有机小分子与金属共不对称催化

Organocatalysts and Metal Asymmetric Cocatalysis

Guoqiang Yang

有机小分子与金属共不对称催化

1. 有机小分子与金属Lewis酸的共不对称催化

2. 有机小分子与金属有机结合的不对称催化

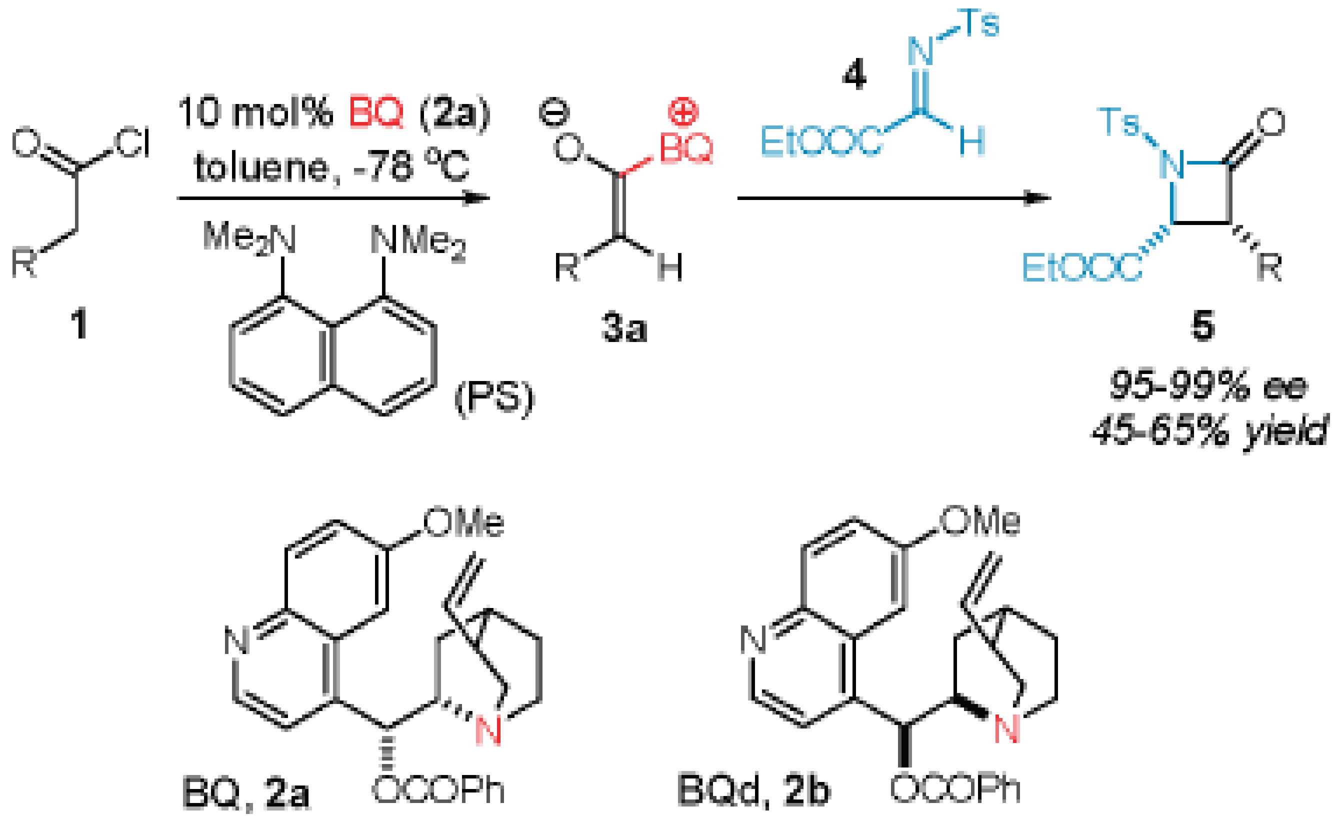
3. 手性有机小分子离子作为金属的抗离子不对称催化

有机小分子与金属Lewis酸的共不对称催化

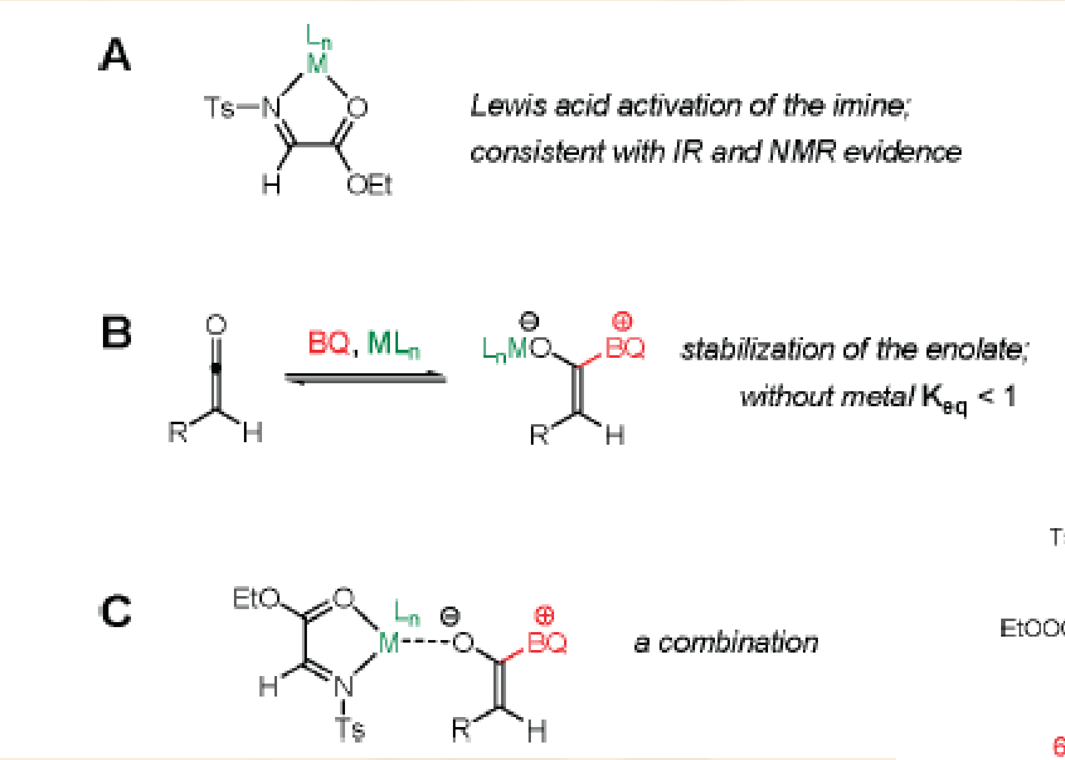
- 有机小分子催化剂为手性分子
- 金属Lewis酸配合物为手性分子

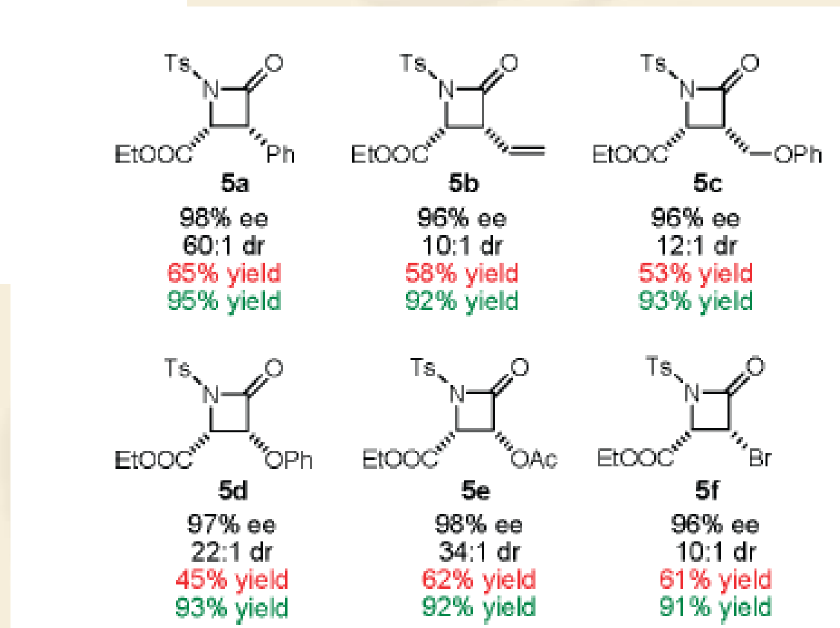
1.1 Combine Achiral Lewis Acids with Chiral Cinchona Alkaloid Nucleophiles

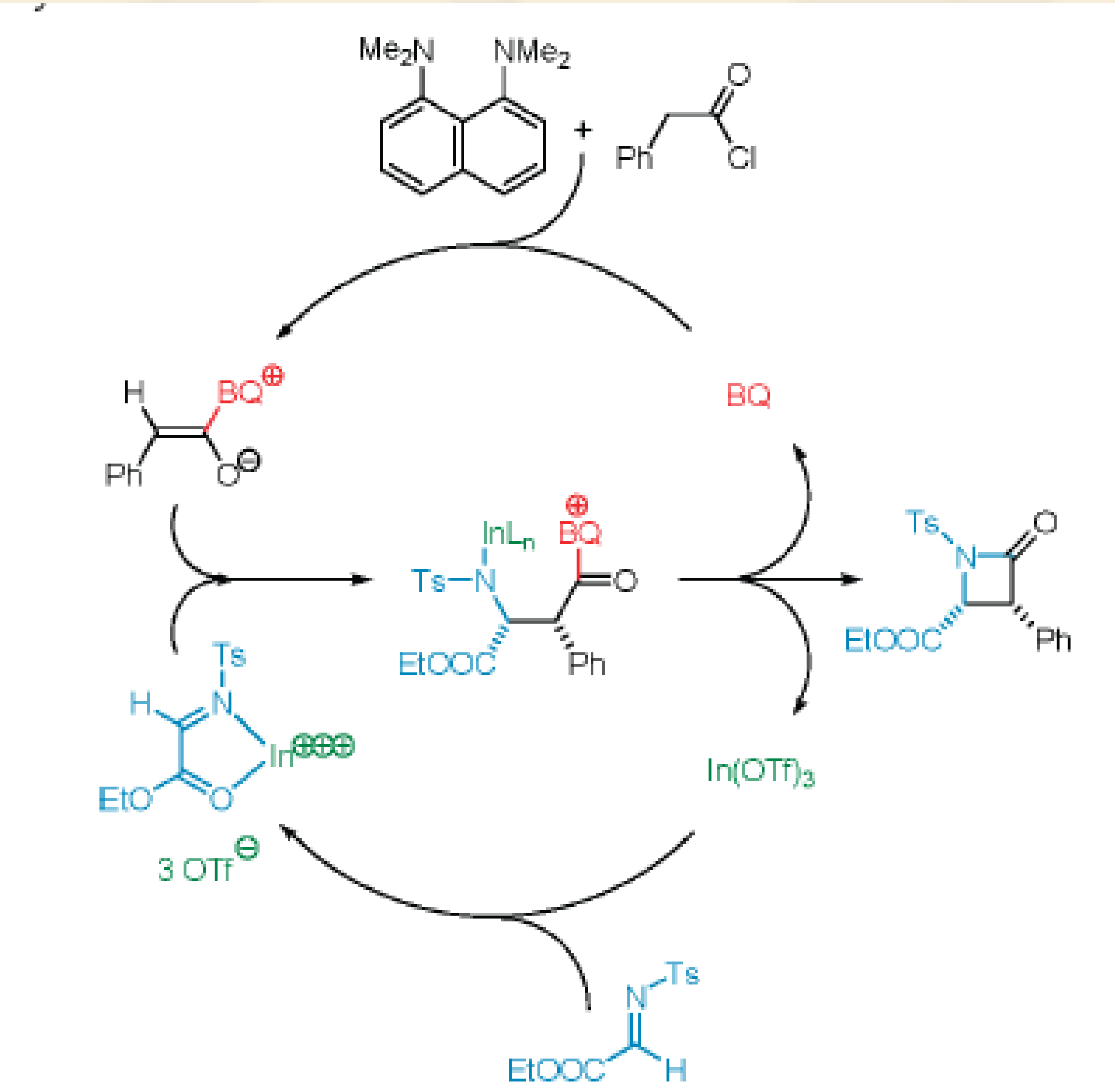
SCHEME 2. Original β-Lactam Method



Ref.1: Accounts of Chemical Reseach XXX XXX XXX

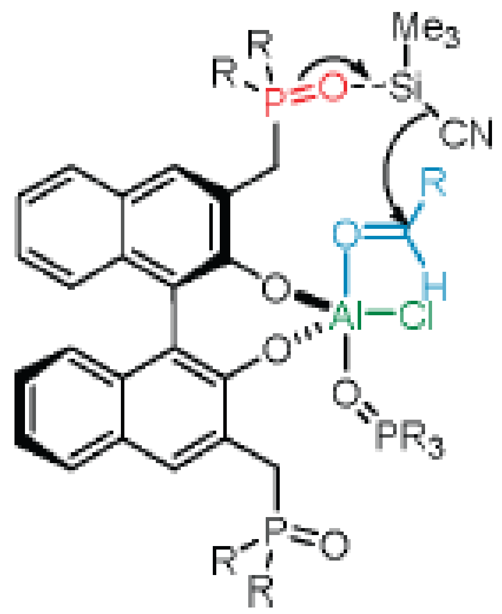

A
Lewis acid activation of the imine;
consistent with IR and NMR evidence
B
BQ, ML$_n$
stabilization of the enolate;
without metal K_{eq} < 1
C
a combination


5a
98% ee
60:1 dr
65% yield
95% yield
5b
96% ee
10:1 dr
58% yield
92% yield
5c
96% ee
12:1 dr
53% yield
93% yield
5d
97% ee
22:1 dr
45% yield
93% yield
5e
98% ee
34:1 dr
62% yield
92% yield
5f
96% ee
10:1 dr
61% yield
91% yield

