K.ISHIHARA GROUP
green catalysis

Asymmetric tandem reaction with multiple catalysts including organocatalyst

2022/9/26(Mon)

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Contents

1. Introduction

1-1. Tandem Reaction

Natural product synthesis

→ **Development of pharmaceutical, functional material**

However, its public image has deteriorated

consume mass resource

Generation of waste

consume mass energy

Danger of toxic, unstable, or explosive intermediates

↓

Tandem Reaction

Multiple reactions proceed continuously
by adding substrates and reagents and changing reaction conditions

save time, energy, labour, and other resources

reduce the usage of chemicals

alleviate the generation of waste

maximize synthetic efficiency

circumvent the yield losses associated with the purification of intermediates

help lower the risk in the storage, transportation,
and the handling of toxic, unstable, or explosive intermediates

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Solutions for energy shortages and environmental pollution

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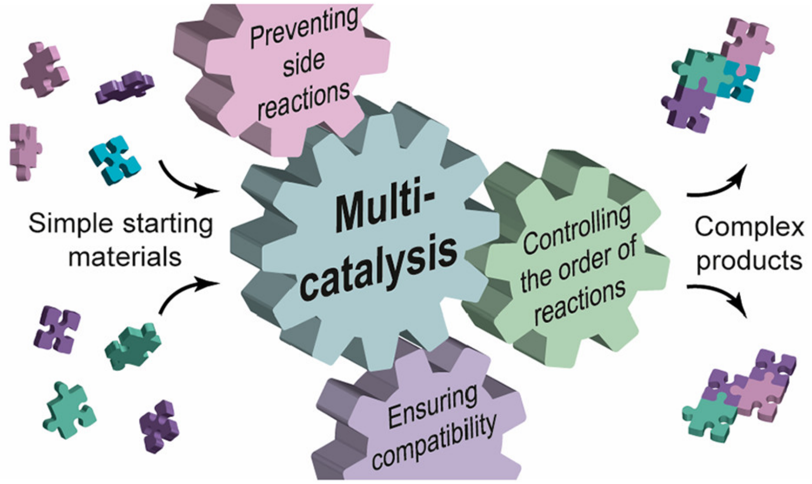
1) Zhou, J. et. al. . Chem. Asian J. **2010**, 5, 422-434.

1-2. Multicatalyst



Simple starting material $\xrightarrow{\substack{\text{Catalyst A}\\ \text{Catalyst B}}}$ **More complex value-added products**

✔Expansion of coupling response range
✔Improvement the reactivity and selectivity
✔Diastereoselectivity and enantioselectivity can be controlled and tuned
✔Suppression some side reactions

🚨 Big challenge of Multicatalytic asymmetric tandem reactions

- **the compatibility** of the chiral catalyst with
  - residual material
  - solvent
  - substrates
  - other catalyst
  - intermediates generated in situ
- **Reaction selectivity :**
  each step should have high regioselectivity, diastereoselectivity, and enantioselectivity.

↓

Developed the following four strategies
1) Use of compatible catalysts system.
Soft metal Lewis acid × Hard organic Lewis base catalyst.
2) Use of site-isolated techniques.
3) Use of phase-separation techniques.
4) Sequential addition of catalyst and substrates.

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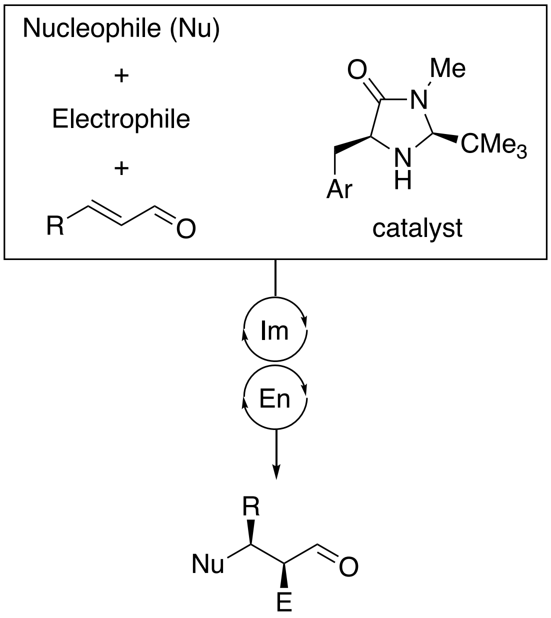
2) Dydio, P. et. al. ACS Catal. **2021**, 11, 3891–3915

