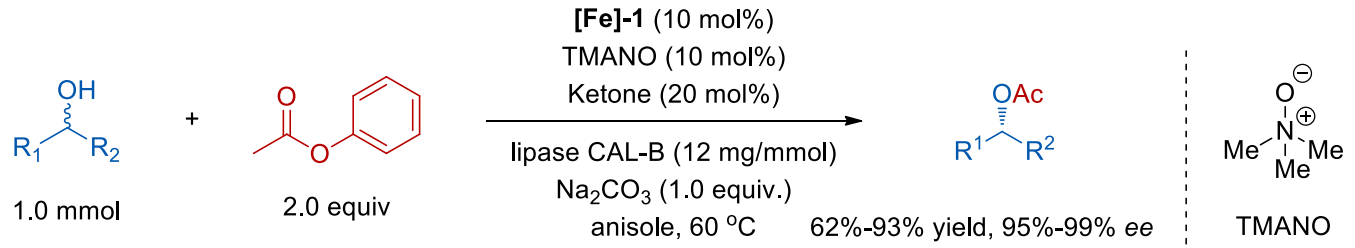
(*S*)-isomer　　3.0 equiv　　(*R*)-isomer, 88% yield, 99% *ee*

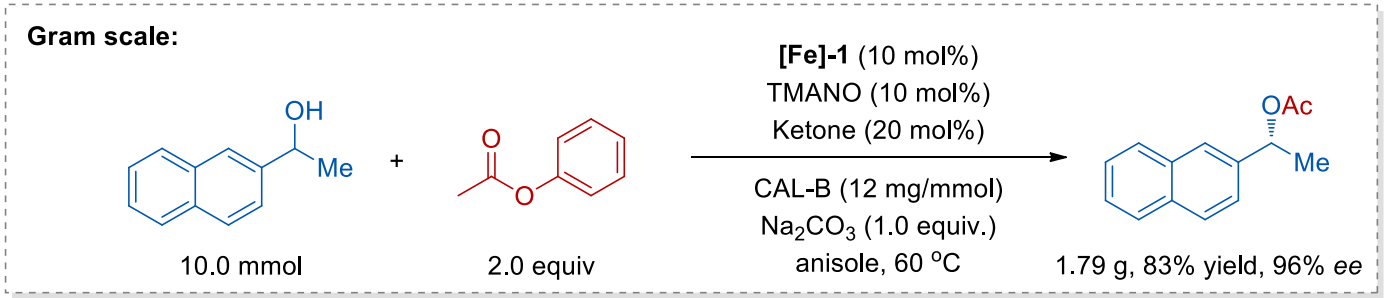
Magnus Rueping *et al.*, *Angew. Chem. Int. Ed.* **2016**, *55*, 13602–13605

Part II: Redox racemization via *ketone* intermediates: *Fe catalysts*

2017, B äckvall group:



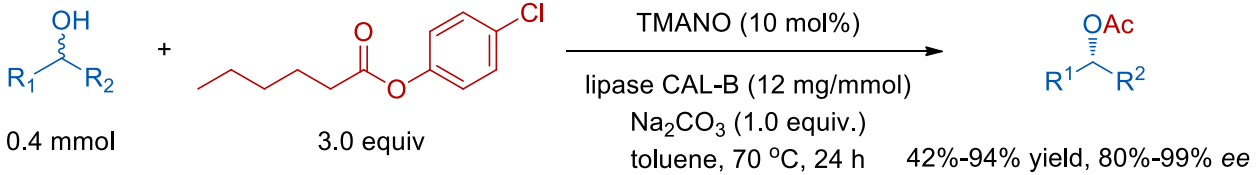


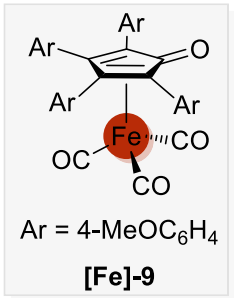


J. E. B äckvall *et al*., *Chem. Eur. J.* **2017**, *23*, 1048–1051

Part II: Redox racemization via ***ketone*** intermediates: *Fe catalysts*

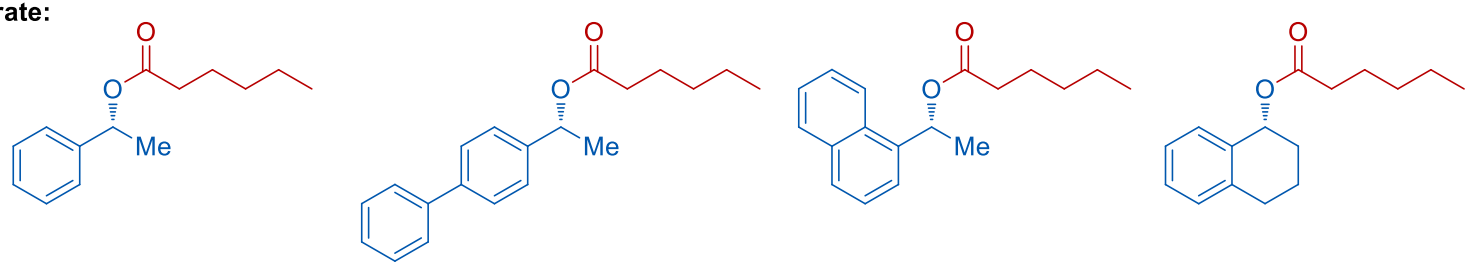
2017, Zhou Shaolin group:

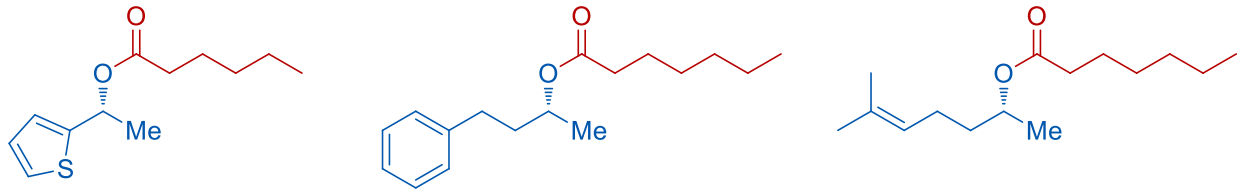




new air-stable iron catalyst

Selected substrate:

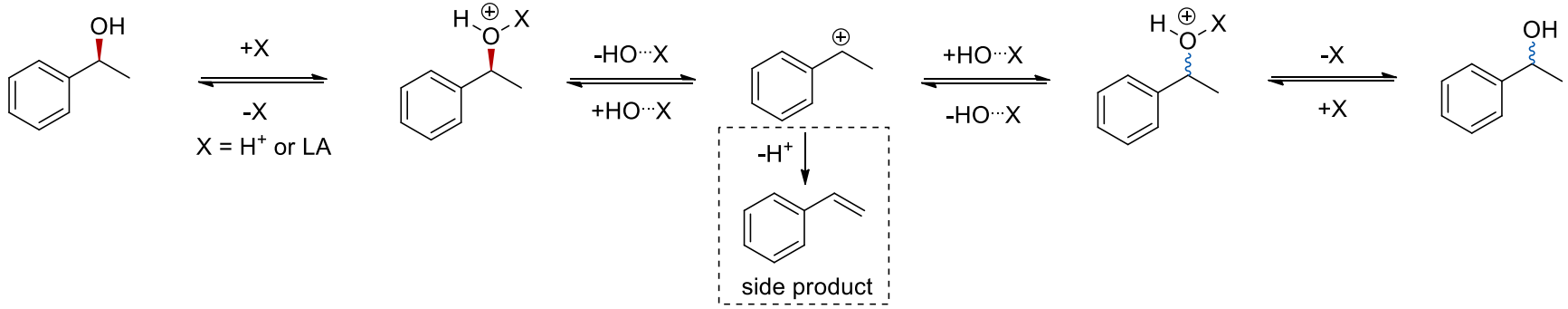




Zhou Shaolin *et al*., *Tetrahedron Letters* **2017**, *58*, 2487–2489

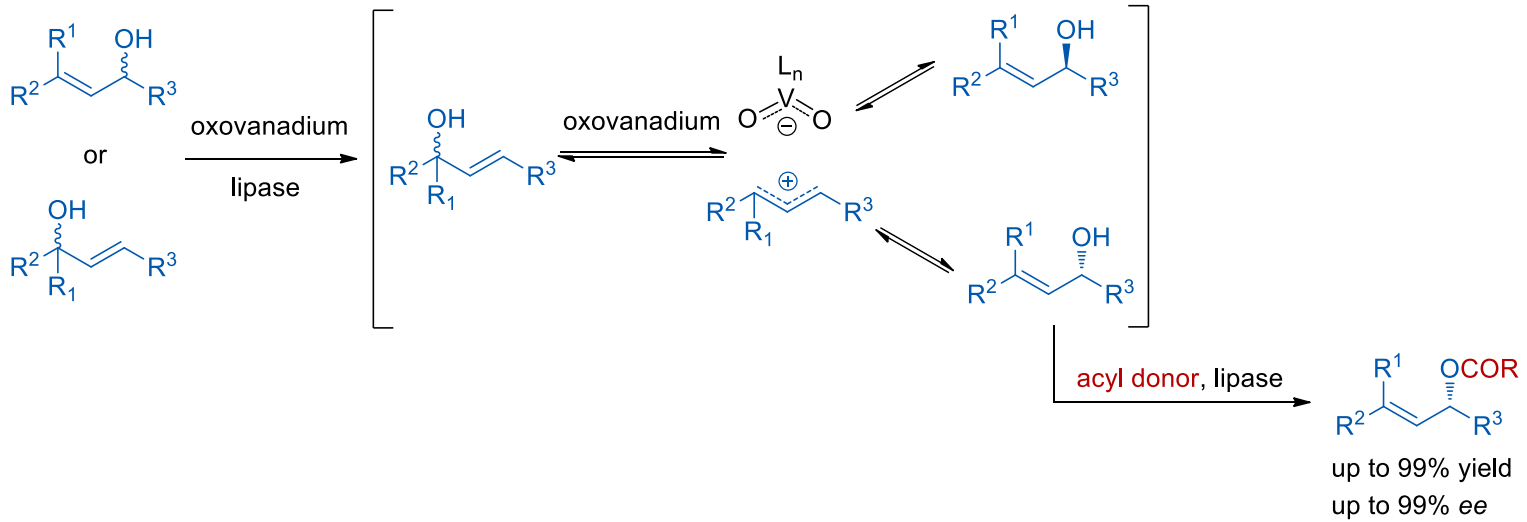
CONTENTS

Part III: Racemization via ***carbocation*** intermediates: *V catalysts*



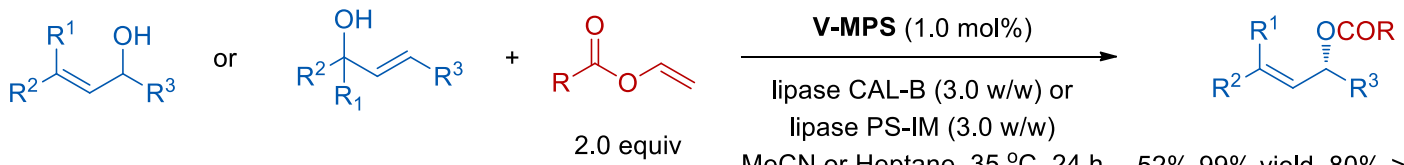
Racemization via carbocation intermediates

2013, Akai group:

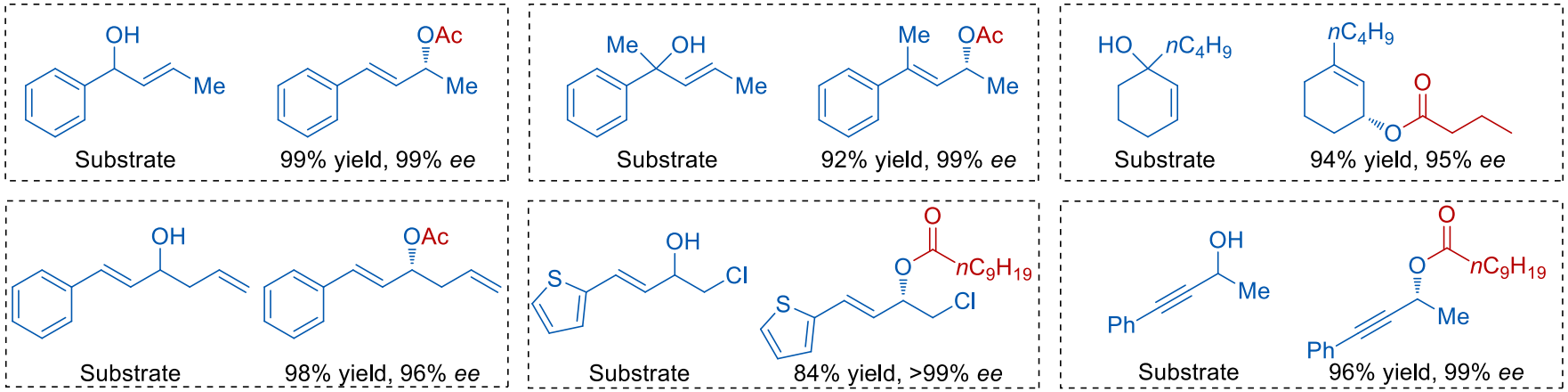


S. Akai *et al*., *Angew. Chem. Int. Ed.* **2013**, *52*, 3654–3658

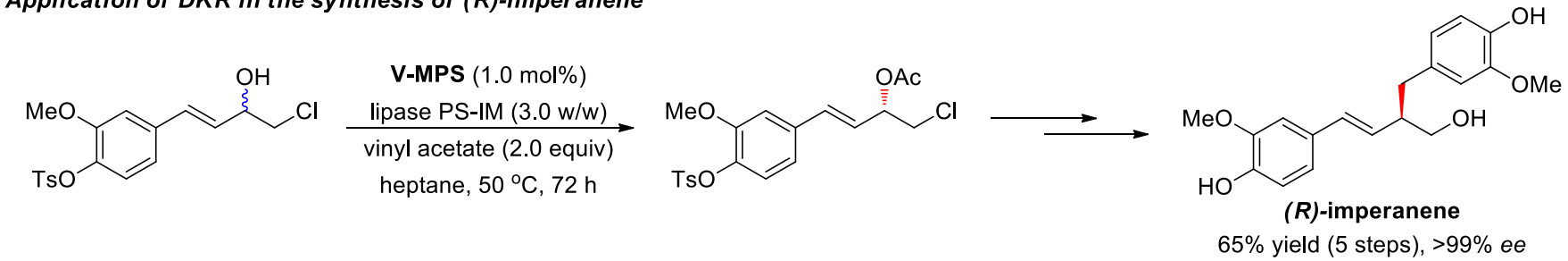
Part III: Racemization via *carbocation* intermediates: *V catalysts*