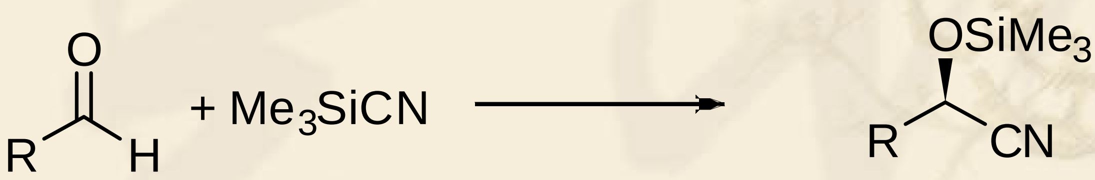


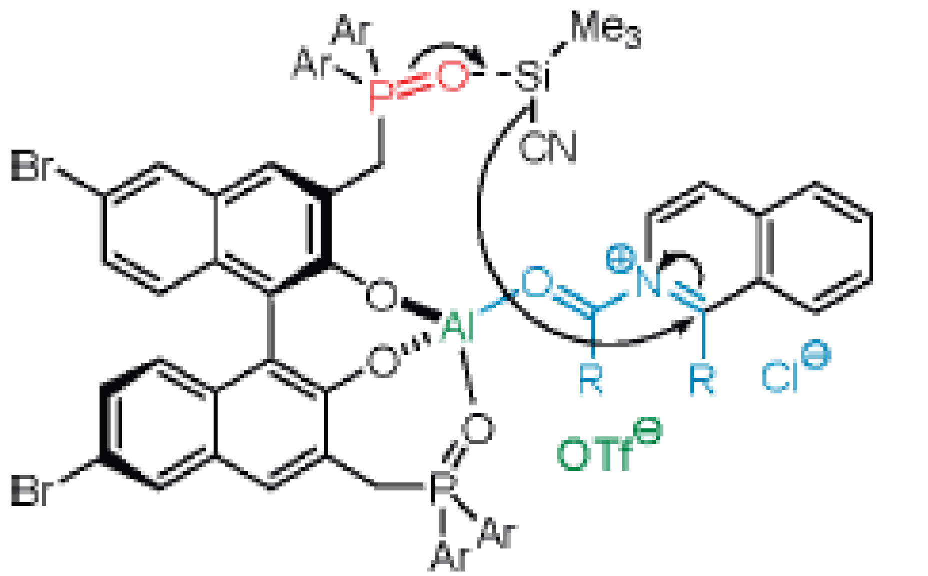
Me2N
NMe2
+
Ph
O
Cl
H
BQ⊕
Ph
O⊖
BQ
InLn
⊕
BQ
Ts–N
O
EtOOC
Ph
Ts
N
O
EtOOC
Ph
Ts
H
N
In⊕⊕⊕
EtO
O
3 OTf⊖
In(OTf)3
N
Ts
EtOOC
H

1.2 Lewis Acid–BINOL–Phosphine Oxide Catalysts.

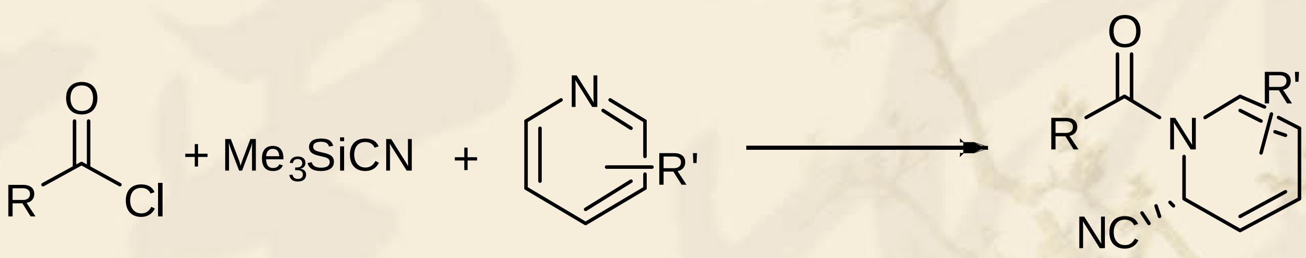


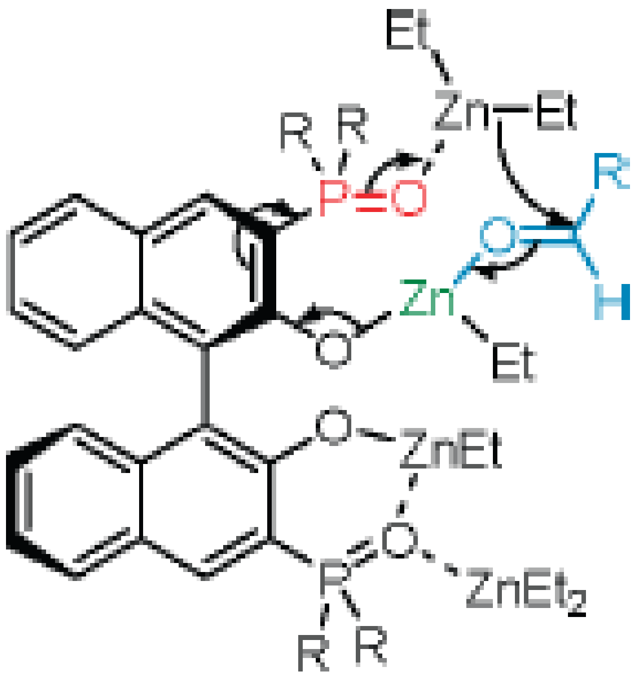
3. Dual activation in Shibasaki's Strecker reaction.





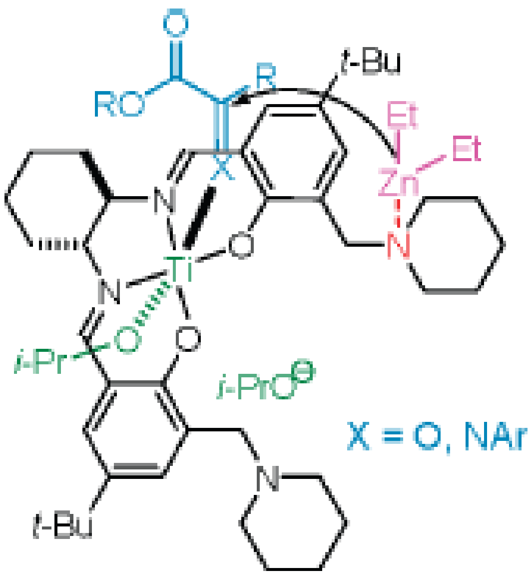
Shibasaki's bifunctional Reissert reaction.



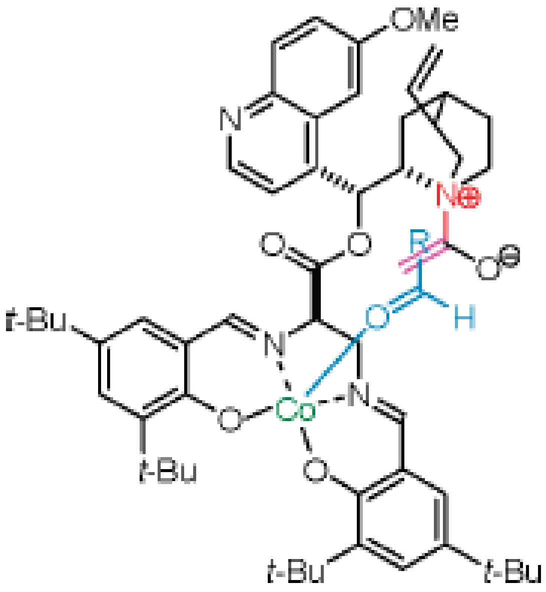


Ishihara's asymmetric alkylation reaction.

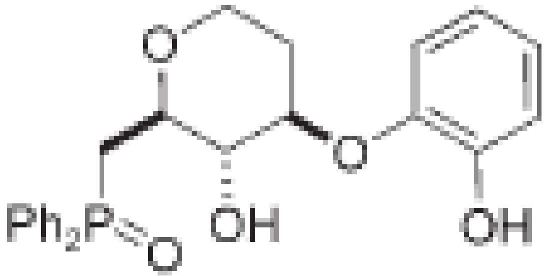
1.3 Other Noteworthy Systems



Kozlowski's proposed intermediate.



Lin's proposed activated complex.



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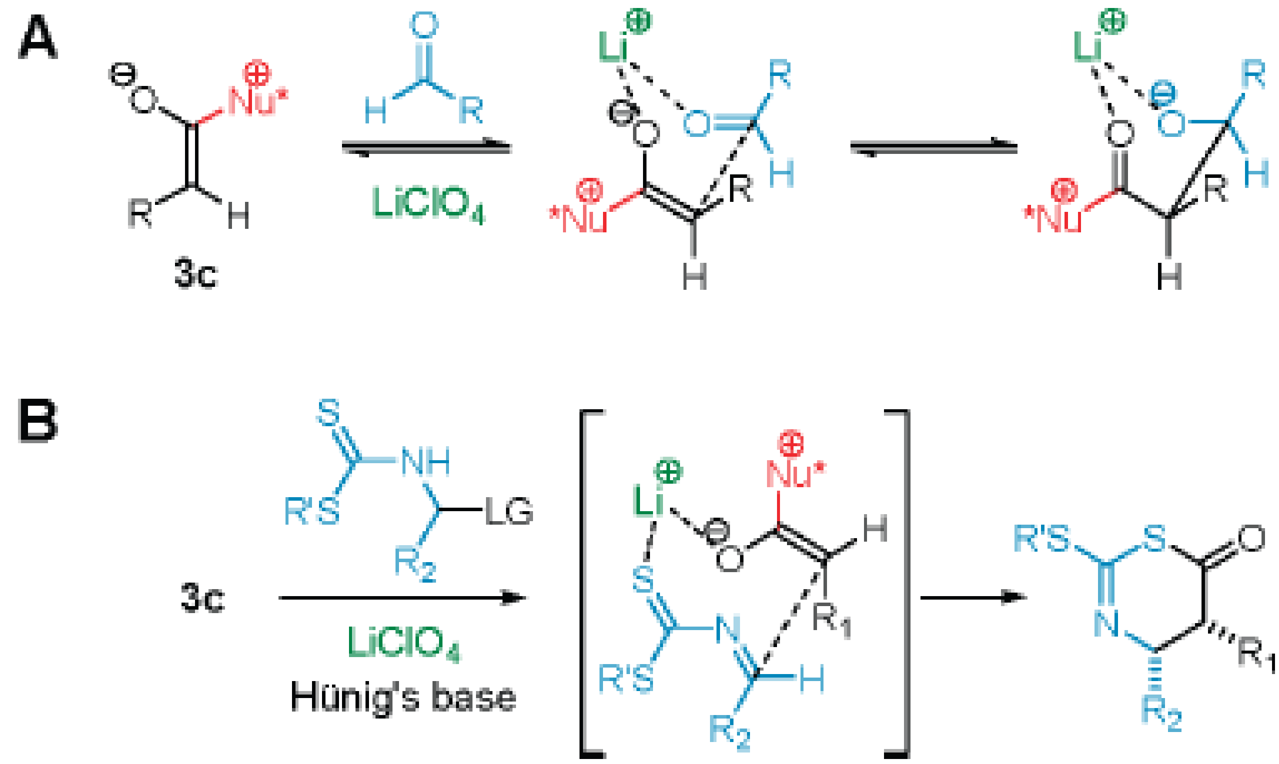
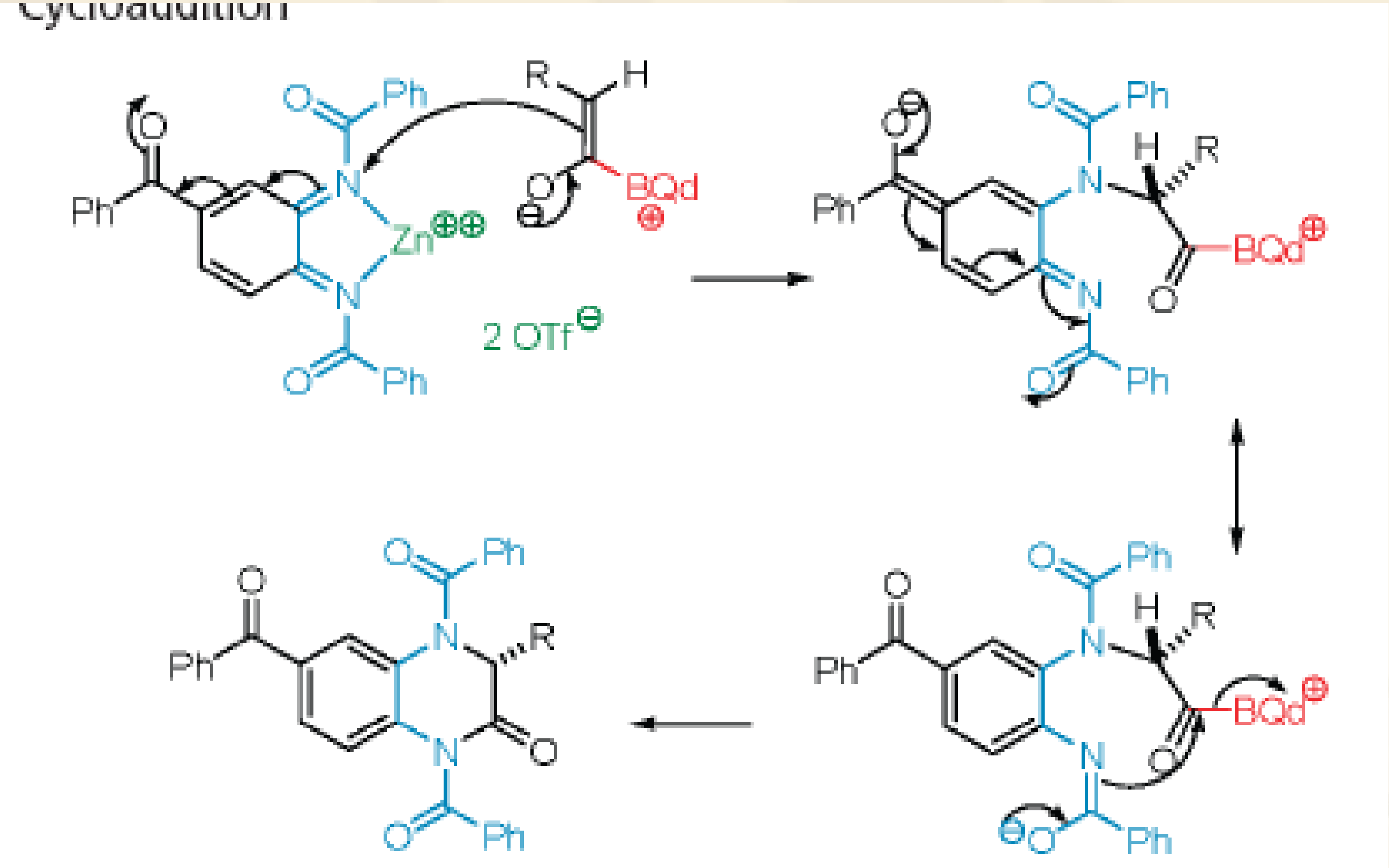
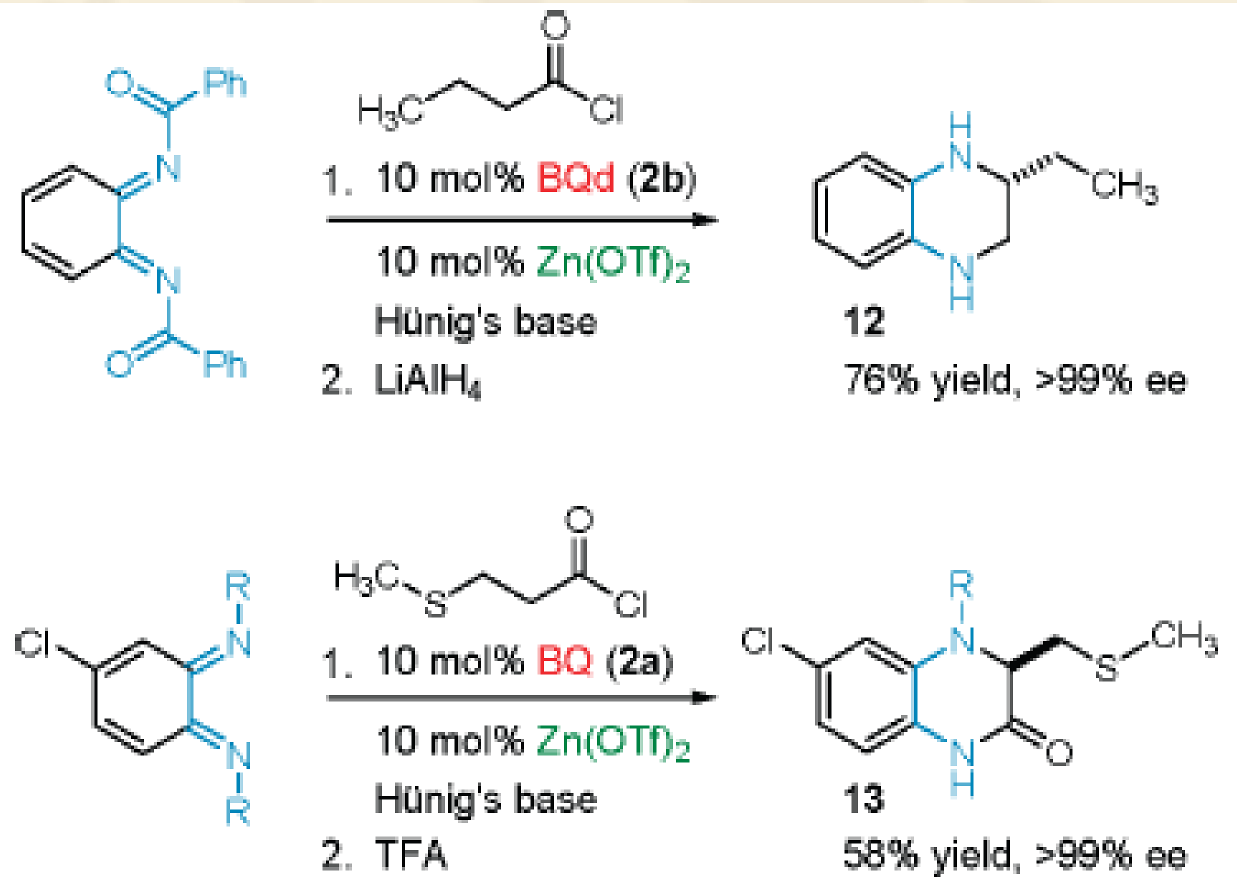
SCHEME 7. Nelson's Lithium-Organized Activated Complex