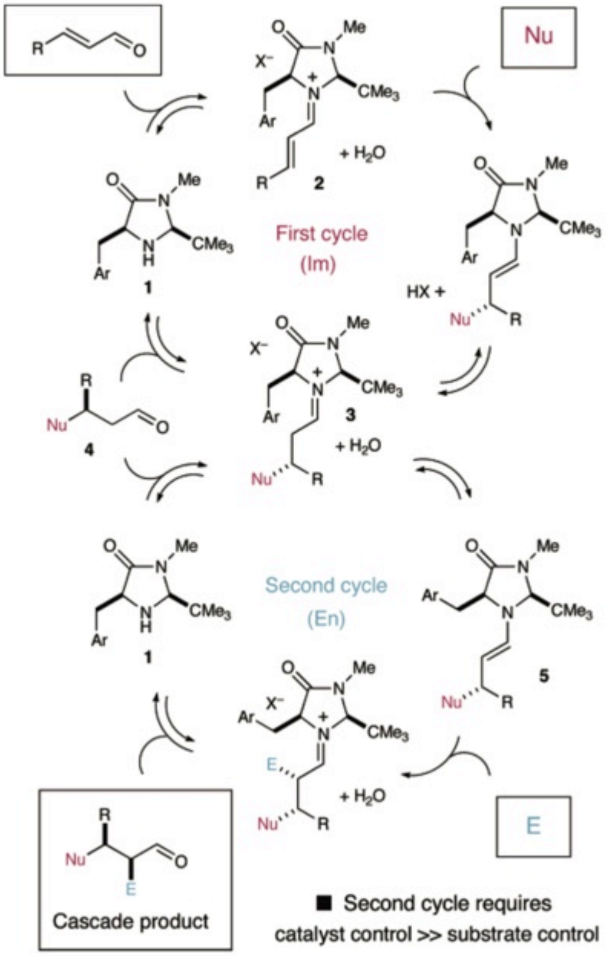
2. Organocatalyst × Organocatalyst

2-1. Iminiumu-Enamine Activation

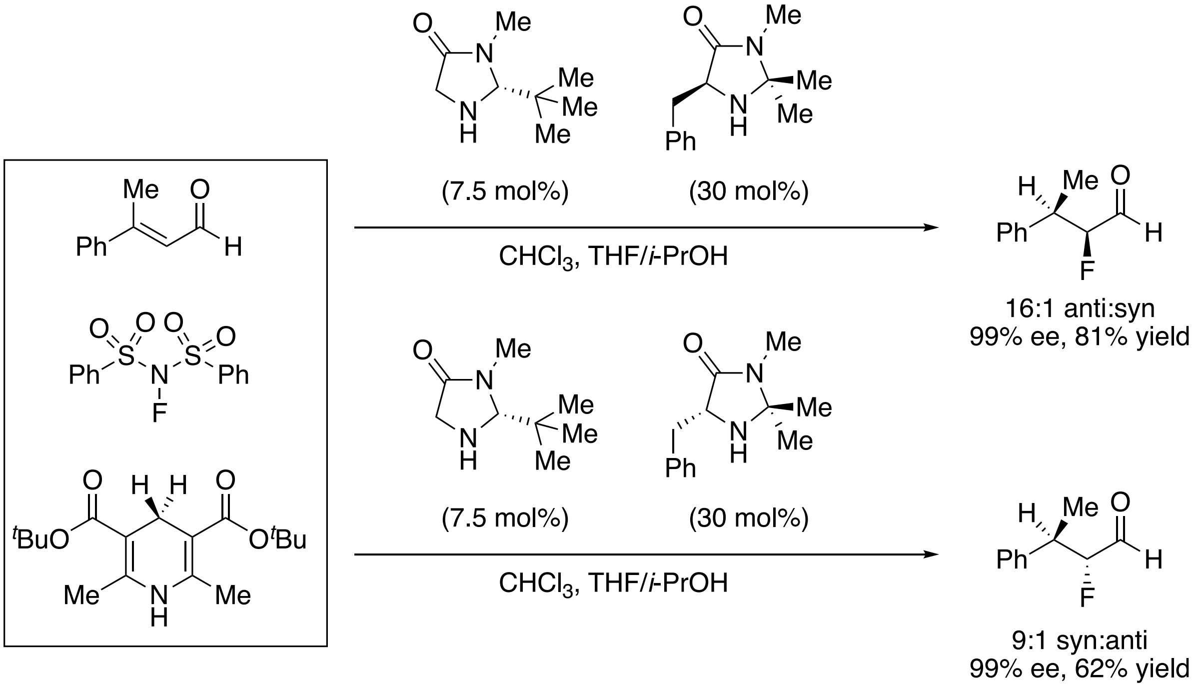
Merging Iminium (Im) and Enamine (En) Activation (2005, MacMillan)



cascade product



■ Second cycle requires catalyst control >> substrate control



16:1 anti:syn
99% ee, 81% yield

9:1 syn:anti
99% ee, 62% yield

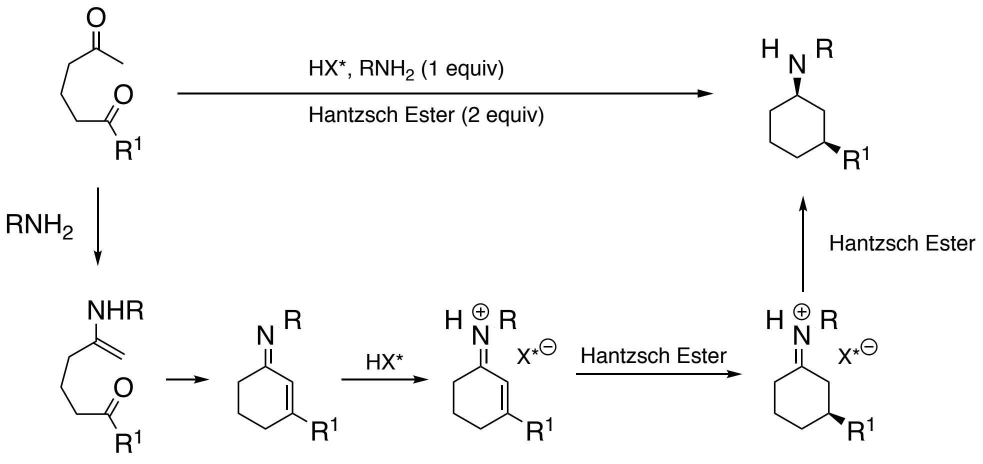
Two discrete amine catalysts can enforce cycle-specific selectivities.

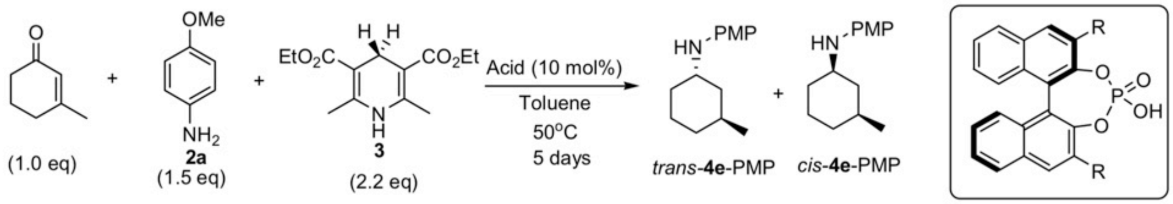
3) MacMillan, David W. C, J. Am. Chem. Soc. **2005**, 127, 15051-15053

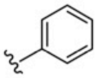
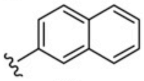
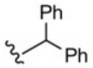
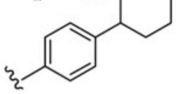
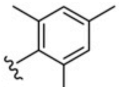
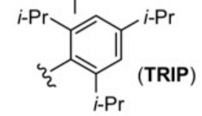
2. Organocatalyst × Organocatalyst

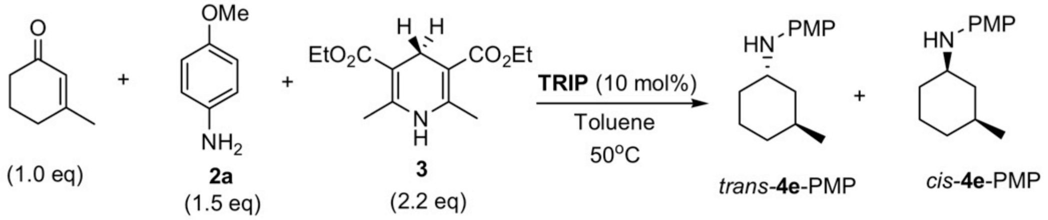
2-2. Triple Organocatalytic Tandem Reaction

Enamine and iminium catalysis with Brønsted acid (2007, List)





Entry	R	Conversion	*dr* (*trans*:*cis*)	*er* of *cis*
1		80%	72:28	55:45
2		100%	64:46	50:50
3		50%	65:35	50:50
4		80%	60:40	51:49
5		80%	80:20	51:49
6		100%	67:33	79:21