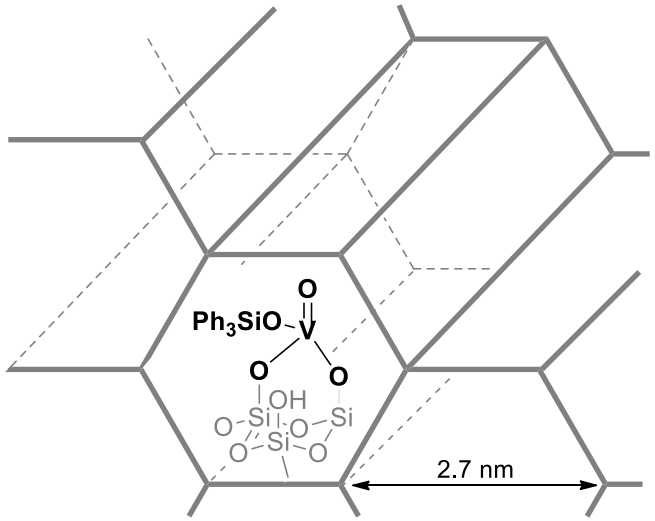


Selected substrate:



Application of DKR in the synthesis of (R)-imperanene





V-MPS

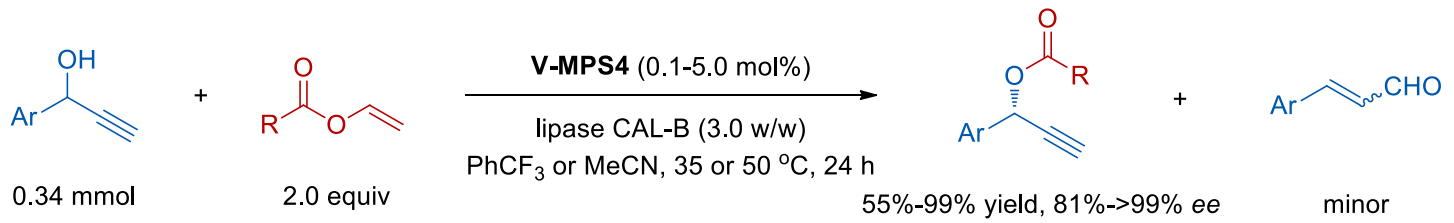
1st run:	**99%, 99% *ee***
2nd run:	**100%, 99% *ee***
3rd run:	**99%, 99% *ee***
4th run:	**100%, 99% *ee***
5th run:	**99%, 99% *ee***
6th run:	**99%, 99% *ee***
7th run:	**85%, 99% *ee***

For standard substrate, V-MPS can be cycled at least 7 times.

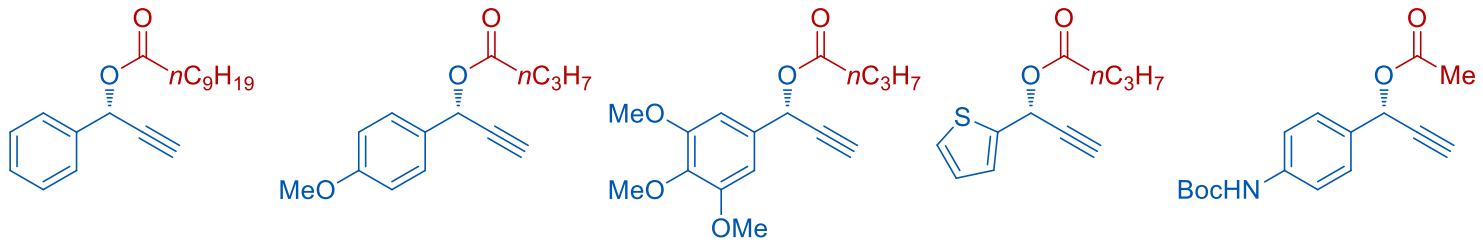
S. Akai *et al*., *Angew. Chem. Int. Ed.* **2013**, *52*, 3654–3658

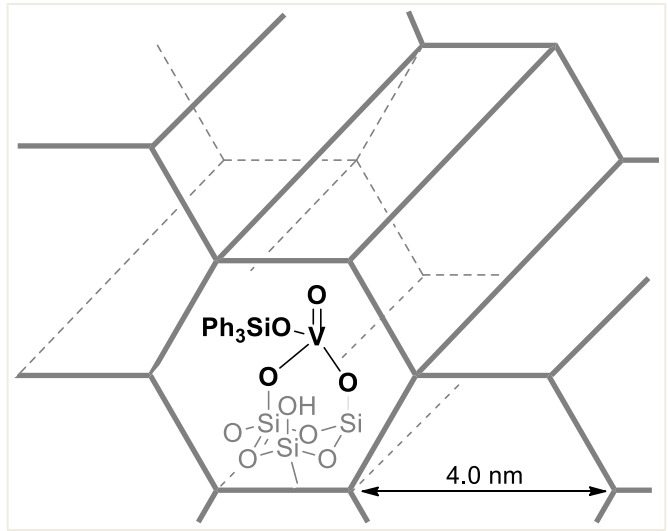
Part III: Racemization via ***carbocation*** intermediates: *V catalysts*

2019, Akai group:



Selected substrate:



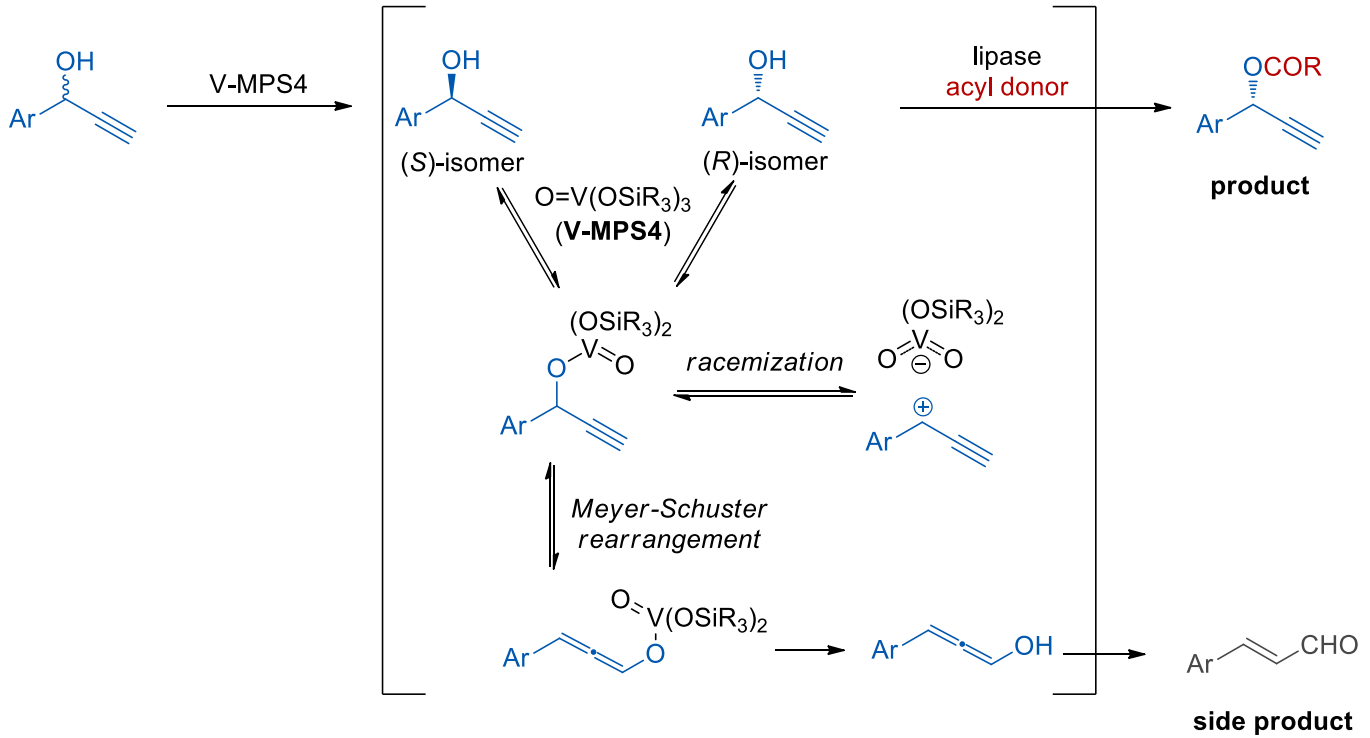


V-MPS4

S. Akai *et al.*, *Organic Letters* **2019**, *21*, 2978–2982

Part III: Racemization via *carbocation* intermediates: *V catalysts*

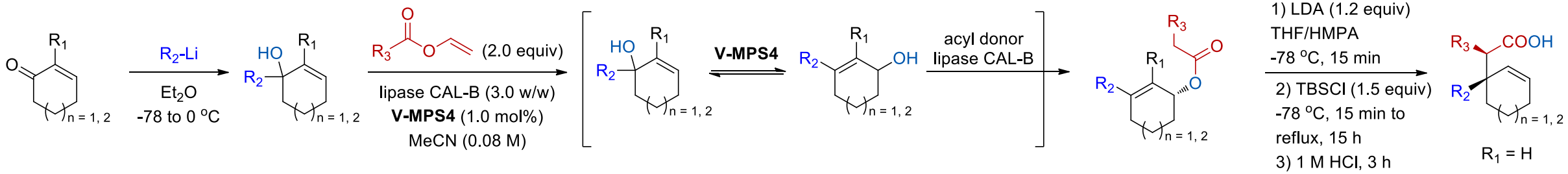
***Proposed mechanism*:**



S. Akai *et al*., *Organic Letters* **2019**, *21*, 2978–2982

Part III: Racemization via ***carbocation*** intermediates: *V catalysts*

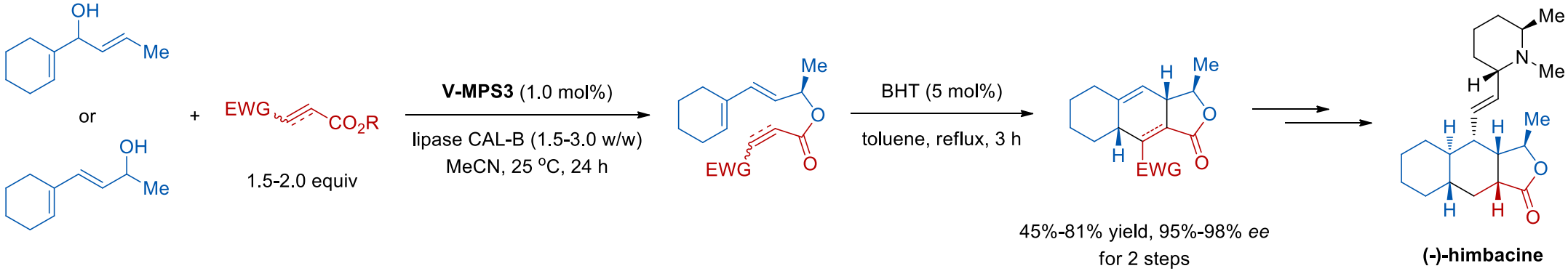
2017, Akai group:



81%-99% yield, 93%-99% *ee*

63%-79% yield, 90%-99% *ee*

2018, Akai group:



45%-81% yield, 95%-98% *ee*
for 2 steps

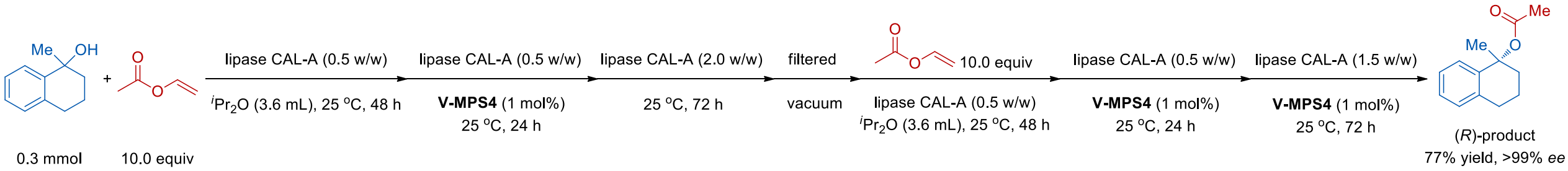
(-)-himbacine

Dynamic kinetic resolution ***intramolecular Diels-Alder reaction***

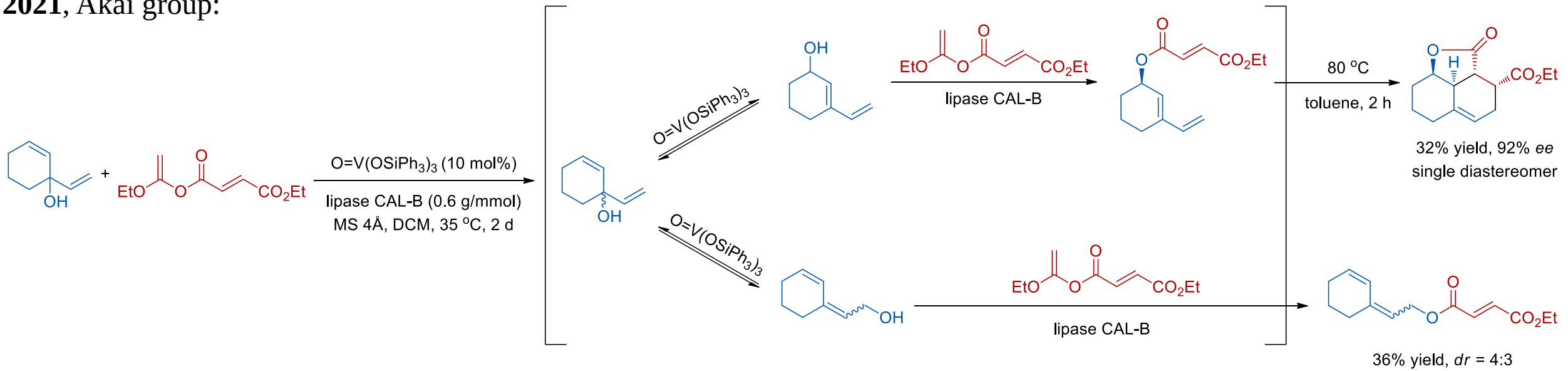
1) S. Akai *et al*., *Green Chem.* **2017**, *19*, 411–417; 2) S. Akai *et al*., *Bioorganic & Medicinal Chemistry.* **2018**, *26*, 1378–1386

Part III: Racemization via *carbocation* intermediates: *V catalysts*

2020, Akai group:



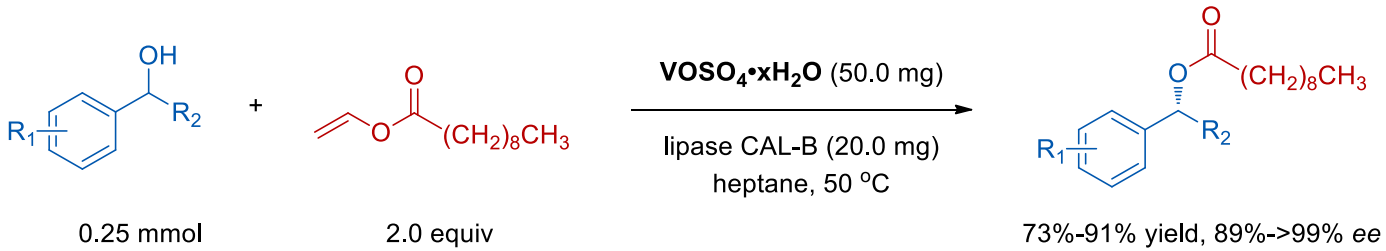
2021, Akai group:



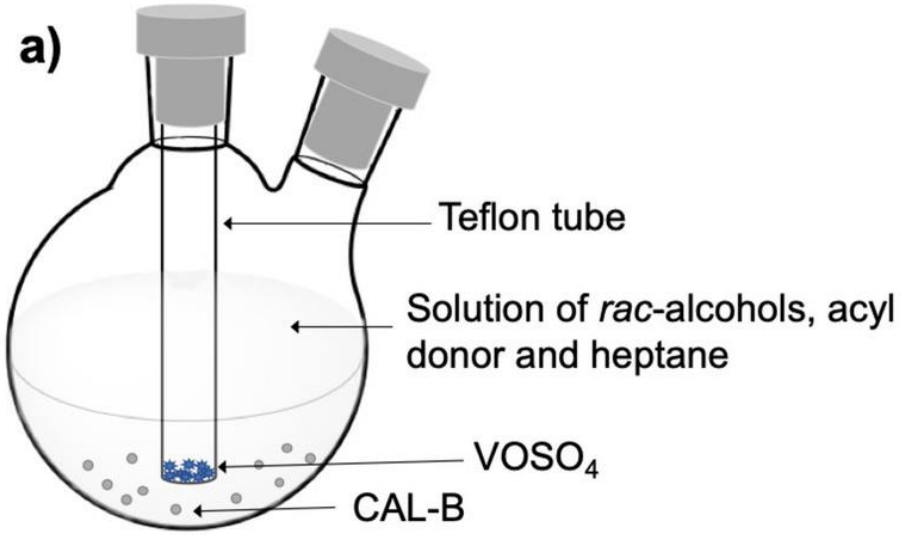
1) S. Akai *et al*., *Chem. Commun.* **2020**, *56*, 2885–2888; 2) S. Akai *et al*., *Synlett.* **2021**, *32*, 822–828

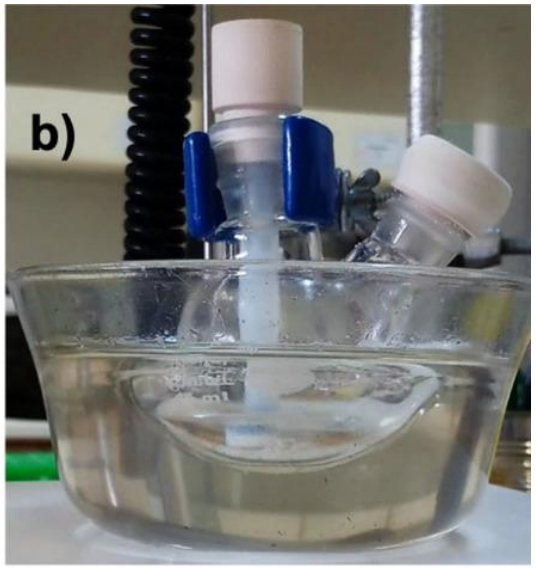
Part III: Racemization via ***carbocation*** intermediates: *V catalysts*

2020, Milagre group:



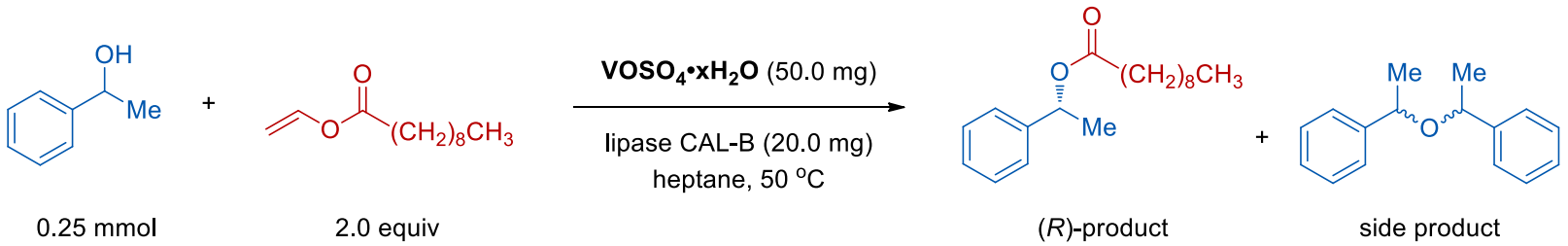
0.25 mmol　　2.0 equiv　　73%-91% yield, 89%->99% *ee*





Humberto M. S. Milagre *et al*., *ChemCatChem*. **2020**, *12*, 2849–2858

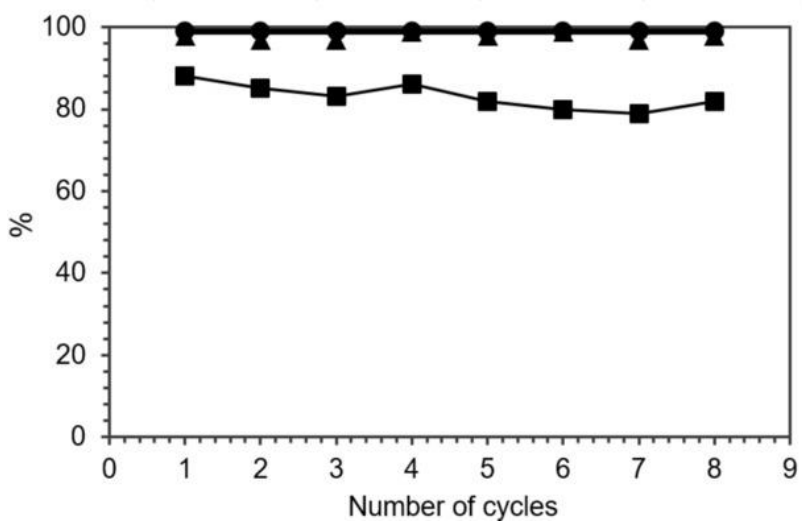
Part III: Racemization via ***carbocation*** intermediates: *V catalysts*



0.25 mmol | 2.0 equiv | (*R*)-product | side product

entry	condition	time [h]	*c* [%]	*ee* [%]	*Sel* [%]
1	Without tube	2	82	>99	92
2	CAL-B into the tube	2	20	>99	>99
3	$VOSO_4$ ·xH_2O into the tube	1	91	>99	98
4	$VOSO_4$ ·xH_2O into the tube 5.0 mmol scale	2	90	>99	98