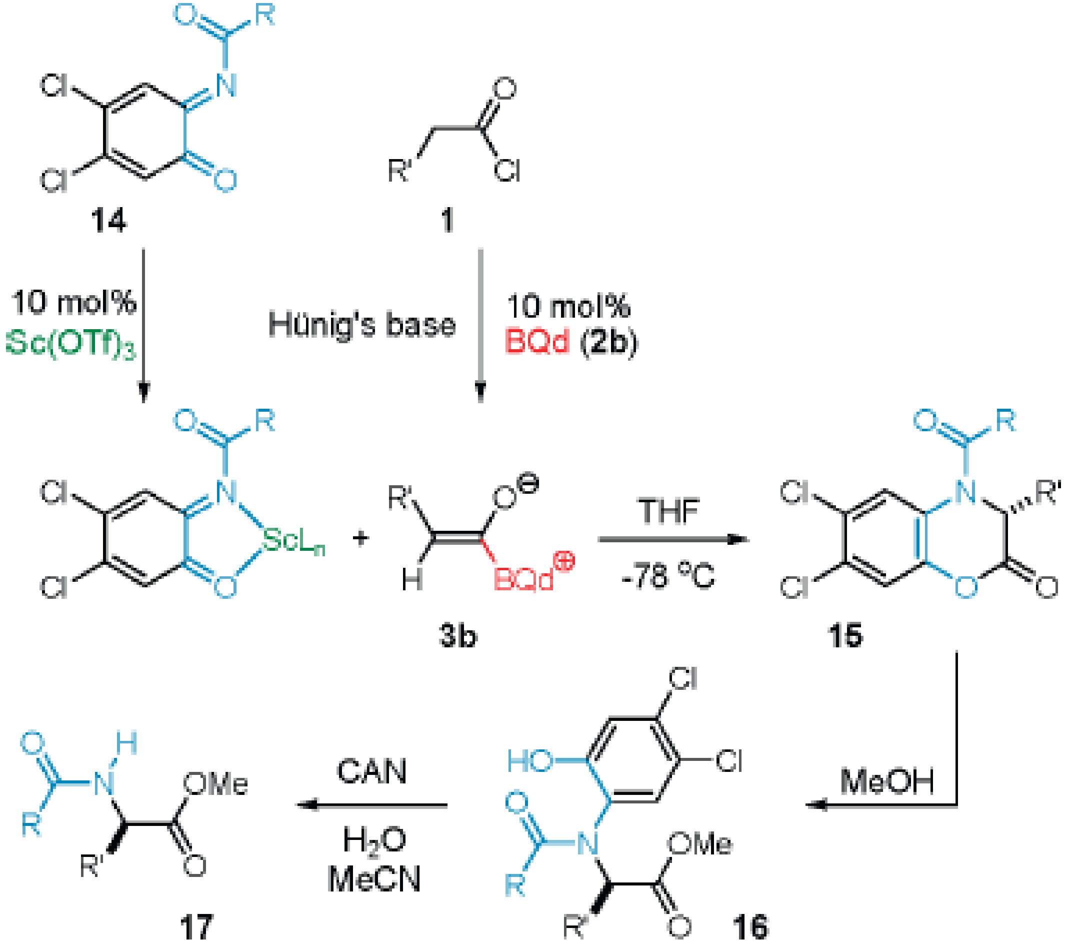
1.4. [4 + 2]Cycloaddition of *o*-Benzoquinone Derivatives and Ketenes

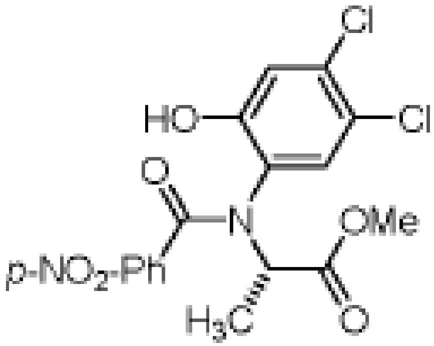




1. 10 mol% BQd (2b)
10 mol% Zn(OTf)2
Hünig's base
2. LiAlH4
12
76% yield, >99% ee
1. 10 mol% BQ (2a)
10 mol% Zn(OTf)2
Hünig's base
2. TFA
13
58% yield, >99% ee

SCHEME 11. Bifunctional QI Reaction To Form α-Amino Acid Derivatives, R = *p*-NO_2−Ph

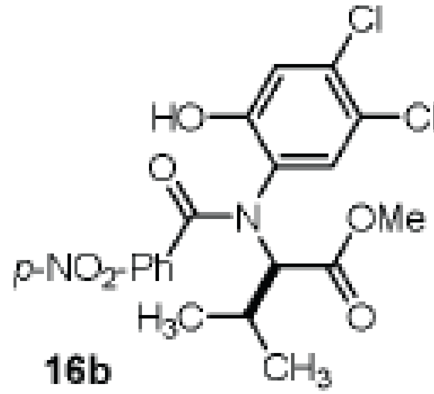




16a

71% yield, >99% ee

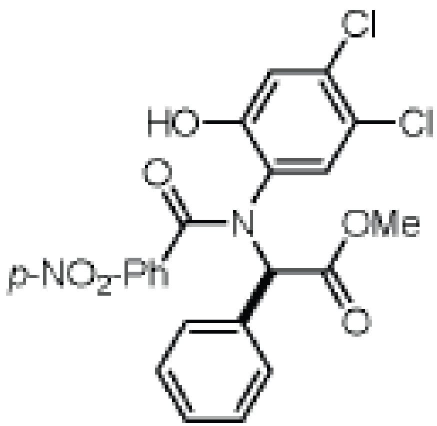
92% yield, >99% ee



16b

59% yield, >99% ee

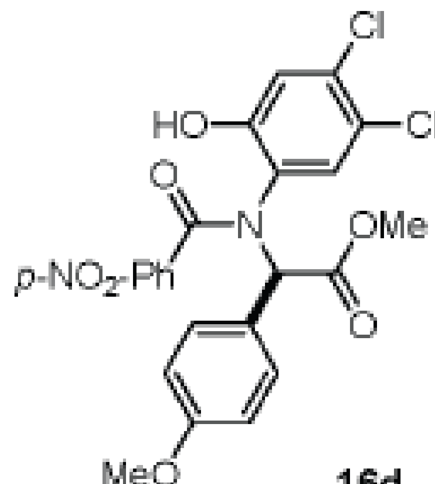
84% yield, >99% ee



16c

66% yield, >99% ee

92% yield, >99% ee



16d

83% yield, >99% ee

87% yield, >99% ee

2.1 有机小分子与手性Lewis酸金属配合物共催化

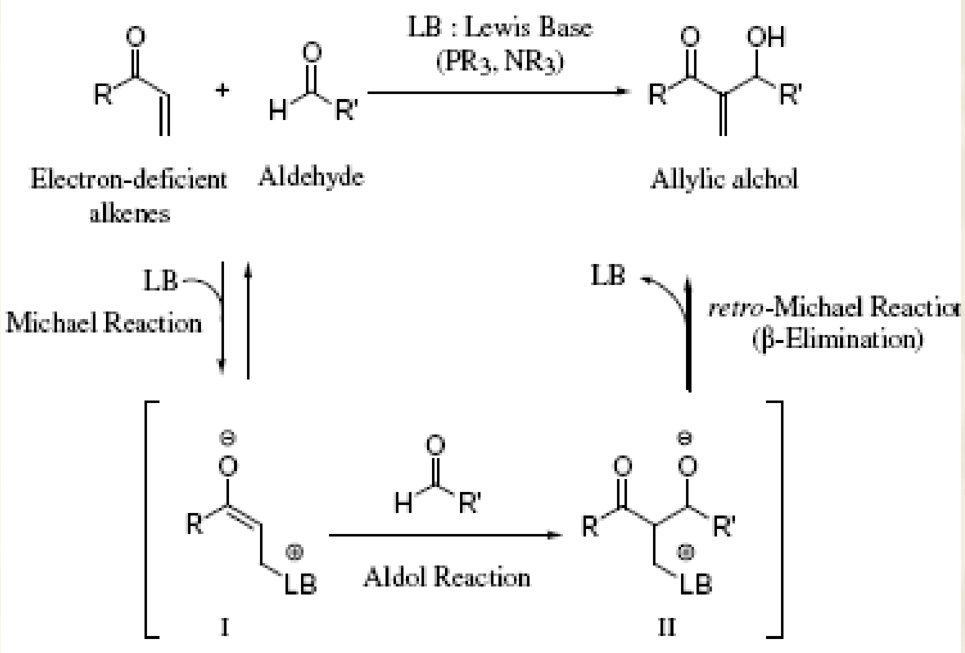


Figure 1. Mechanism of the MBH reaction.