Without MS 5Å: 3 days full conversion *trans/cis*: 67:33 er of *cis*: 79:21

With MS 5Å: 1 day full conversion *trans/cis*: 24:76 er of *cis*: 87:13

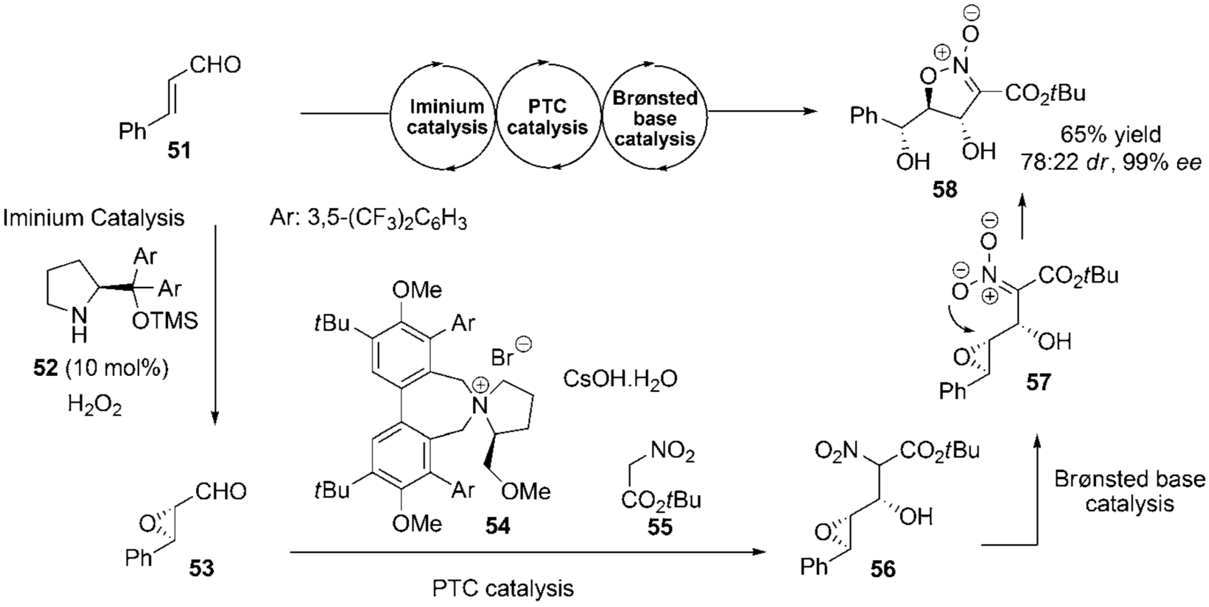
4) List, B., J. Am. Chem. Soc. **2007**, 129, 7498-7499

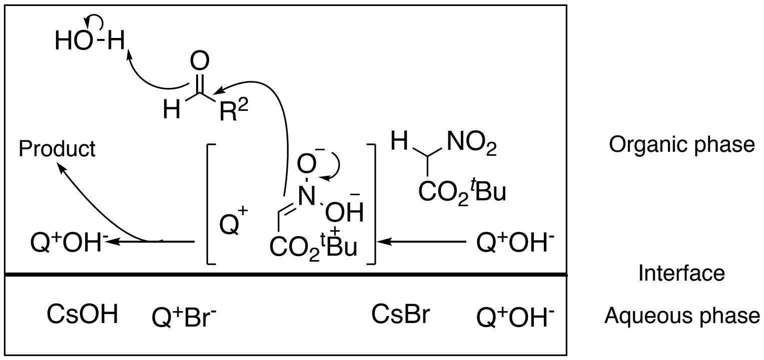
5) List, B., Angew. Chem. **2009**, 121, 1491 –1494

2. Organocatalyst × Organocatalyst

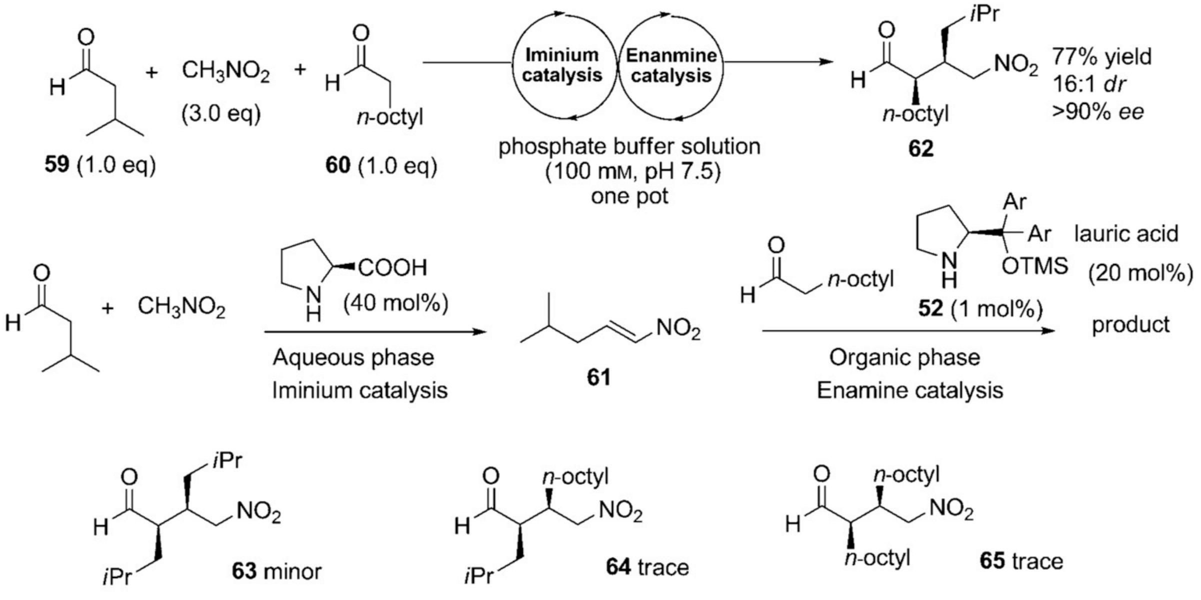
2-3. Phase-transfer condition

Iminium catalyst and PTC catalyst and Brønsted base catalysis (2009, Karl)





Polarity-Directed One-Pot Asymmetric Cascade Reactions (2010, Frechet)



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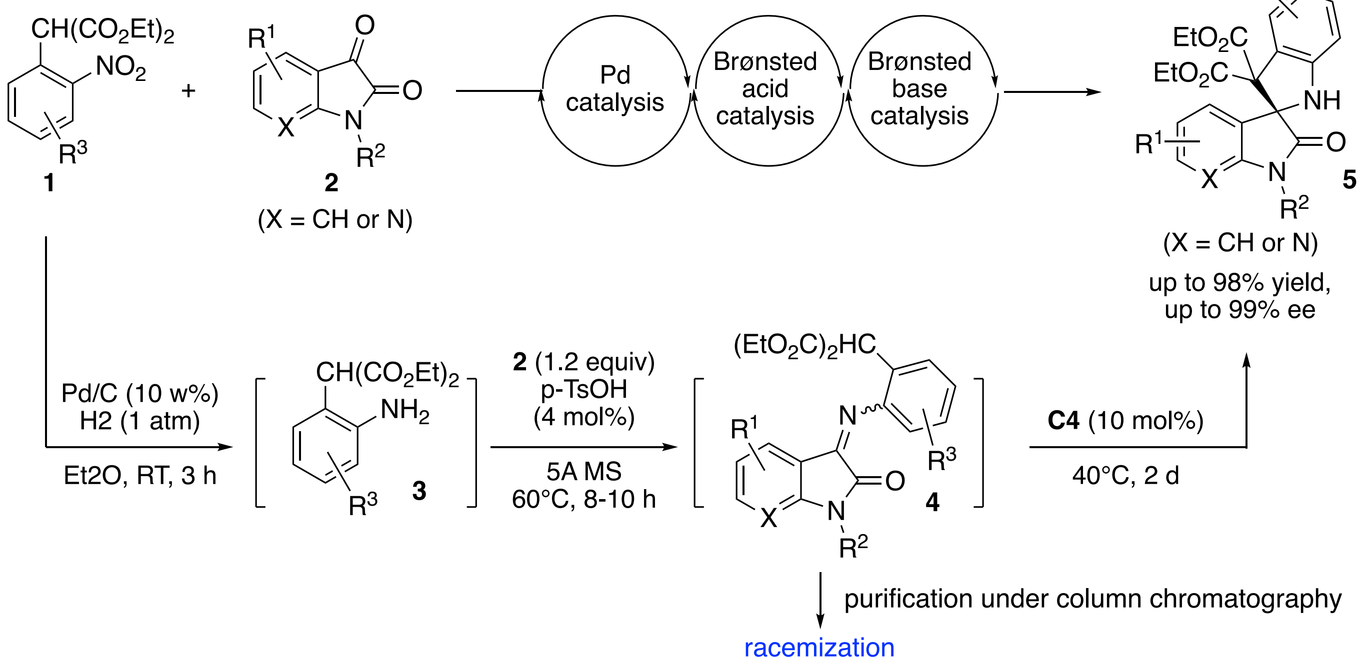
6) Karl A-J. et al. Angew. Chem. **2009**, 121, 6976 –6980
7) Frechet. et al. Angew. Chem. Int. Ed. **2010**, 49, 2393 –2396