Recycling of CAL-B and $VOSO_4$ ·xH_2O experiment

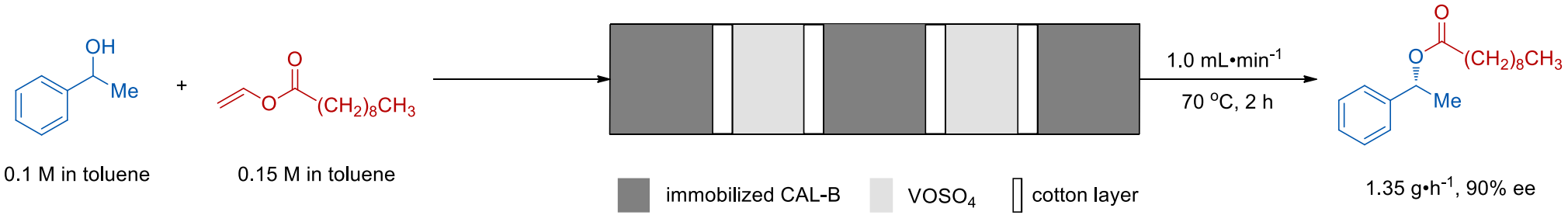


• ee of the (*R*)-product at the end of each cycle; ▪ conversion; ▲ selectivity.

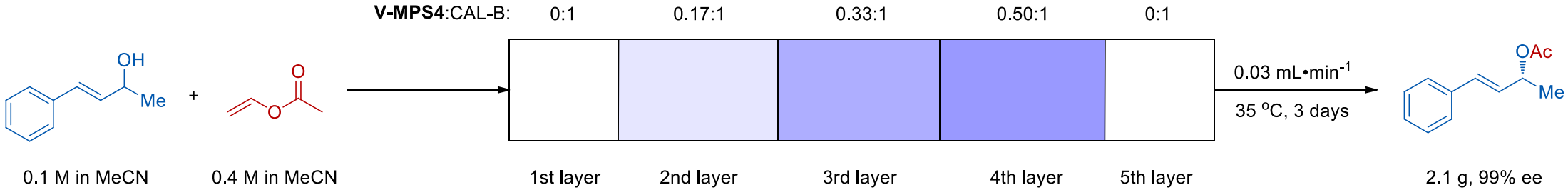
Humberto M. S. Milagre *et al*., *ChemCatChem*. **2020**, *12*, 2849–2858

Part III: Racemization via *carbocation* intermediates: *V catalysts*

2017, Souza group:



2020, Akai group:

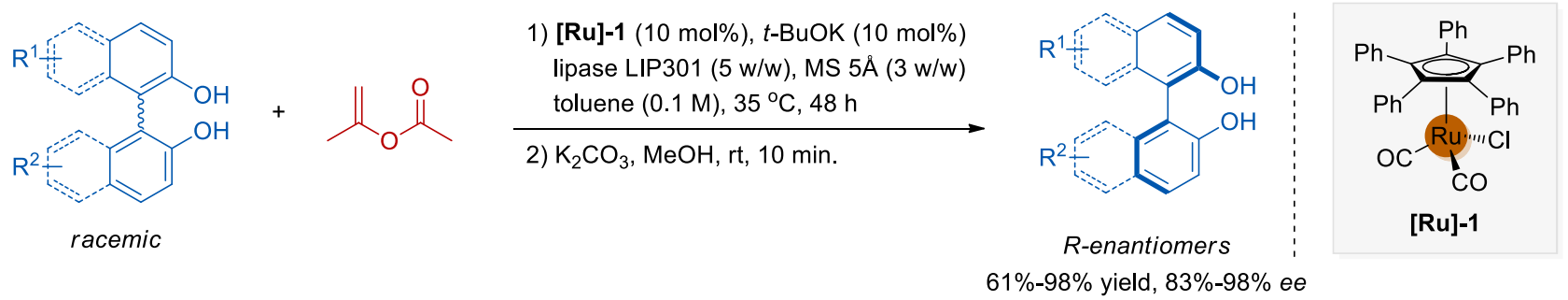


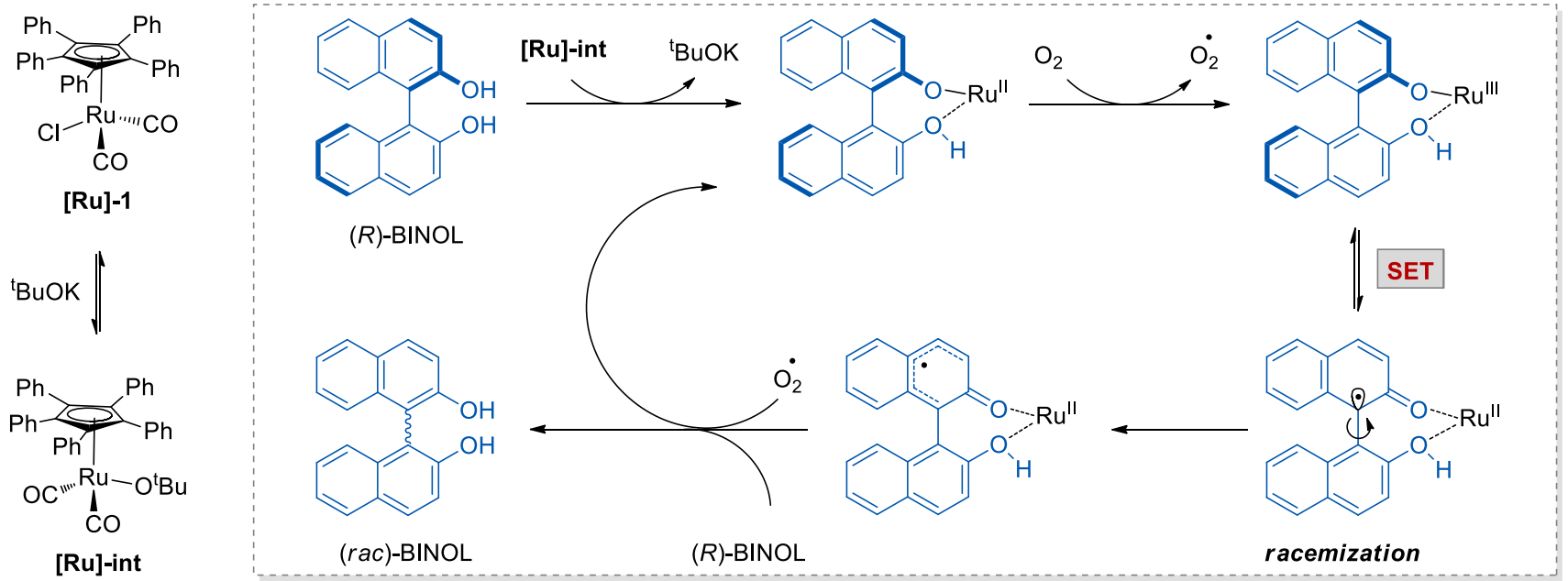
1) Rodrigo O. M. A. de Souza *et al*., *React. Chem. Eng*. **2017**, *2*, 375–381; 2) S. Akai *et al*., *Eur. J. Org. Chem.* **2020**, 1961–1967

CONTENTS

Part IV: Racemization via ***radical*** intermediates: *Ru catalysts*

2018, Shuji Akai group:

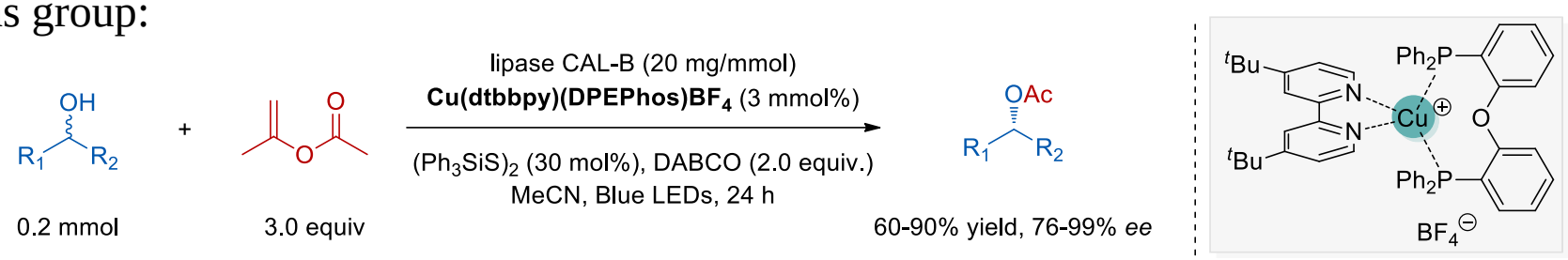


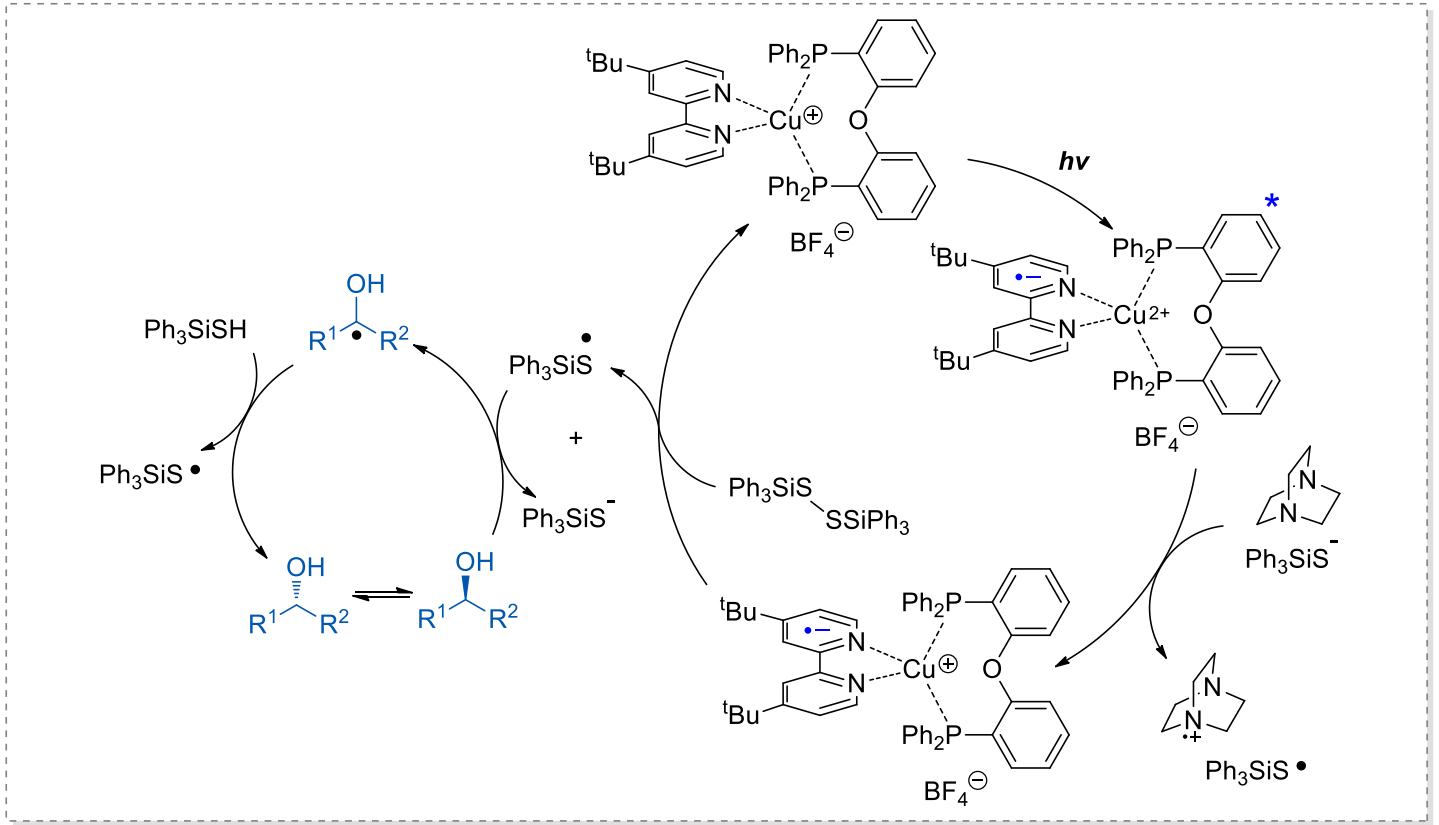


S. Akai *et al*., *Angew. Chem. Int. Ed.* **2018**, *57*, 10278–10282

Part IV: Racemization via ***radical*** intermediates: *Cu catalysts*

2023, Collins group:



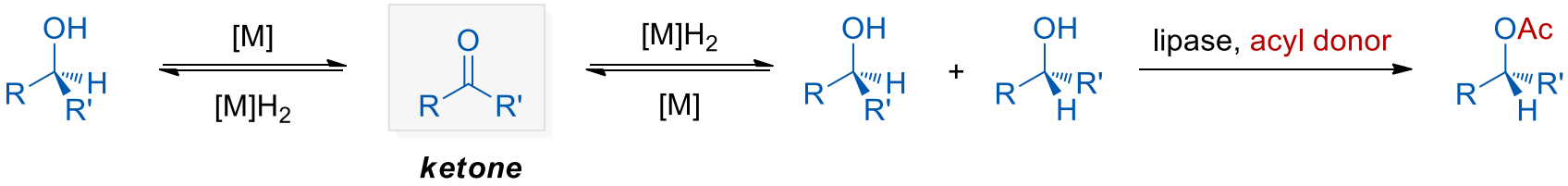


Shawn K. Collins *et al*., *ACS. Catal.* **2023**, 13, 8347–8353

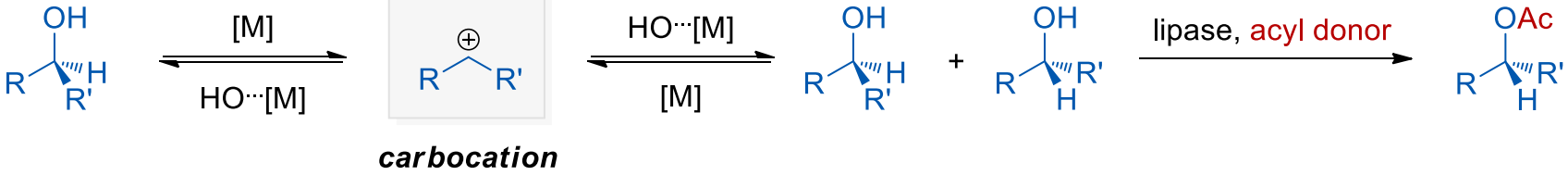
CONTENTS

Part V: Summary and Outlook

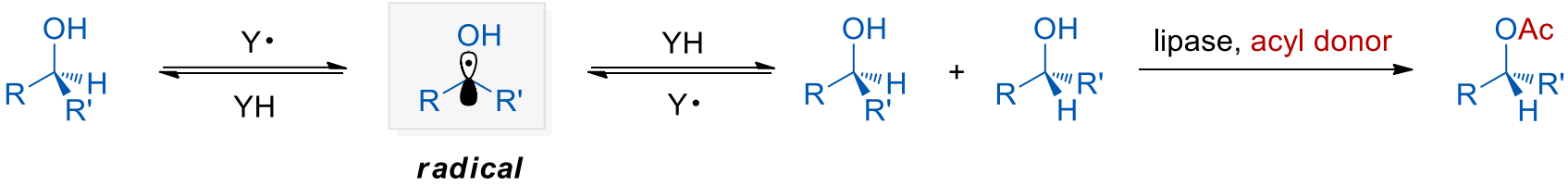
Redox racemization via ketone intermediates