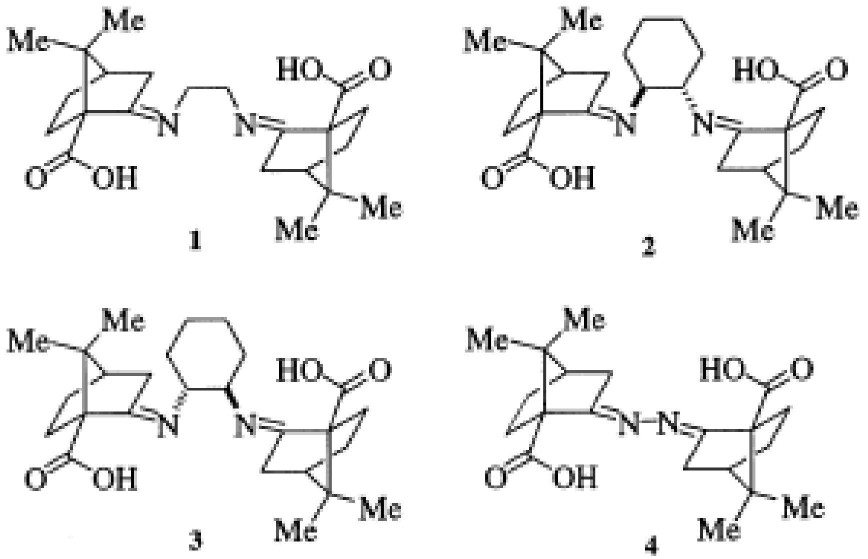
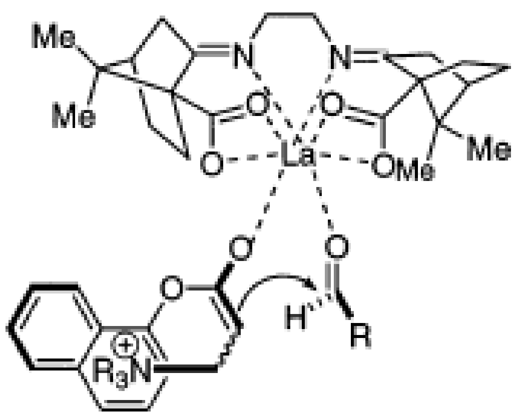
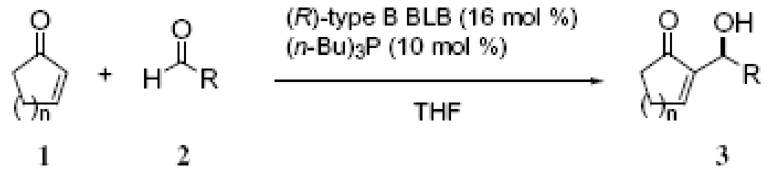


FIGURE 1. Structures of camphor-derived chiral ligands 1–



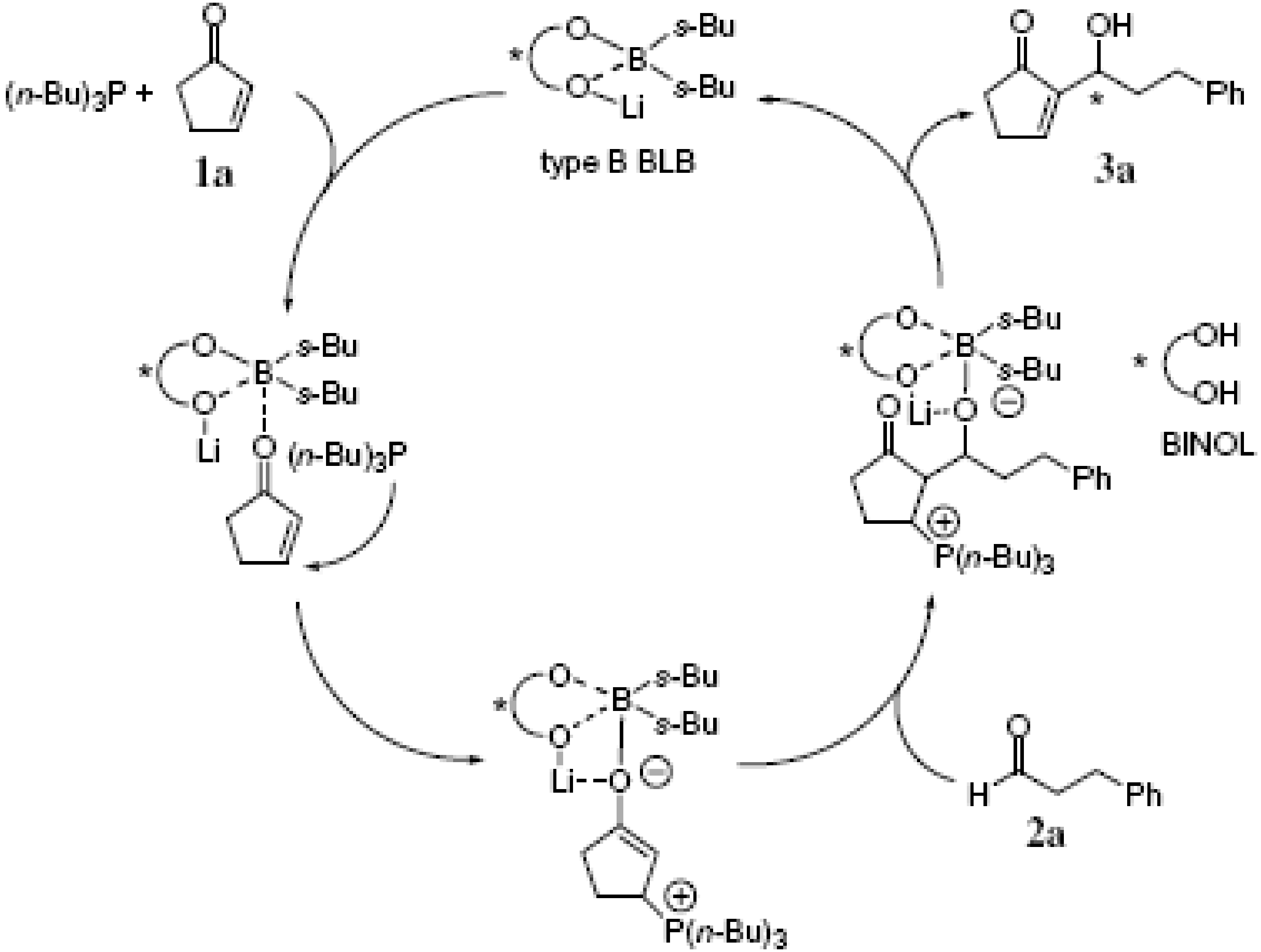
up to 95% *ee*

Ref.2: J. Org. Chem. **2003**, *68*, 915–919



Entry	$n = 1$ or 2	*R*	Temp (°C)	Time (h)	Product	Yield (%)	Ee (%)[b]
1	**1a** (*n* = 1)	$PhCH_2CH_2$ (**2a**)	−40	120	**3a**	70	64
2	**1b** (*n* = 2)	**2a**	0	240	**3b**	49	58
3	**1b**	Et (**2b**)	0	288	**3c**	23	85
4[c]	**1b**	*i*-Pr (**2c**)	0	288	**3d**	94	99
5[c]	**1a**	*t*-Bu (**2d**)	−40	288	**3e**	42	97
6	**1a**	Ph (**2e**)	rt	3.5	**3f**	93	19
7	**1b**	**2e**	0	120	**3g**	32	15
8	**1b**	C_5H_9 (**2f**)	rt	240	**3h**	60	52
9[c]	**1a**	C_6H_{11} (**2g**)	−40	168	**3i**	88	93
10	**1b**	**2g**	rt	48	**3j**	71	63

Ref.3: Tetrahedron Letters. **2005,** *46,* 1943–1946



(n-Bu)3P +
1a
s-Bu
s-Bu
Li
type B BLB
OH
Ph
3a
s-Bu
s-Bu
Li
(n-Bu)3P
s-Bu
s-Bu
Li
Ph
P(n-Bu)3
OH
OH
BINOL
s-Bu
s-Bu
Li
P(n-Bu)3
H
Ph
2a

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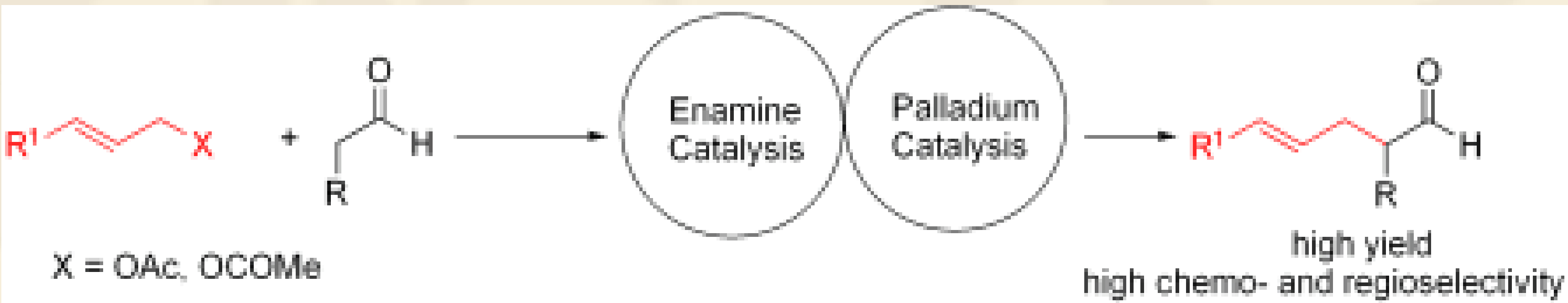
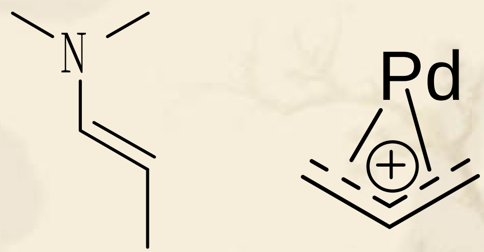
2. 有机小分子与金属有机结合的不对称催化

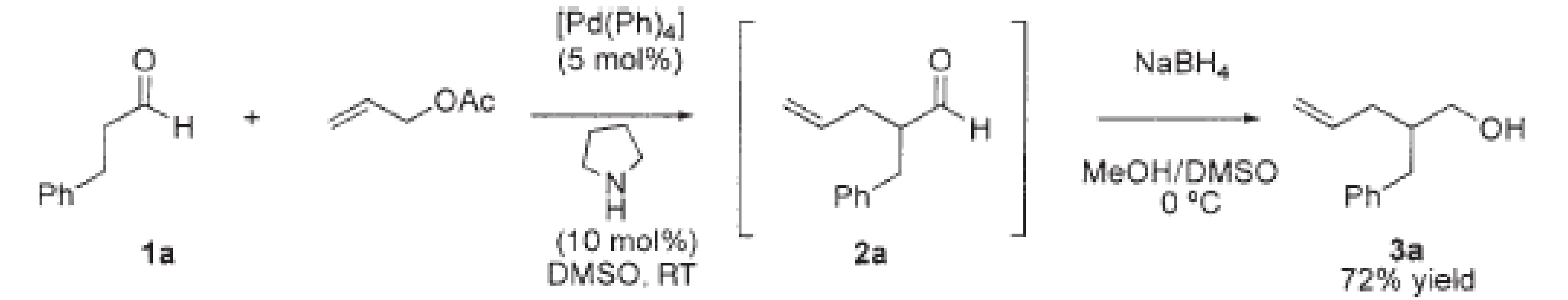
3. 手性有机小分子离子作为金属的抗离子不对称催化

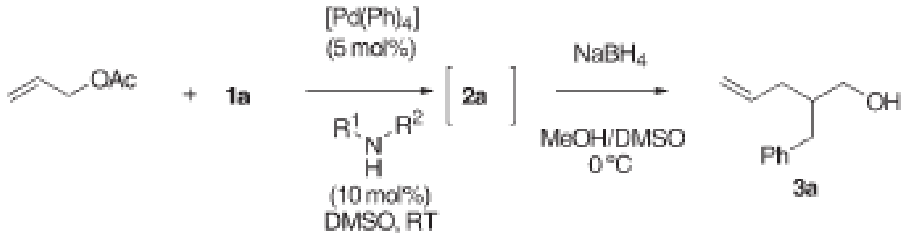
有机小分子催化与金属有机结合的(不对称)催化反应

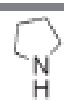
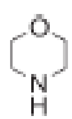


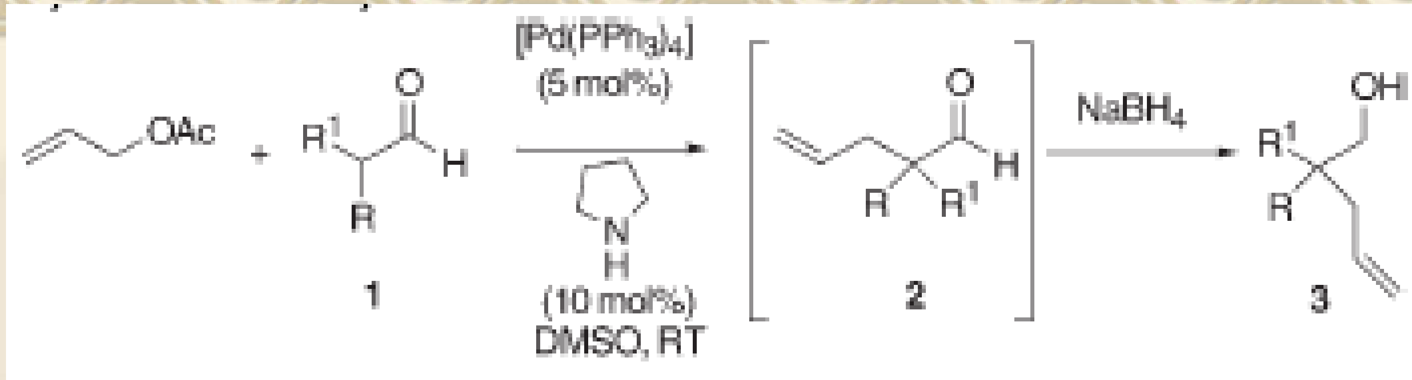


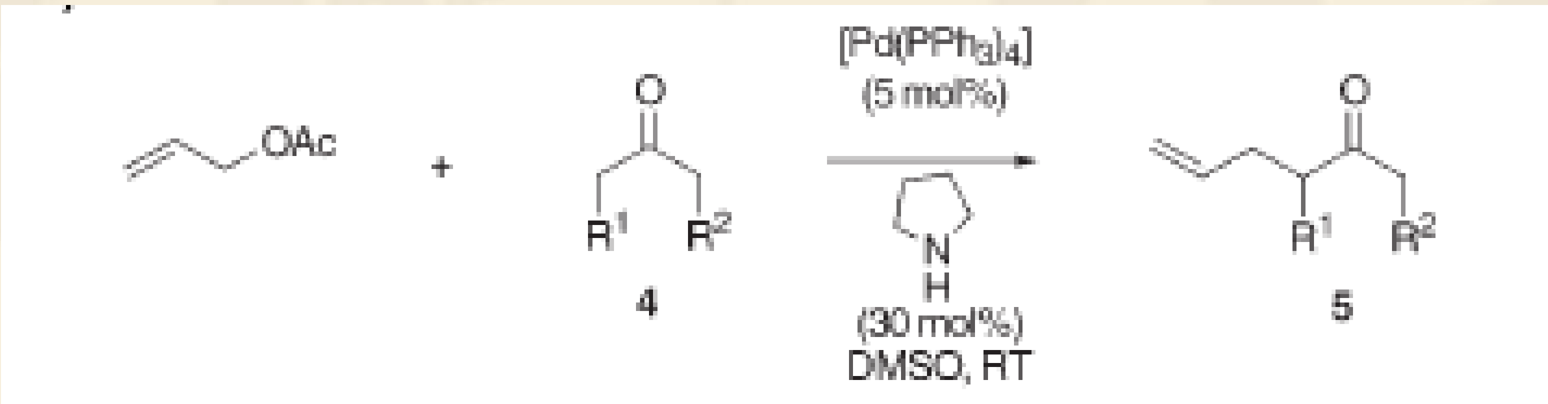
Ref.4: I. Ibrahem; A. Crdova. *Angew. Chem. Int. Ed*. **2006**, *45*, 1952 –1956