3. Organocatalyst × Metal

3-1. Organo- and Pd catalyst

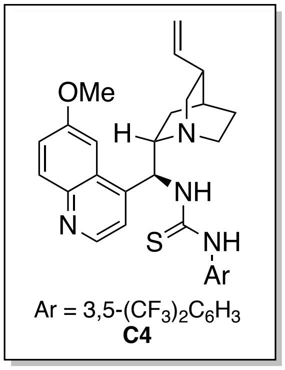
Asymmetric Triple Relay catalyst (2014, Zhou)



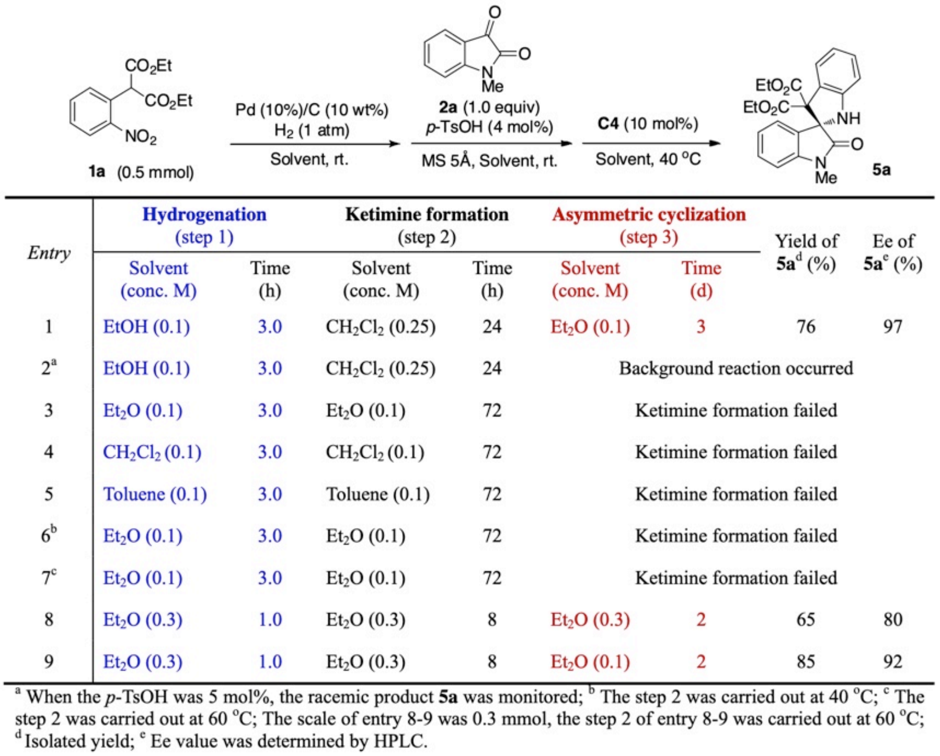
$$4a \xrightarrow[\text{Et}_2\text{O, 40°C, 2 d}]{\textbf{C4}\text{ (10 mol\%)}, \; p\text{-TsOH (}\mathbf{x}\text{ mol\%)}} 5a$$

x=2, 98% yield, 98% ee
x=4, 97% yield, 98% ee
x=6, 88% yield, 97% ee
x=10, 35% yield, 70% ee

R^1=H, R^2=Me, R^3=H



Ar = 3,5-$(CF_3)_2C_6H_3$
C4



Entry	Hydrogenation (step 1)		Ketimine formation (step 2)		Asymmetric cyclization (step 3)		Yield of 5a[d] (%)	Ee of 5a[e] (%)
	Solvent (conc. M)	Time (h)	Solvent (conc. M)	Time (h)	Solvent (conc. M)	Time (d)		
1	EtOH (0.1)	3.0	CH_2Cl_2 (0.25)	24	Et_2O (0.1)	3	76	97
2[a]	EtOH (0.1)	3.0	CH_2Cl_2 (0.25)	24	Background reaction occurred			
3	Et_2O (0.1)	3.0	Et_2O (0.1)	72	Ketimine formation failed			
4	CH_2Cl_2 (0.1)	3.0	CH_2Cl_2 (0.1)	72	Ketimine formation failed			
5	Toluene (0.1)	3.0	Toluene (0.1)	72	Ketimine formation failed			
6[b]	Et_2O (0.1)	3.0	Et_2O (0.1)	72	Ketimine formation failed			
7[c]	Et_2O (0.1)	3.0	Et_2O (0.1)	72	Ketimine formation failed			
8	Et_2O (0.3)	1.0	Et_2O (0.3)	8	Et_2O (0.3)	2	65	80
9	Et_2O (0.3)	1.0	Et_2O (0.3)	8	Et_2O (0.1)	2	85	92

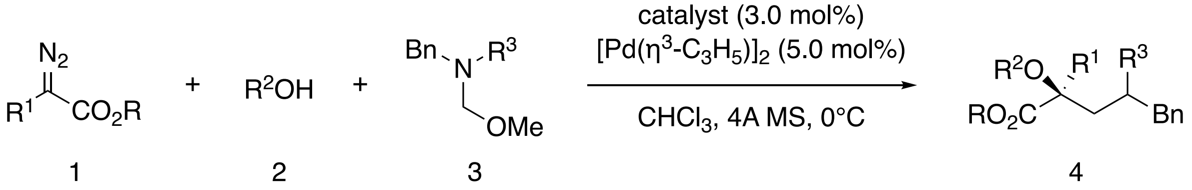
[a] When the *p*-TsOH was 5 mol%, the racemic product **5a** was monitored; [b] The step 2 was carried out at 40 °C; [c] The step 2 was carried out at 60 °C; The scale of entry 8-9 was 0.3 mmol, the step 2 of entry 8-9 was carried out at 60 °C; [d] Isolated yield; [e] Ee value was determined by HPLC.