Racemization via carbocation intermediates

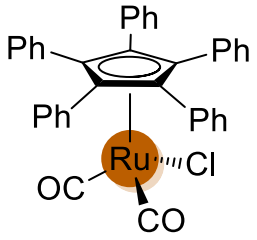


Racemization via radical intermediates

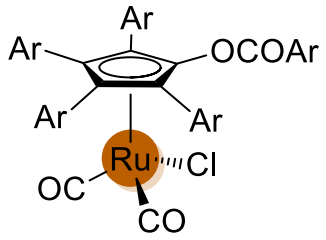


Part V: Summary and Outlook

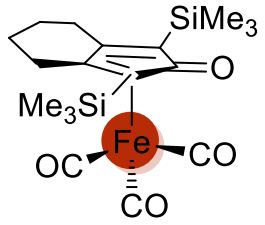
For metal catalysts



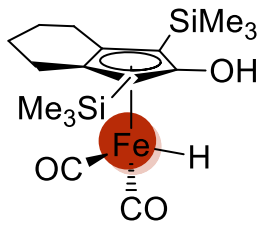
[Ru]-1



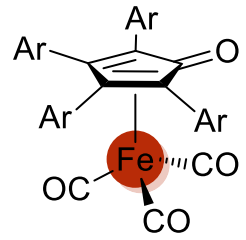
[Ru]-2, Ar = Ph-*p*-OMe



[Fe]-1



[Fe]-8

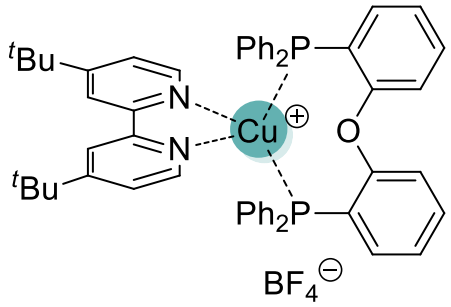


[Fe]-9, Ar = 4-MeOC$_6$H$_4$

Ru catalysts

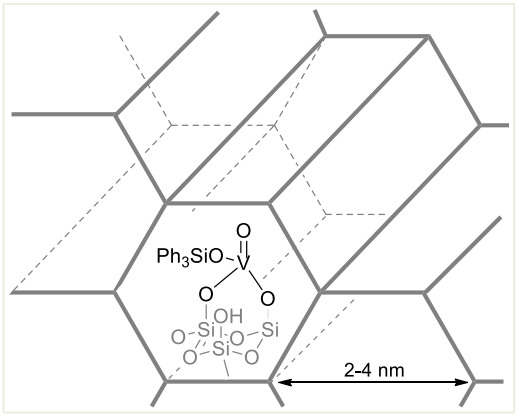
Fe catalysts

large ligands protected metal complexes

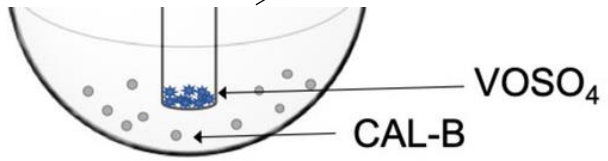


Cu catalysts

attached to cellular materials



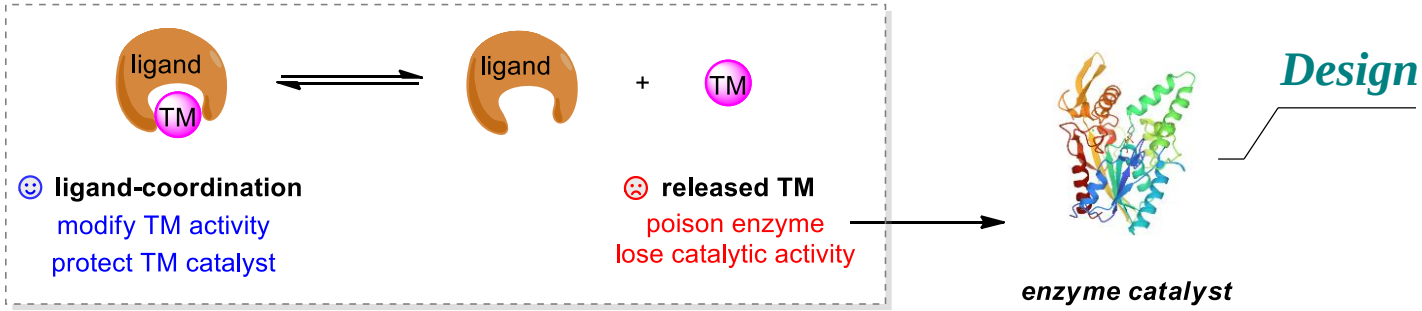
physical separation



V catalysts

Part V: Summary and Outlook

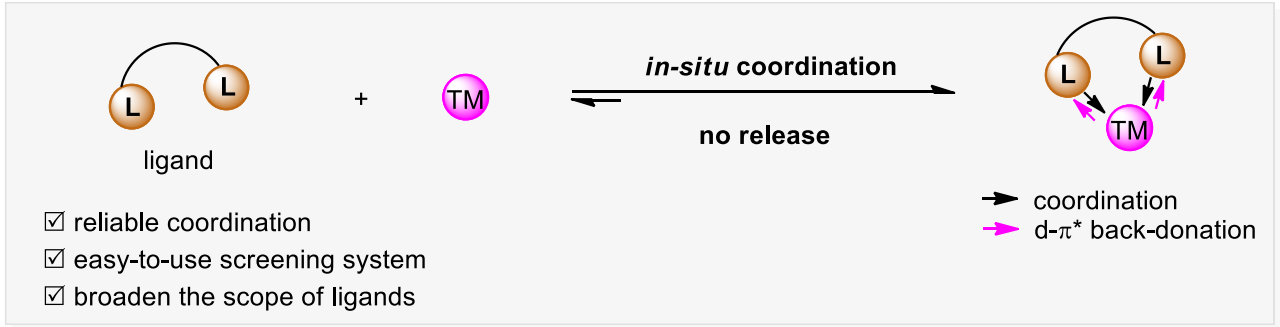
Key issue: compatibility of **TM** catalysis with enzyme



Design

1. Attached to Celite, porous materials, and polyester balls;
2. Directed evolution

Racemization catalysts Design: complexes with reliable and netural ligand



Thanks for your attention !

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Supervisor：Can Zhu

Fudan University

2024.05.10