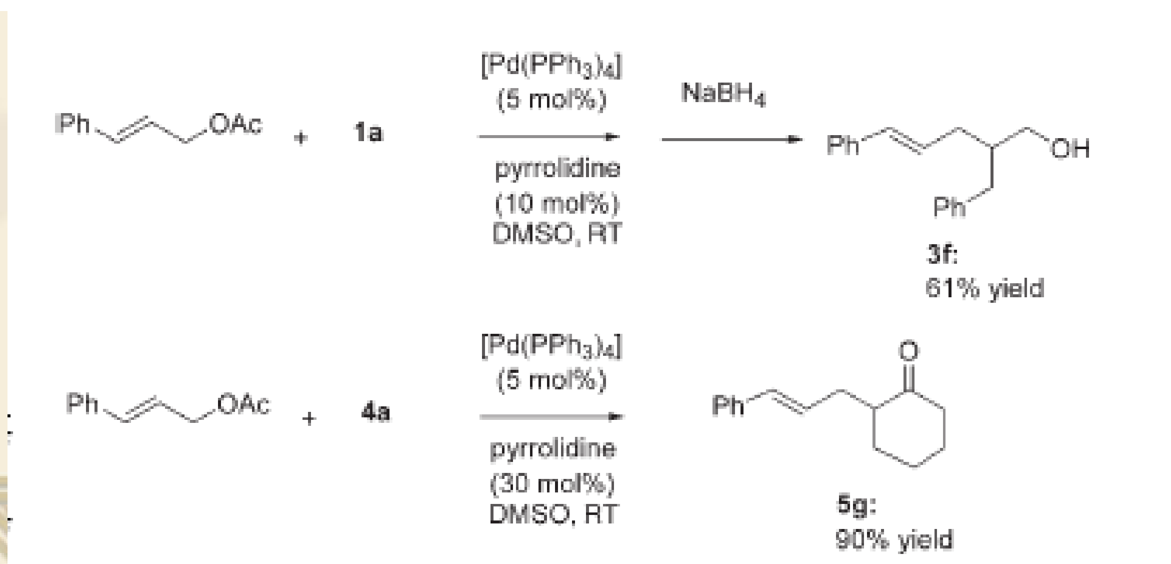


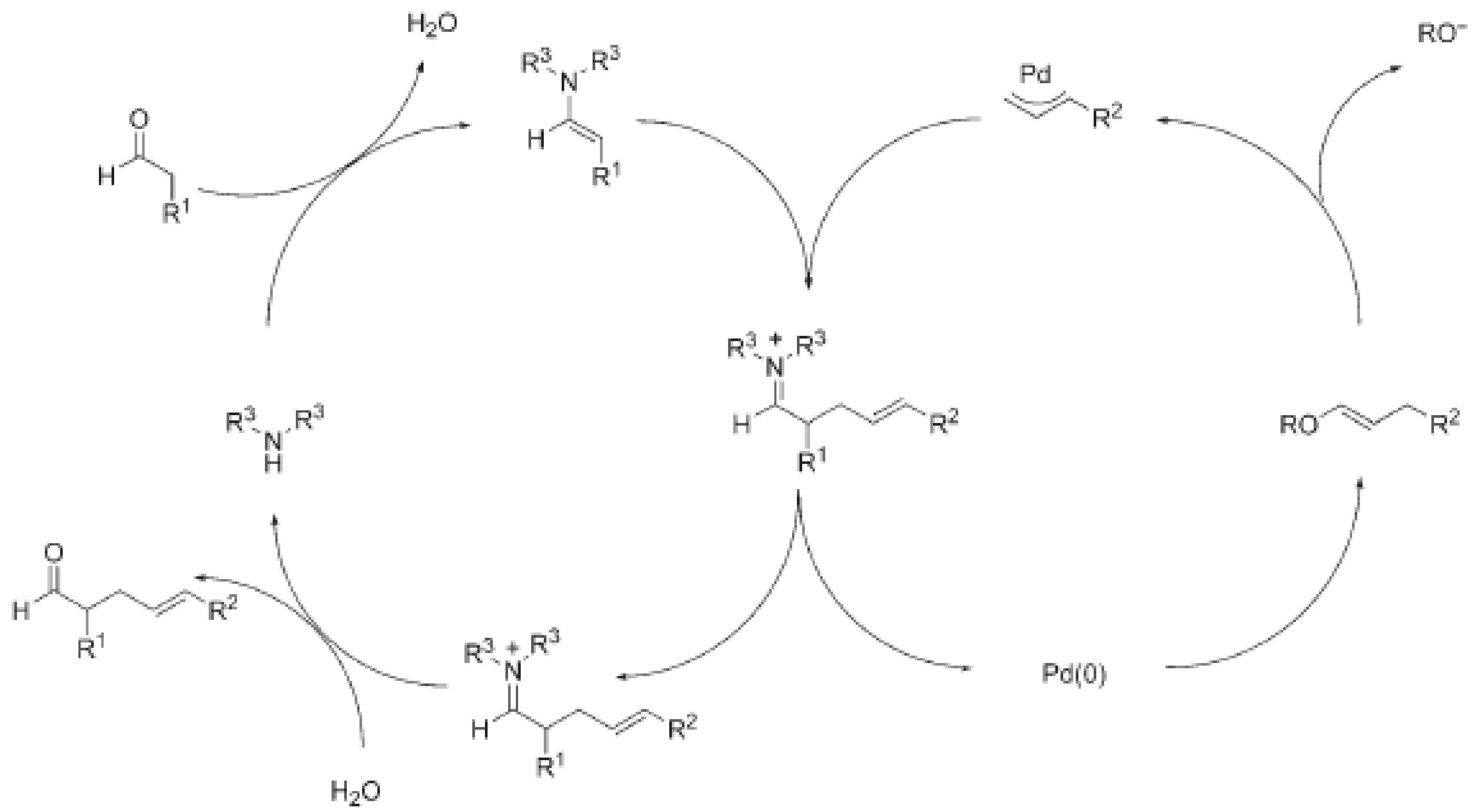


Entry	Amine catalyst	3a	
		t [h]	Yield [%][b]
1		16	72
2		16	45
3		16	20
4		16	37

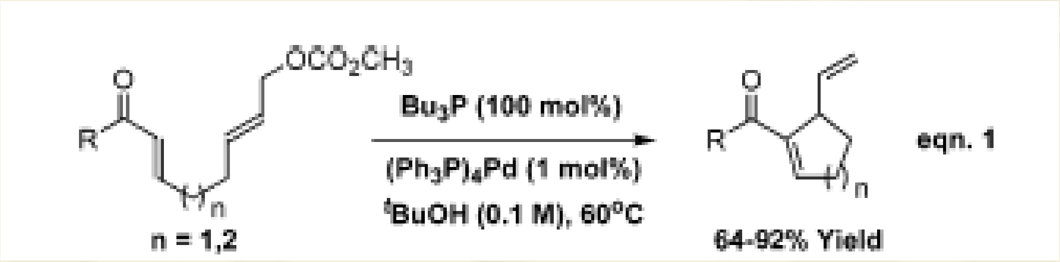

OAc
R1
H
O
R
1
[Pd(PPh3)4]
(5 mol%)
N
H
(10 mol%)
DMSO, RT
2
NaBH4
OH
3

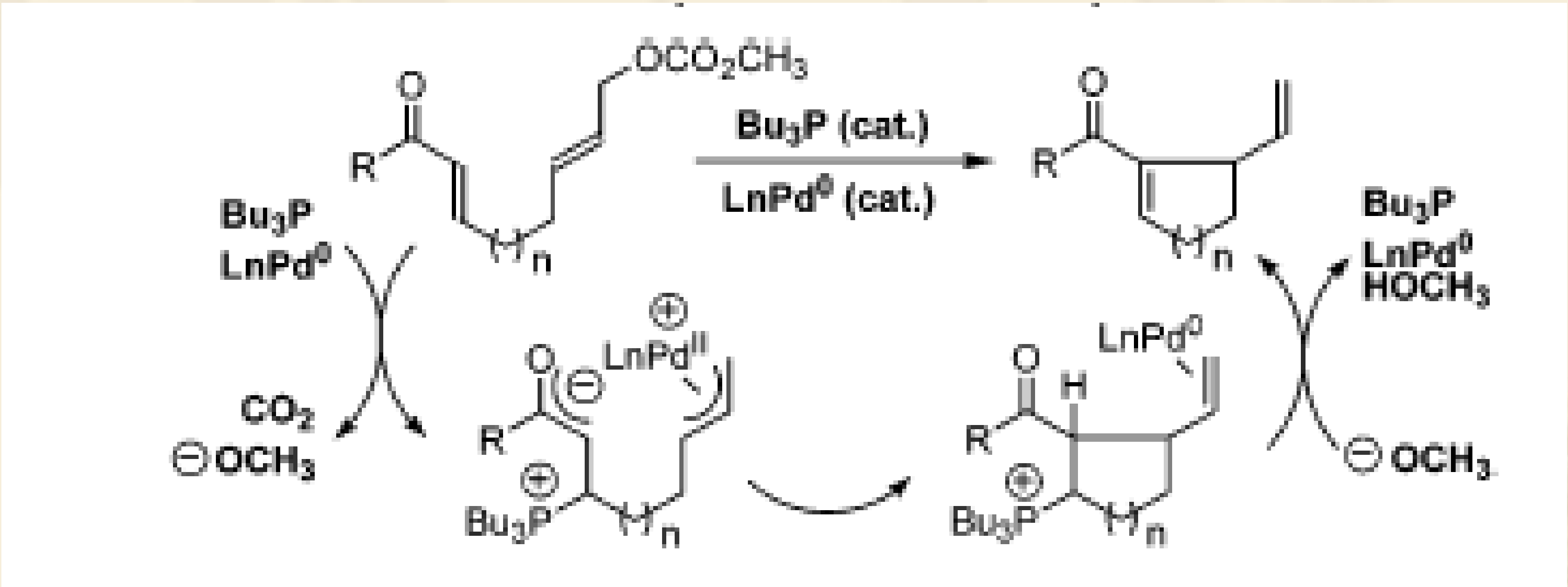

OAc
+
O
R1
R2
4
[Pd(PPh3)4]
(5 mol%)
N
H
(30 mol%)
DMSO, RT
5


Ph
OAc
+
1a
[Pd(PPh3)4]
(5 mol%)
pyrrolidine
(10 mol%)
DMSO, RT
NaBH4
OH
3f:
61% yield
4a
pyrrolidine
(30 mol%)
O
5g:
90% yield

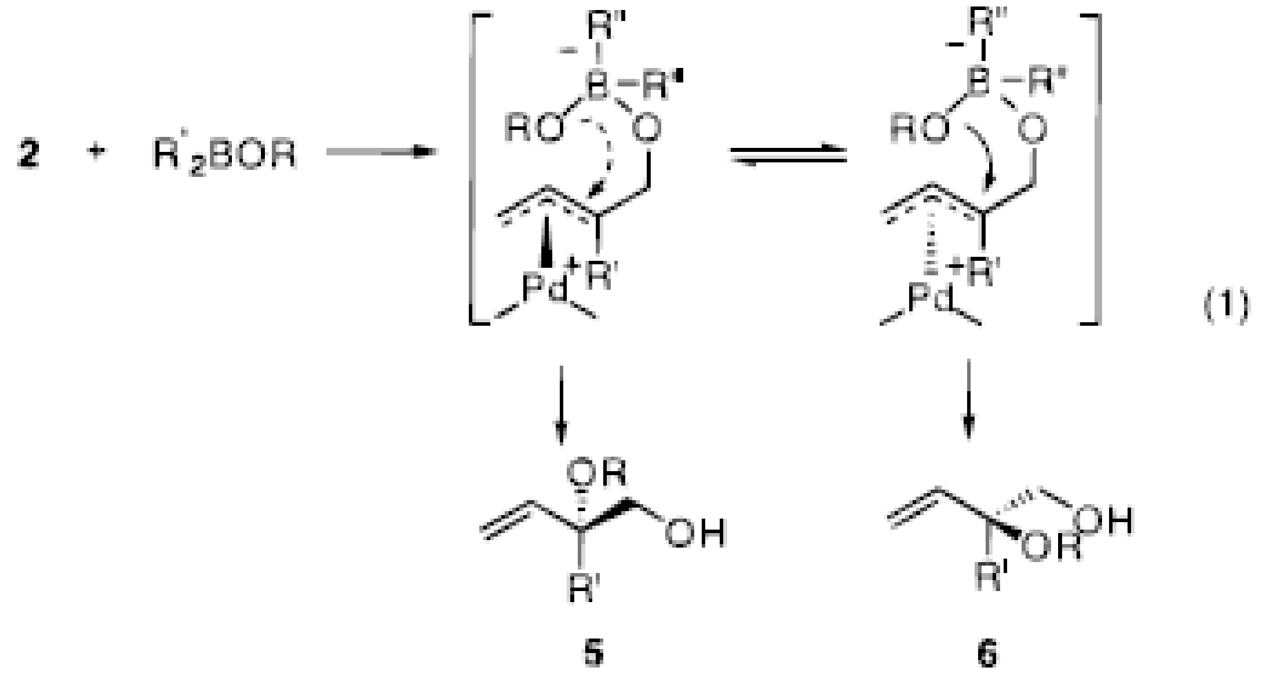


ombined transition-metal and enamine catalysis.