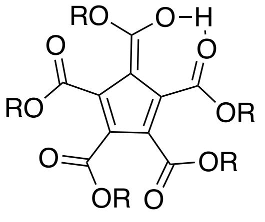
8) Zhou, J. et al. Angew. Chem. Int. Ed. **2014**, 53, 13740 –13745

3. Organocatalyst × Metal

3-1. Organo- and Pd catalyst

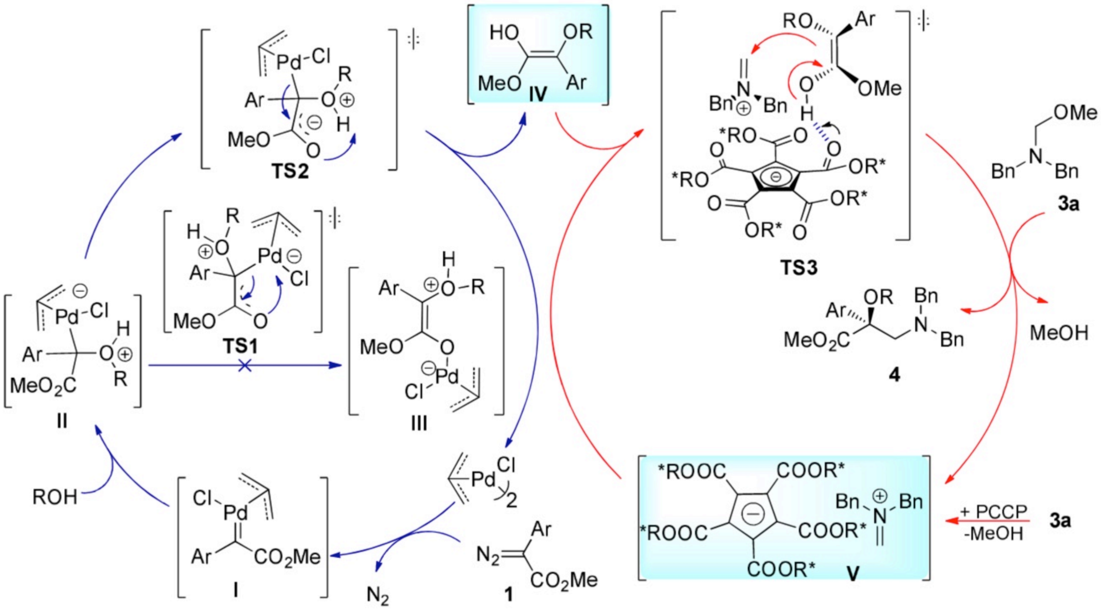
Asymmetric Counter-Anion-Directed Aminomethylation (2019, Hu)

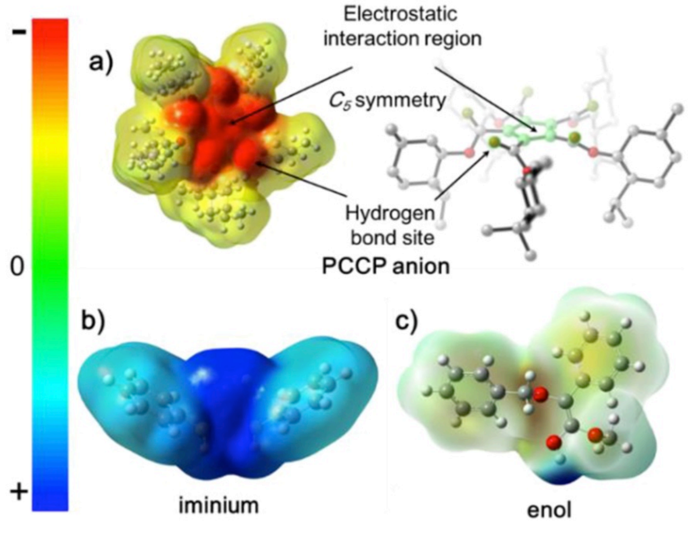


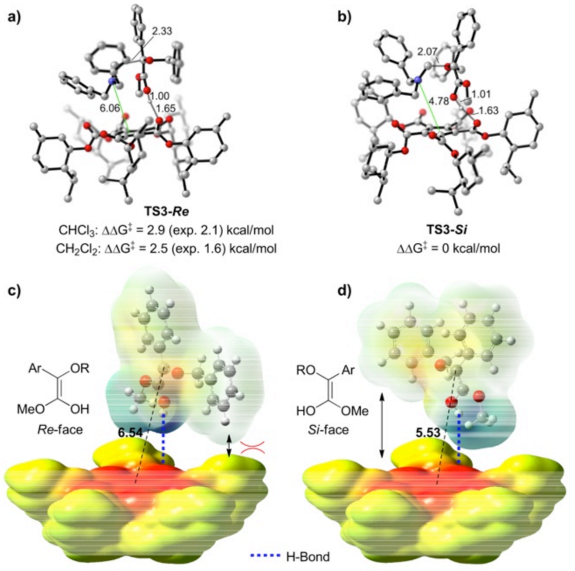


catalyst

$M(OTf)_n$	equiv	*t* (h)	yield (%)
$Sc(OTf)_3$	0.05	0.5	98
$Cu(OTf)_2$	0.1	1	99
$Lu(OTf)_3$	0.1	3	98
$LuCl_3•6H_2O$	0.1	18	98
$YbCl_3•6H_2O$	0.1	18	97





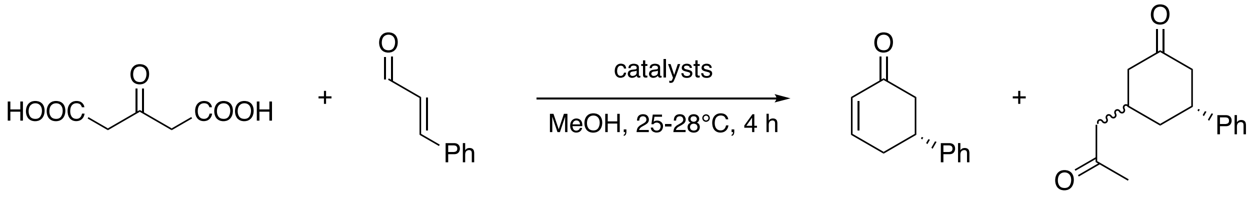


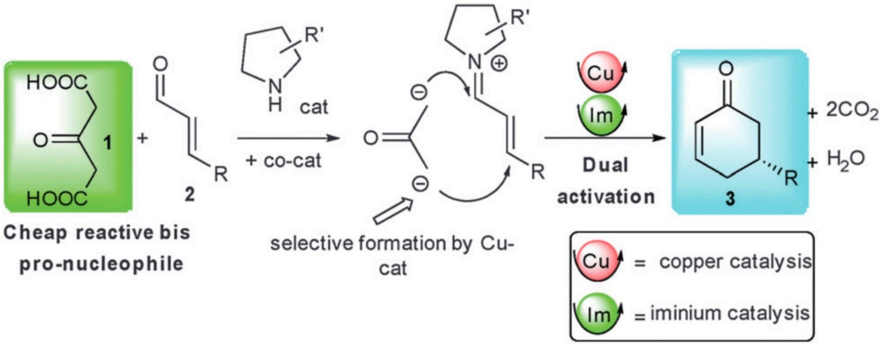
9) Hu, W. et al. J. Am. Chem. Soc. **2019**, 141, 1473–1478