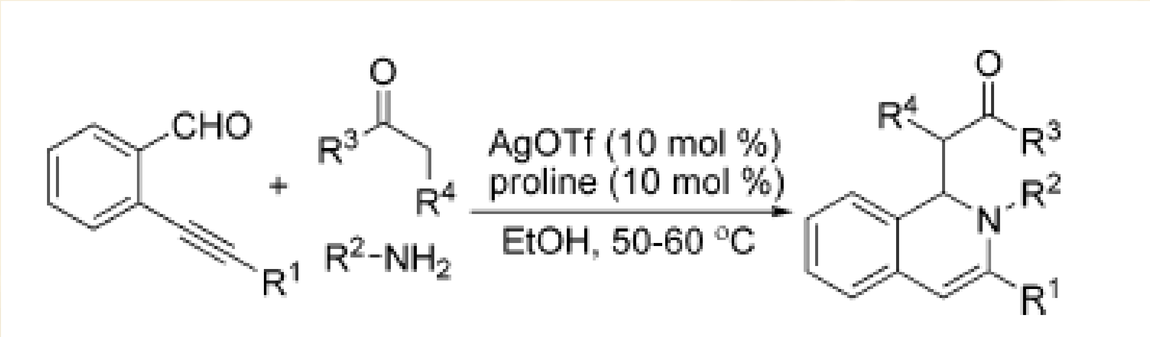




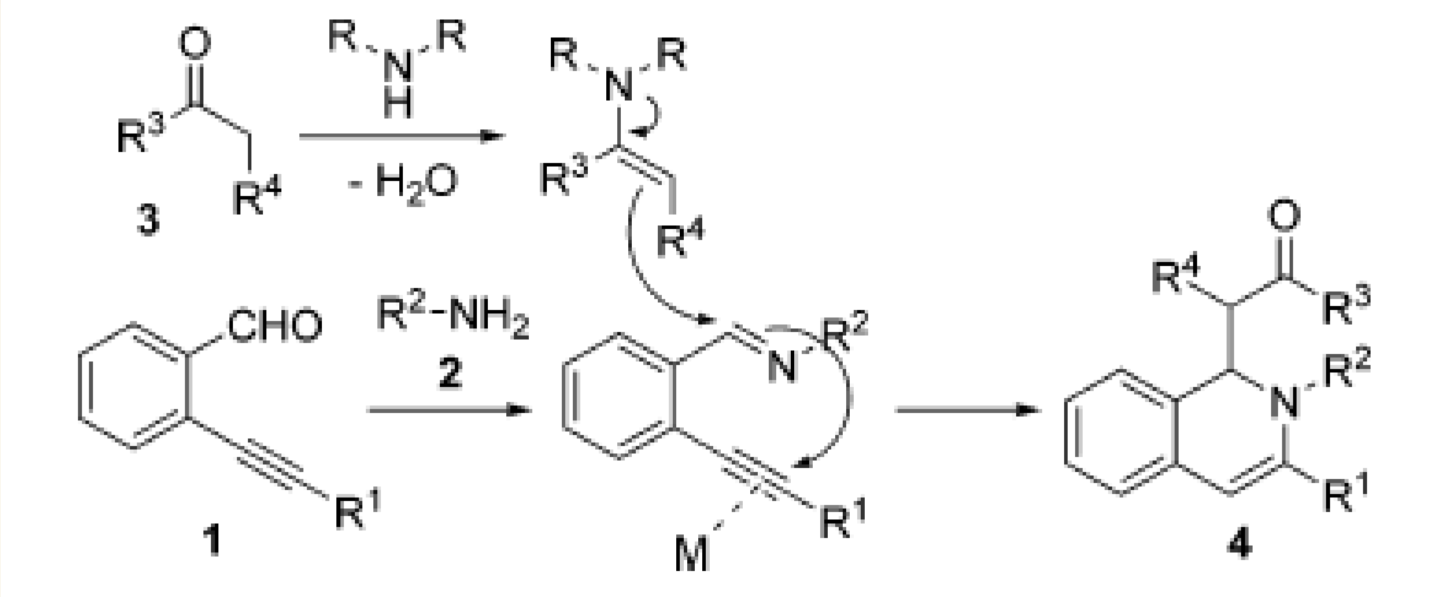
Ref.5: B. G. Jellerichs; J. R. Kong; M. J. Krische. *J. AM. CHEM. SOC*. **2003**, *125*, 7758-7759



B. M. Trost



Combination of Metal and Enamine Catalysis



Ref.6: Qiuping Ding and Jie Wu, *Org. Lett.*

有机小分子与金属共不对称催化

1. 有机小分子与金属Lewis酸的共不对称催化

2. 有机小分子与金属有机结合的不对称催化

3. 手性有机小分子离子作为金属的抗离子不对称催化

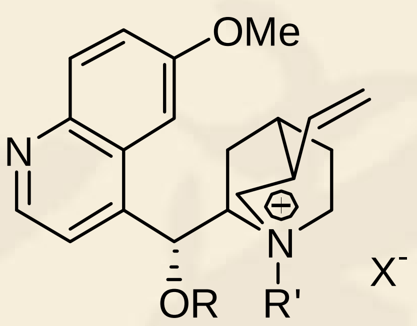
3. 手性有机小分子离子作为金属的抗离子不对称催化

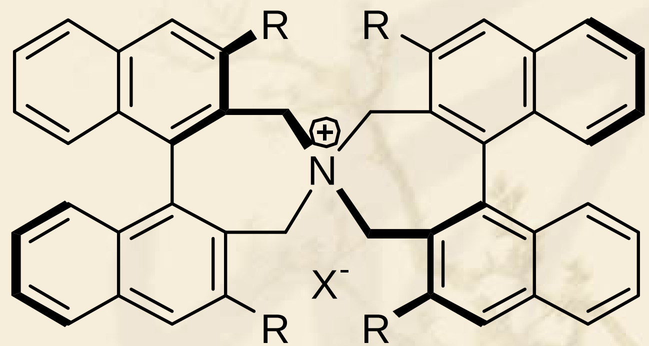
- Counterion Strategy:

  利用与反应过渡态电荷相反的离子对反应过渡态产生能量稳定影响的化学反应催化及选择性控制策略。

Ref.7: Jerome Lacour; David Linder. *Science*, **2007**, *317*, 462-463

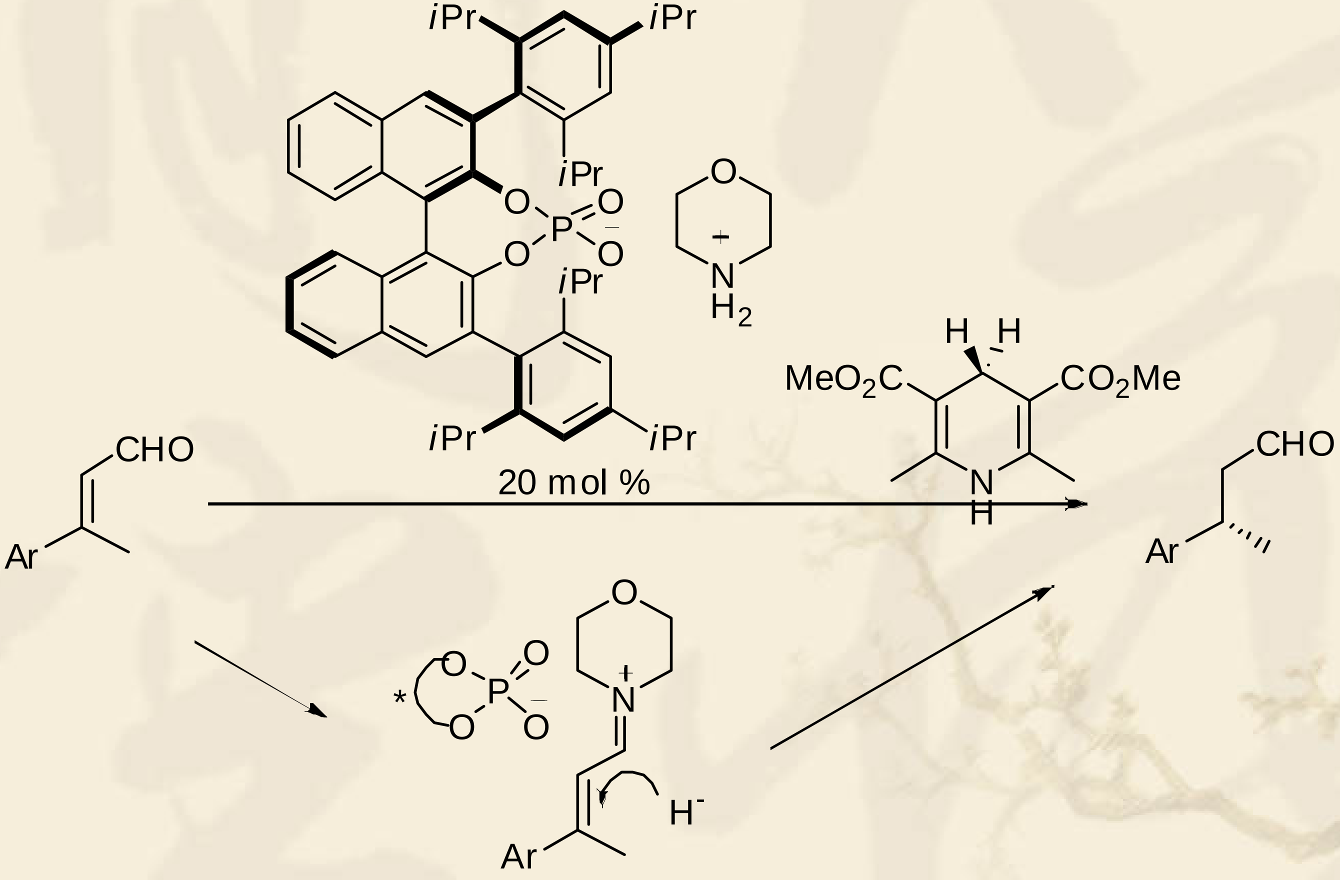
- 用正电荷的相转移催化剂催化反应，其中用手笥的相转移催化剂不对称催化反应已经得到了很好的开发。



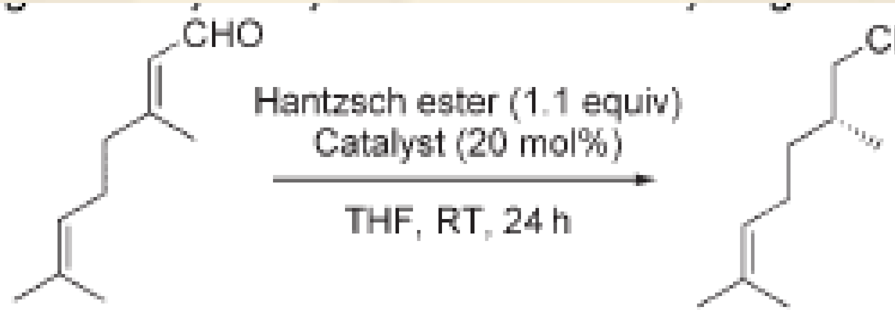


- 而利用手性负电荷作为抗离子来催化反应或对反应的手性选择性等产生影响的研究还比较手，尤其是用手性负离子与金属正离子组合不对称催化金属有机反应更少。

已报道的手性负离子与小分子催化结合的 Paper

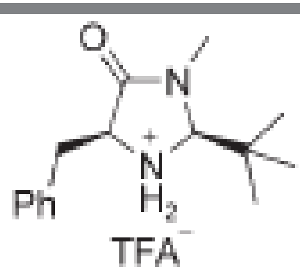
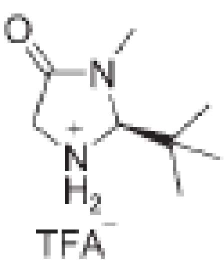


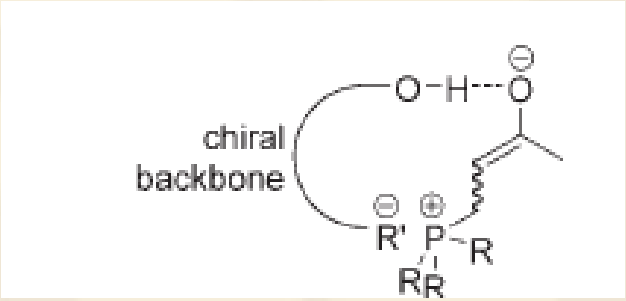
Ref.8: S. Mayer; B. List. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193 –4195