3. Organocatalyst × Metal

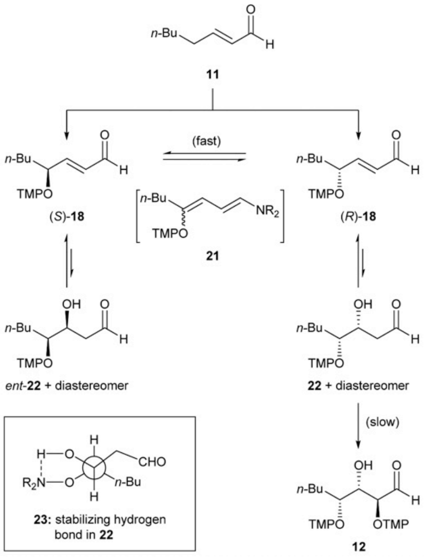
3-3. Organo- and Cu catalyst

Michael/aldol/dehydration (2015, Rodriguez)

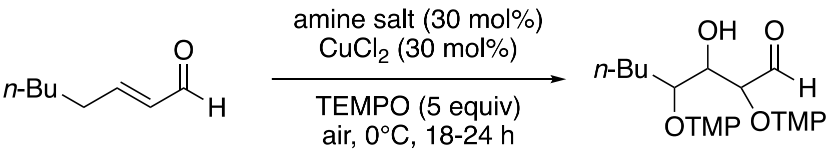




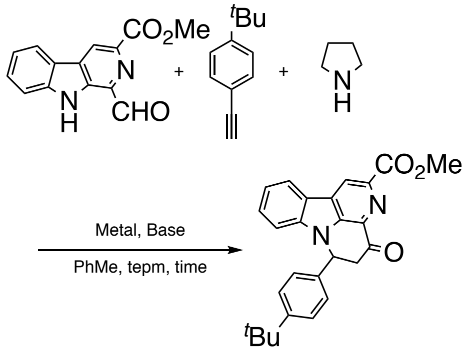
J. Org. Chem. 2016, 81, 4751–4761

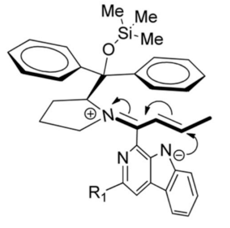


α,β,γ-Trioxygenation (2015, Chen)

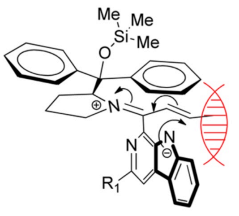


Jorgensen–Hayashi catalyst, copper iodide, and Hunig base (2016, Batra)

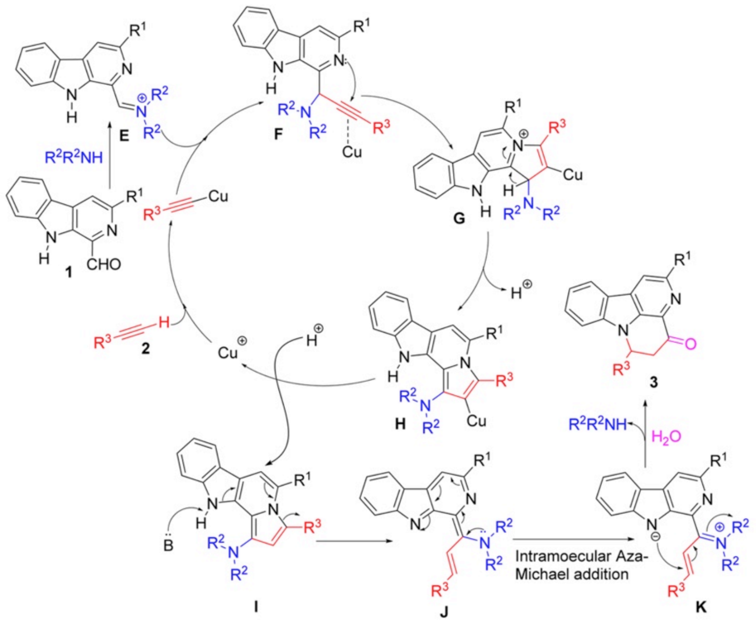




Sterically favored Si-face attack



Sterically hindered Re-face attack

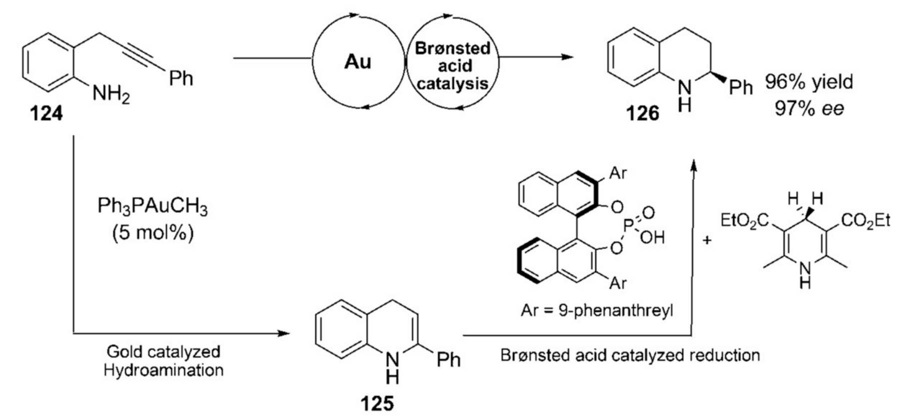


10) Rodriguez, et al. Chem.Commun.,**2015**,51,9523–9526
11) Chen, J-S, et al. Org. Lett. **2015**, 17, 6050–6053
12) Batra, S, et al.J. Org. Chem. **2016**, 81, 4751–4761

3. Organocatalyst × Metal

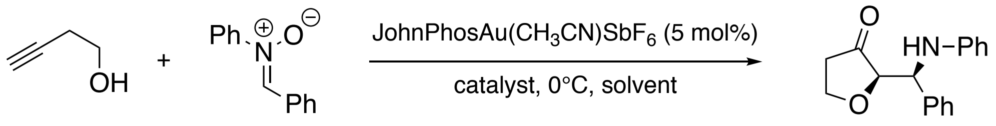
3-4. Organo- and Au catalyst

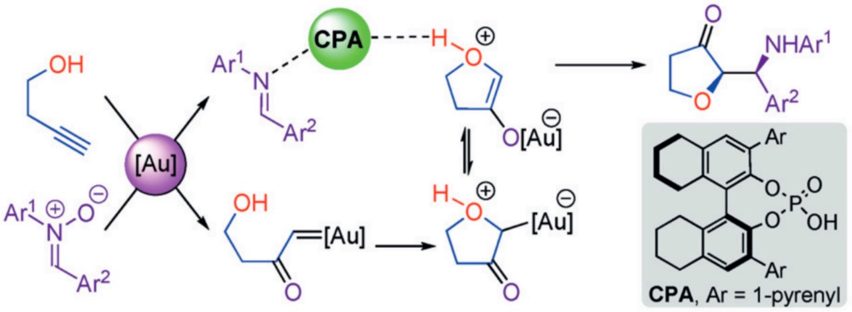
Intramolecular Hydroamination/Asymmetrc Transfer Hydrogenation (2009, Gong)

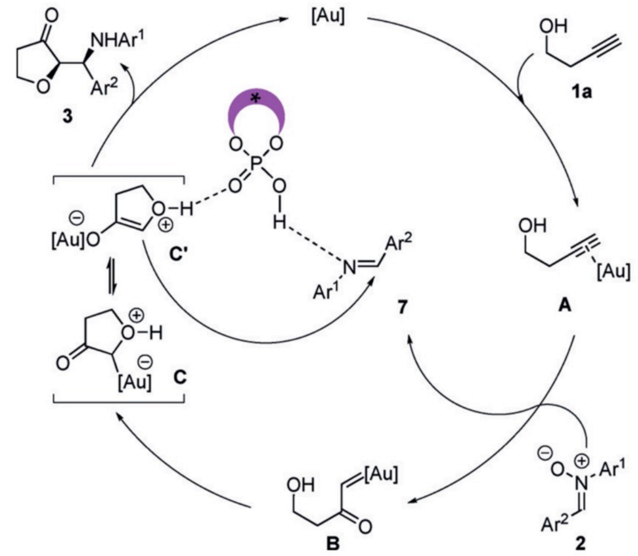


Scheme 23. Combination of gold catalysis with Brønsted acid catalysis.

Oxidative Cyclization/Mannich Addition (2018, Xu)







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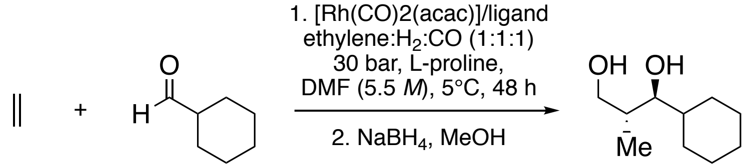
13) Gong, L-Z. et al. J. Am. Chem. Soc. 2009, 131, 9182–9183

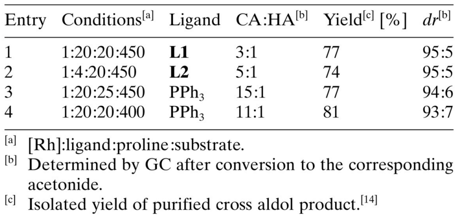
14) Xu, X. et al. Angew. Chem. Int. Ed. 2018, 57, 17200 –17204

3. Organocatalyst × Metal

3-5. Organo- and Rh catalyst

Hydroformylation (2007, Breit)





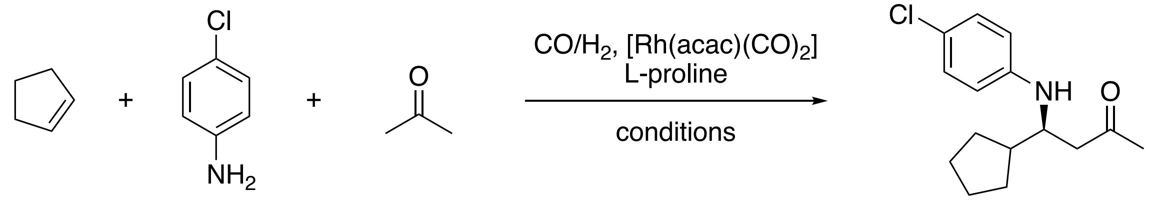
Entry	Conditions[a]	Ligand	CA:HA[b]	Yield[c] [%]	*dr*[b]
1	1:20:20:450	**L1**	3:1	77	95:5
2	1:4:20:450	**L2**	5:1	74	95:5
3	1:20:25:450	PPh_3	15:1	77	94:6
4	1:20:20:400	PPh_3	11:1	81	93:7

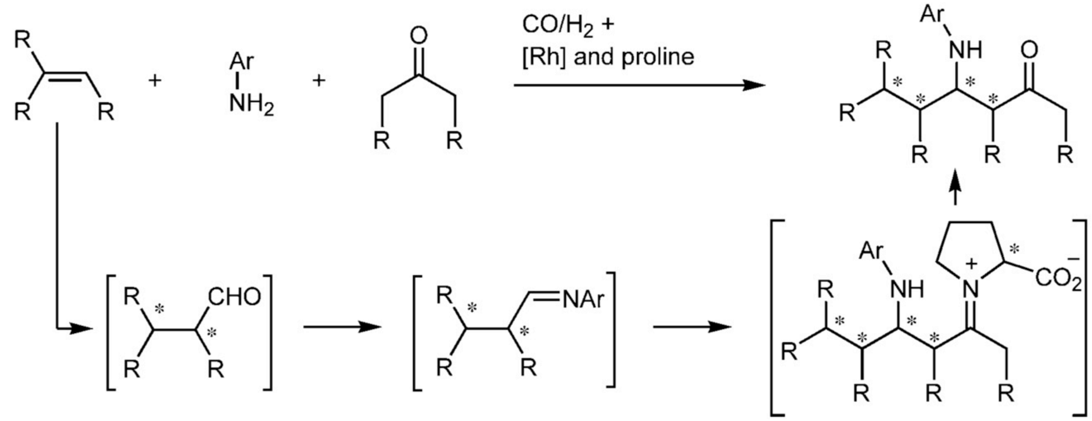
[a] [Rh]:ligand:proline:substrate.

[b] Determined by GC after conversion to the corresponding acetonide.

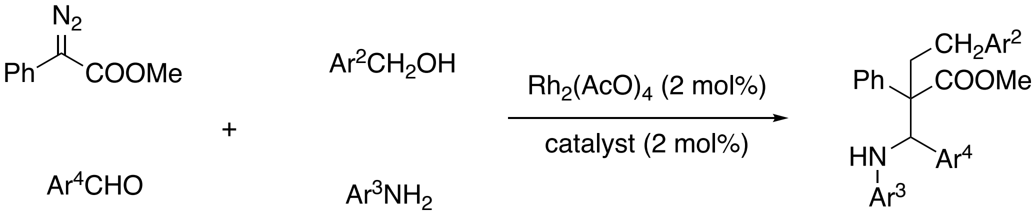
[c] Isolated yield of purified cross aldol product.[14]