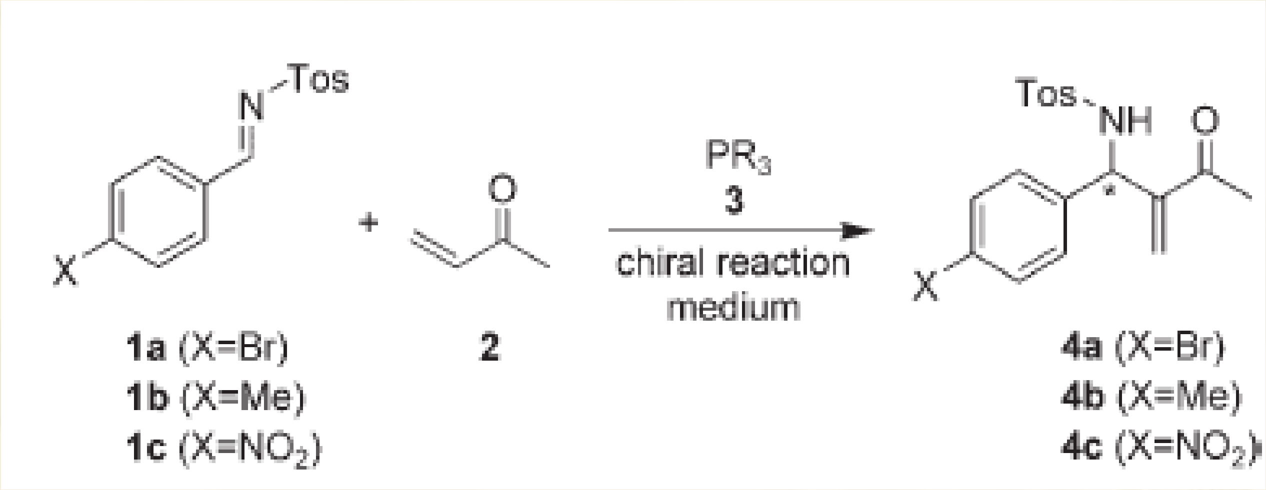


5

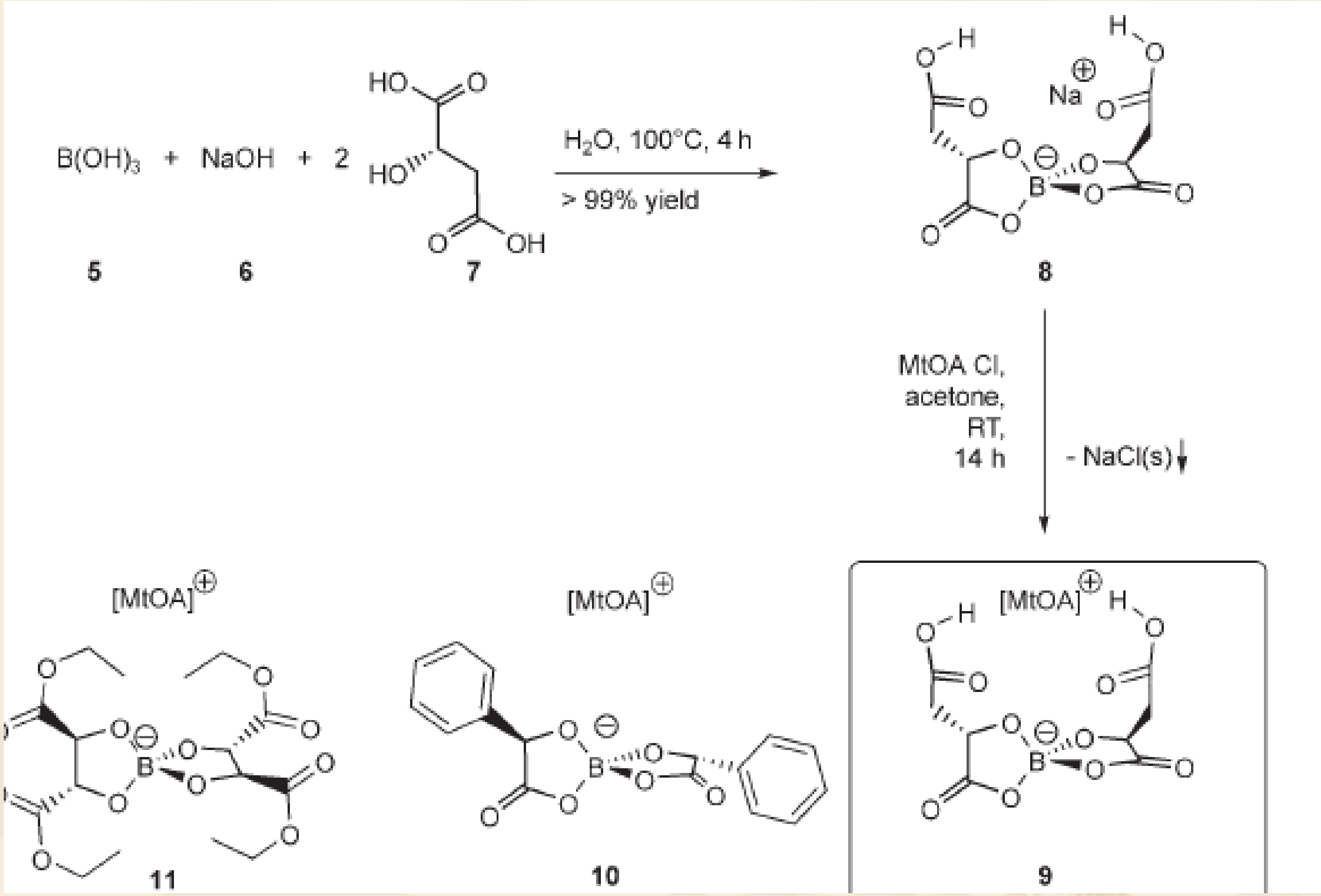
(*R*)-Citronellal (**6**)

Entry	Catalyst	Product	Yield [%]	e.r.[a]
1[b]		(*S*)-**6**	58[a]	70:30[c]
2[b]		(*S*)-**6**	82[a]	70:30[d]
3[e]	**1**	(*R*)-**6**	71	95:5





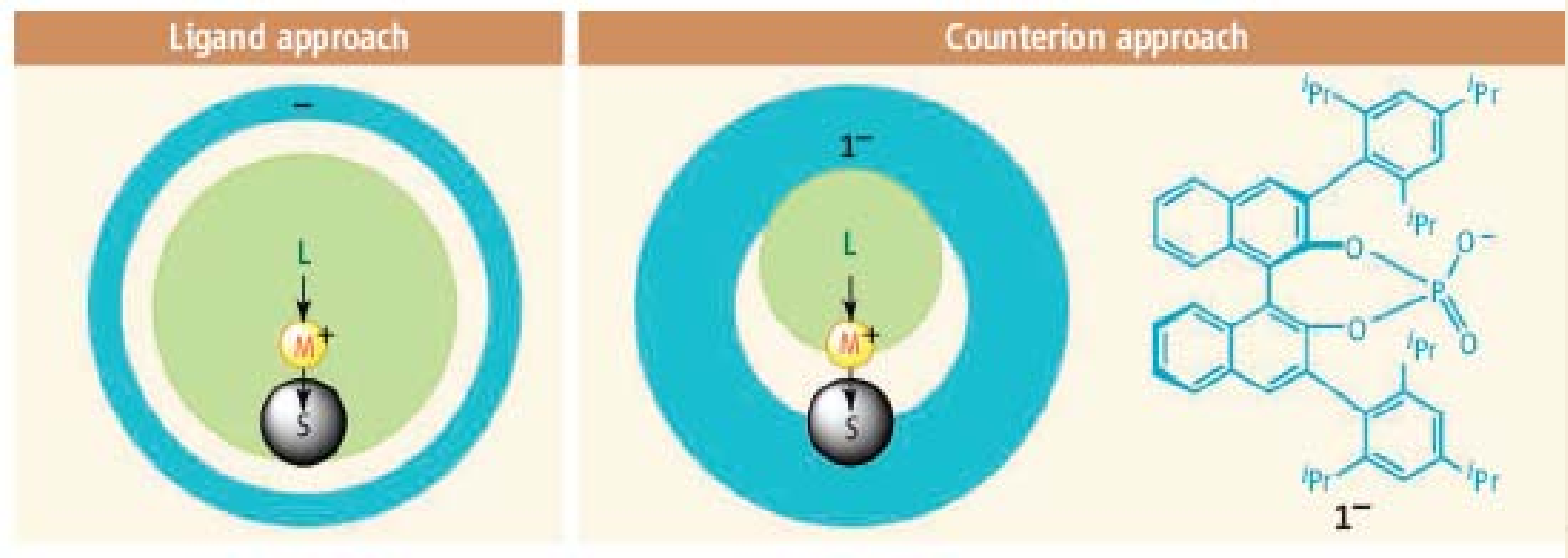
Ref.9: *Angew. Chem. Int. Ed.* **2006**, *45*, 3689 –3692



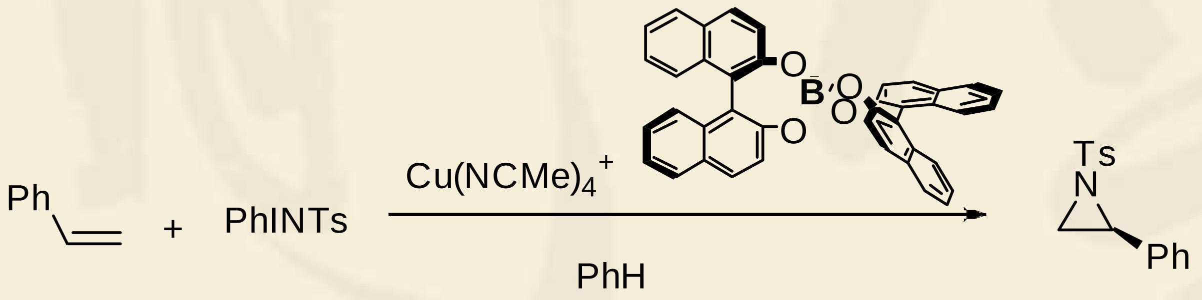
B(OH)$_3$ + NaOH + 2
HO
O
HO
O
OH
5
6
7
H$_2$O, 100°C, 4 h
> 99% yield
8
Na
MtOA Cl,
acetone,
RT,
14 h
- NaCl(s)
[MtOA]
[MtOA]
[MtOA]
B
11
10
9

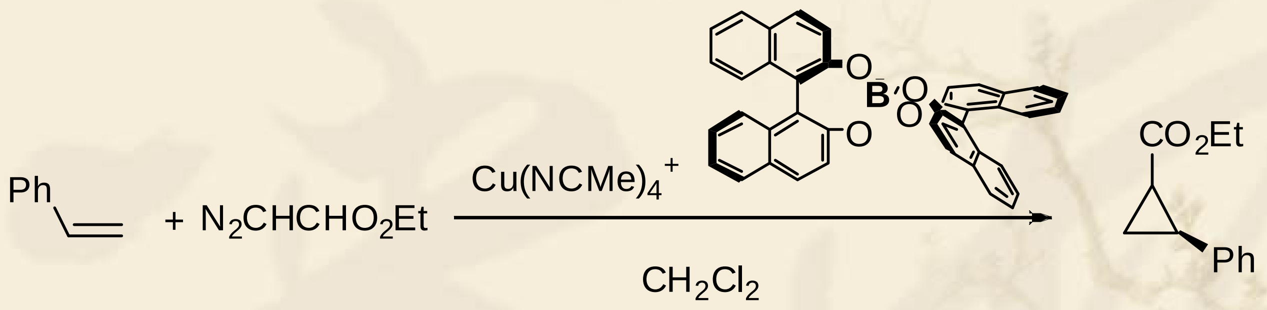
up to 84% *ee*

手性负离子与金属正离子组合不对称催化金属有机反应



已报道的手性负离子与金属有机结合的 Paper





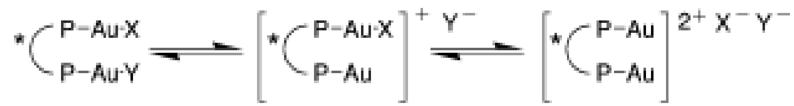
Ref.10: D. B. Llewellyn; D. Adamson; B. A. Arndtsen. *Org. Lett.* **2000**. *2*, 4165-4168

Ref.11: D. B. Llewellyn; B. A. Arndtsen. *Tetrahedron Asymmetry*. **2005**, *16*, 1789

Breakthrough: 手性磷酸与Au催化

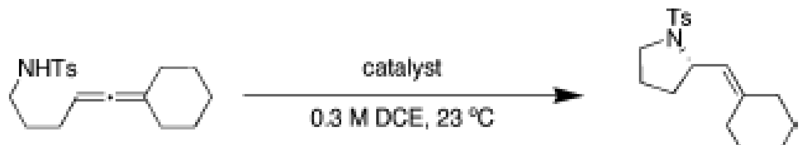
- Au催化的反应中，
- 由于Au的特殊配
- 位（二配位），
- 有很多反应都是
- 受负离子影响很
- 大的如：

Scheme 1. Dinuclear Gold(I)–Phosphine Complexes



A B C

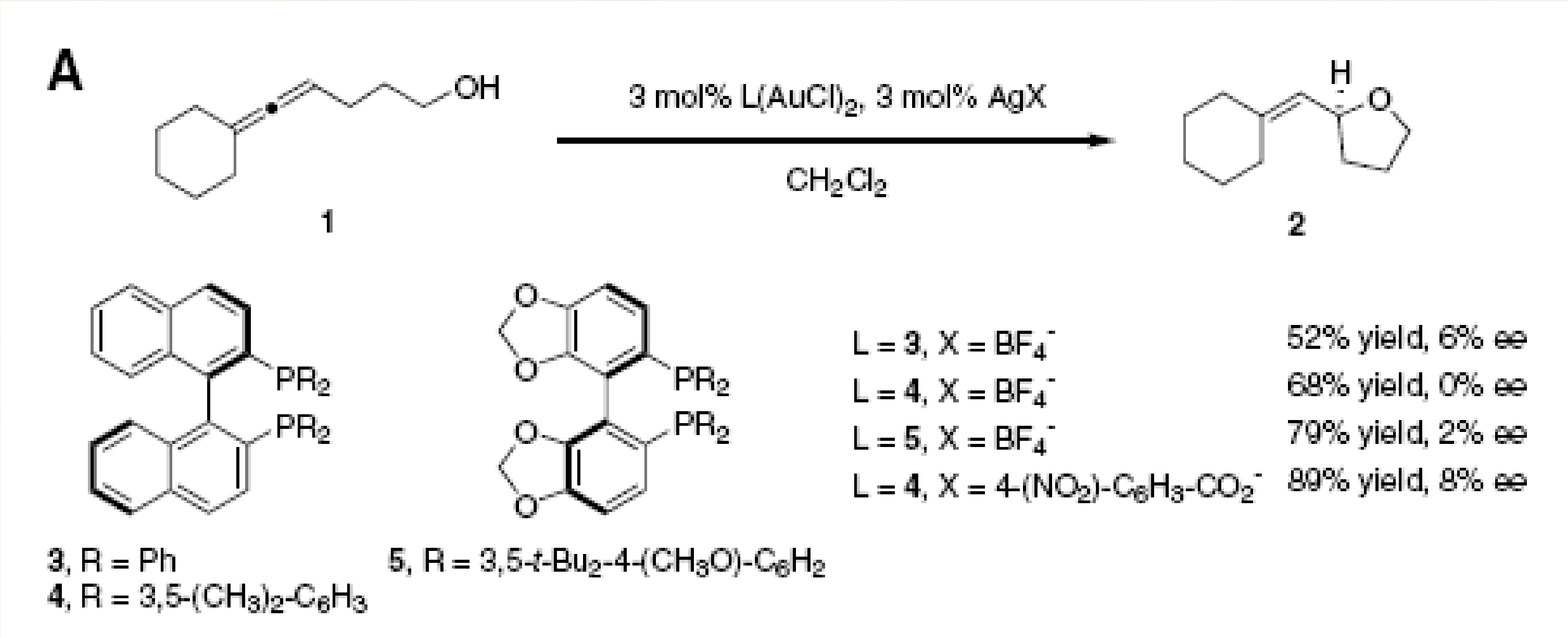
Table 1. Gold(I)-Catalyzed Asymmetric Hydroamination