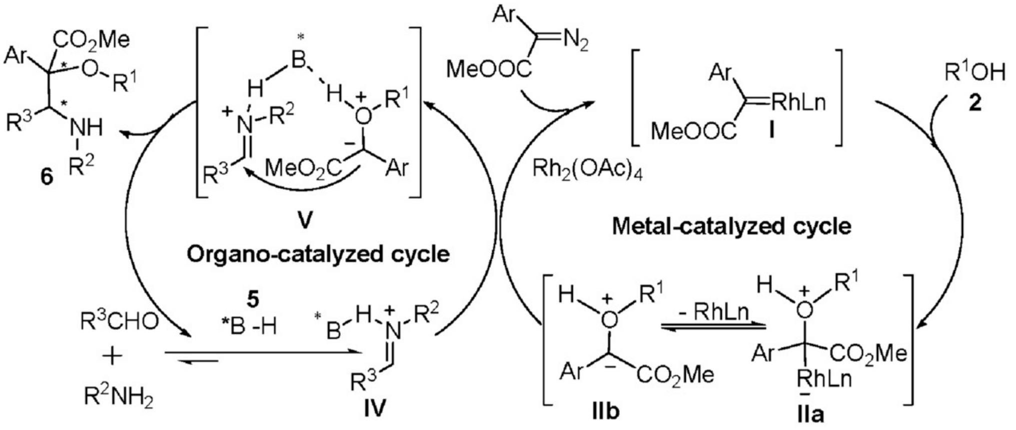
Hydroformylation and Mannich Reaction (2009, Eilbracht)





Four-component reactions (2008, Hu)





15) Breit, B. et al. Adv. Synth. Catal. **2007**, 349, 1891 – 1895

16) Eilbracht, P et al. Adv. Synth. Catal. **2009**, 351, 339 – 344

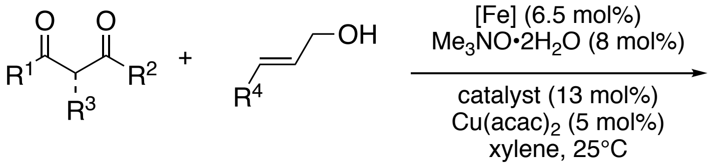
17) Hu, W, e al. Chem. Commun., **2008**, 6564–6566

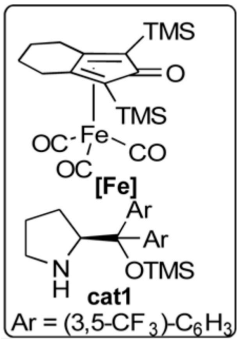
3. Organocatalyst × Metal

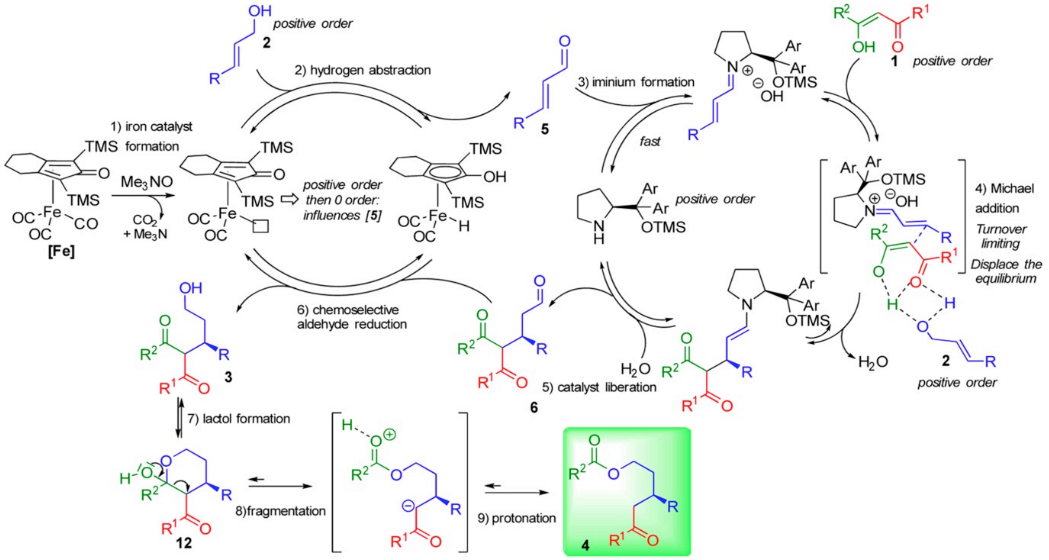
3-6. Organo- and Fe catalyst

Triple Iron/Copper/Iminium Activation

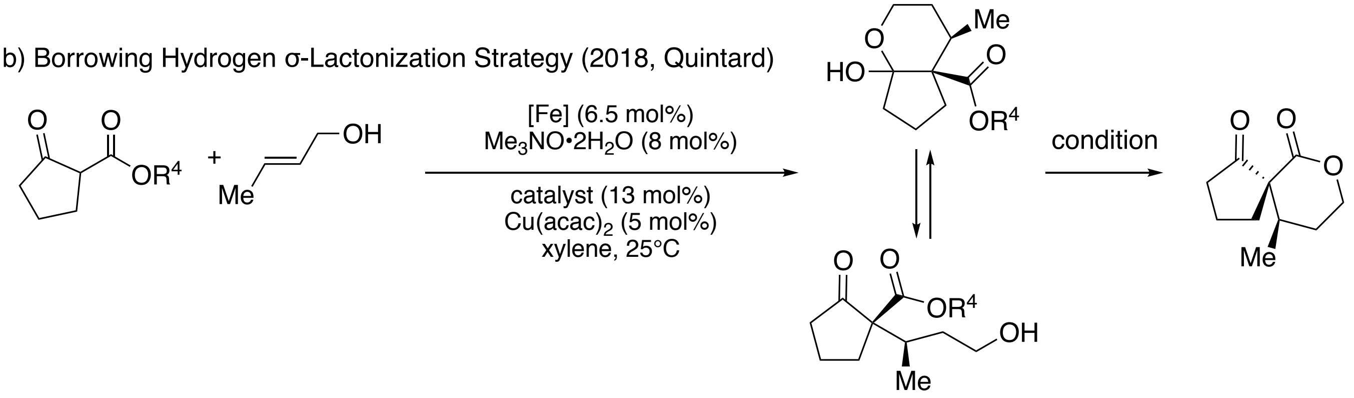
a) Functionalization of Allylic Alcohols (2016, Rodriguez)







b) Borrowing Hydrogen σ-Lactonization Strategy (2018, Quintard)



Entry	R^4 (**3**)	Lactonization conditions	Yield (%) of **4**
1	Et (**3b**)	toluene, 110 °C, 38 h	degradation
2	Et (**3b**)	PTSA, acetone, r.t., 8 h	degradation
3	Et (**3b**)	TBAF, THF, r.t., 1 h	degradation
4	*t*-Bu (**3c**)	toluene, 110 °C, 38 h	degradation
5	Me (**3a**)	NaH, THF, r.t., 8 h	degradation
6	Me (**3a**)	NaH, THF, r.t., 8 h	degradation
7	Me **(3a)**	TBAF, THF, 0 °C, 1 h	50%[a]
8	**Me (3a)**	**Cs_2CO_3, THF, r.t., 1 h**	**88**[b]
9	**Me (3a)**	**DBU, toluene, r.t., 2 h**	**90**[b]

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18) Rodriguez. et al. ACS Catal. **2016**, 6, 5236–5244
19) Quintard, A. et al. Synthesis **2018**, 50, 785–792