1 2

entry	catalyst	time (h)	yield[a] (%)	ee[b] (%)
1	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgBF$_4$[c]	0.5	82	1
2	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 3 mol % AgBF$_4$[c]	0.5	81	51
3	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgOBz[c]	24	27	98
4	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgOPNB[c,d]	24	76	98
5	3 mol % (*R*)-xylyl-BINAP(AuCl)$_2$; 6 mol % AgODNB[c]	17	82	95
6	3 mol % (*R*)-xylyl-BINAP(AuOPNB)$_2$ (4)	17	88	98
7	3 mol % (*R*)-BINAP(AuOPNB)$_2$ (5)	15	82	93
8	3 mol % (*S*)-BINAP(AuOPNB)$_2$ (6)	15	86	94[f]
9	3 mol % (*R*)-SEGPHOS(AuOPNB)$_2$ (7)	24	57	83
10	3 mol % (*R*)-SYNPHOS(AuOPNB)$_2$ (8)	24	47	92
11	3 mol % (*R*)-ClMeOBiPHEP(AuOPNB)$_2$ (9)	15	85	97

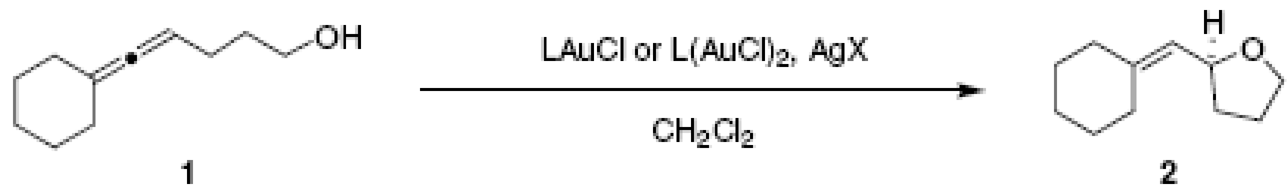
Ref.12: R. L. LaLonde; B. D. Sherry; E. J. Kang; F. D. Toste. *J. Am. Chem. Soc*. **2007**, *129*, 2452–2453

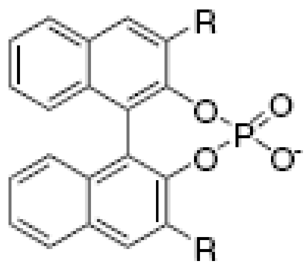


只有Au能催化该反应，但用手性配体只有少数大位阻的底物可以取得较好的ee，

Ref.13: G. L. Hamilton; E. J. Kang; M. Mba; F. D. Toste. *Science*, **2007**, *317*, 496-499

B



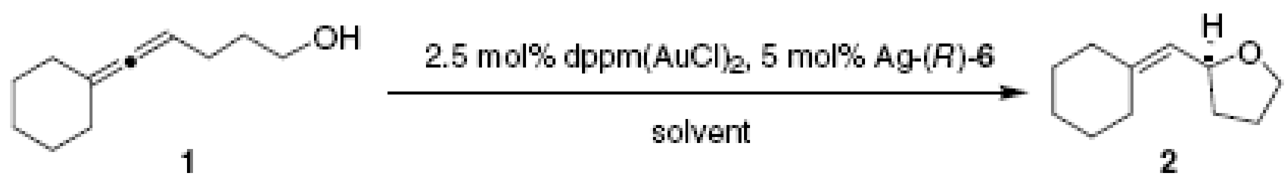


6, R = 2,4,6-*i*-Pr_3-C_6H_2

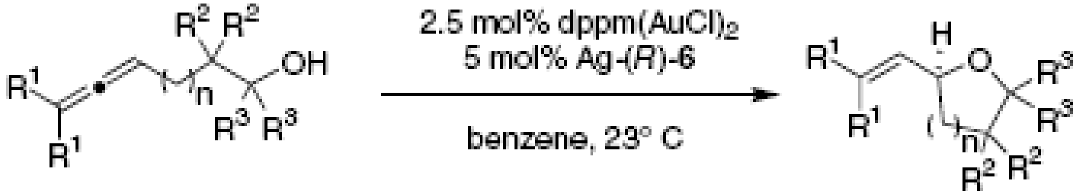
L = Ph_3P (5 mol%), X = (*R*)-**6** (5 mol%) — 89% yield, 48% ee

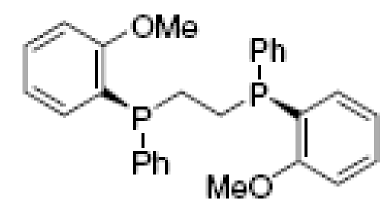
L = dppm (2.5 mol%), X = (*R*)-**6** (5 mol%) — 76% yield, 65% ee

C



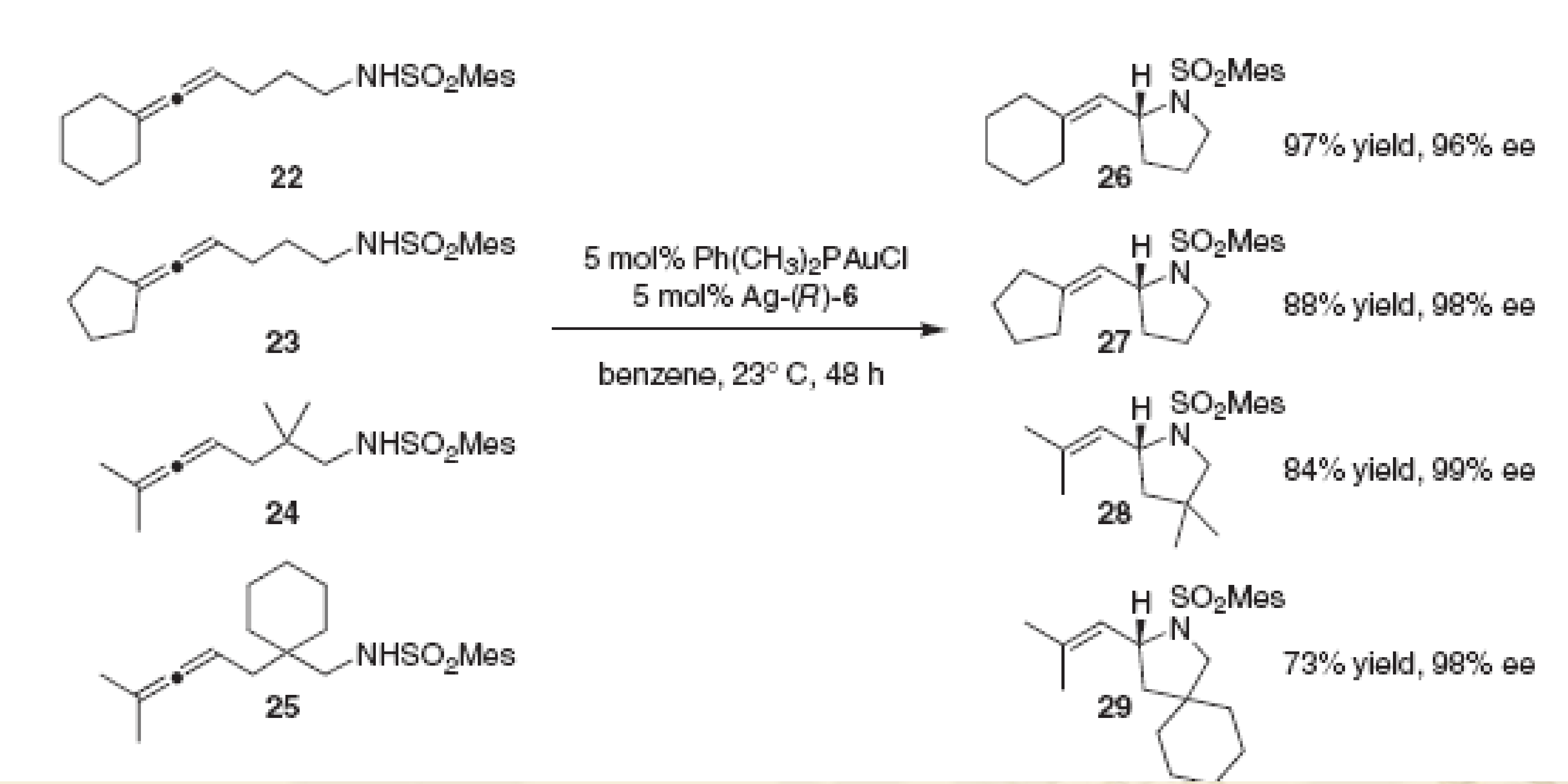
CH_3NO_2	60% yield, 18% ee	THF	83% yield, 76% ee
acetone	71% yield, 37% ee	benzene	90% yield, 97% ee





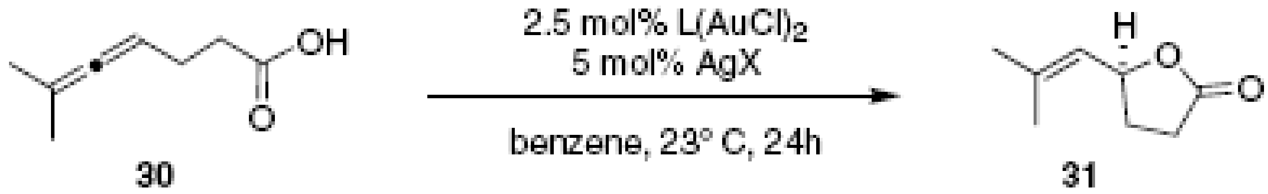
7

Entry	Substrate	n	R^1	R^2	R^3	Time (h)	Product	% Yield	% ee
1	**1**	1	$-(CH_2)_4-$	H	H	1	**2**	90	97
2	**8**	1	CH_3	H	H	1	**15**	91	95
3	**9**	1	CH_2CH_3	H	H	5	**16**	89	96
4	**10**	1	$-(CH_2)_4-$	H	CH_3	2	**17**	79	99
5	**11**	1	$-(CH_2)_4-$	H	Ph	30	**18**	86	92
6	**12**	1	$-(CH_2)_4-$	CH_3	H	13	**19**	90	90
7	**13**	2	CH_3	H	H	15	**20**	81	90
8	**14**	2	H	H	H	24	**21**	96	92 (80)



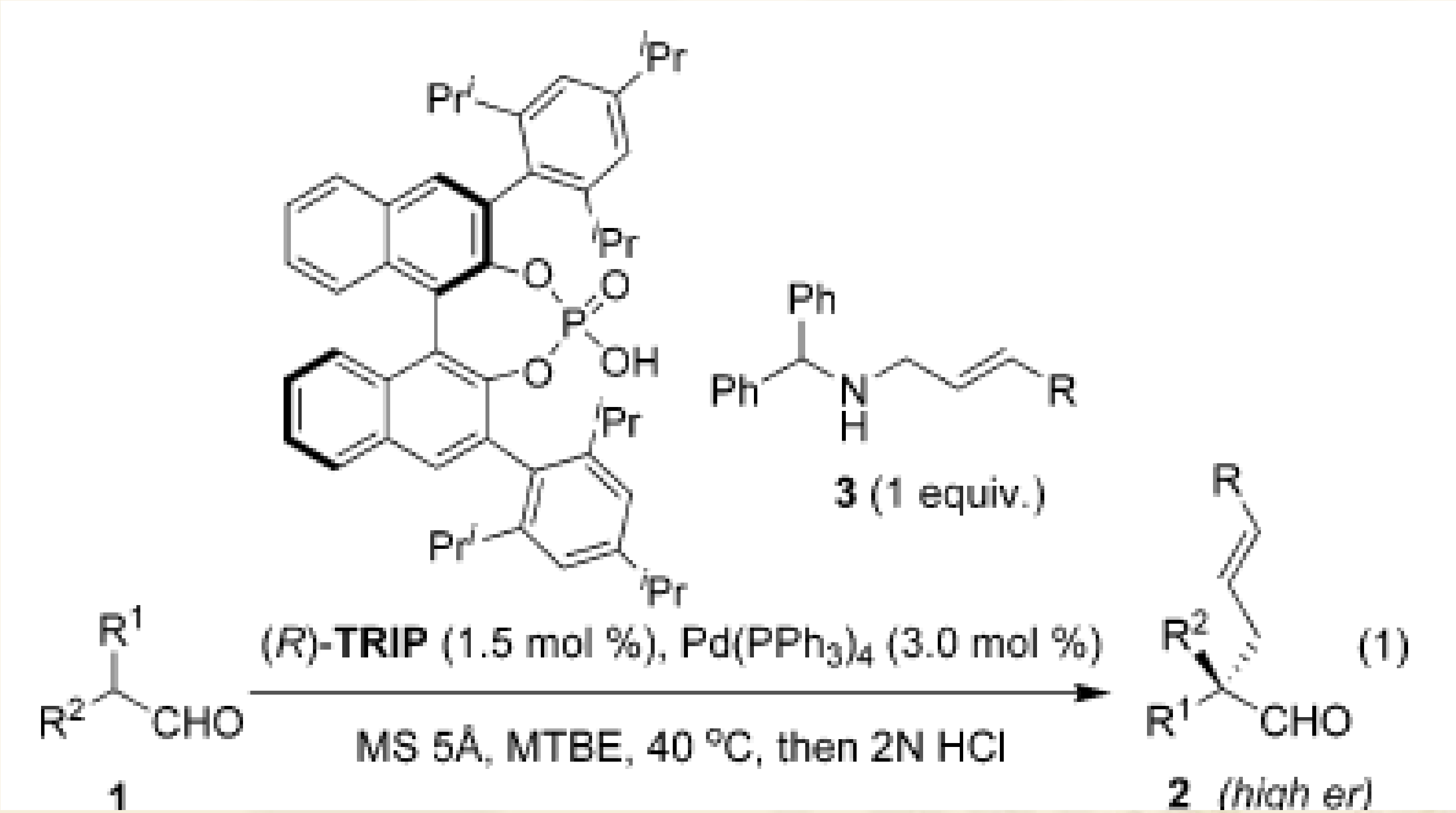
NHSO2Mes
22
23
24
25
5 mol% Ph(CH3)2PAuCl
5 mol% Ag-(R)-6
benzene, 23° C, 48 h
H SO2Mes
N
26
27
28
29
97% yield, 96% ee
88% yield, 98% ee
84% yield, 99% ee
73% yield, 98% ee

Fig. 3. Hydrocarboxylation using chiral ligand and counterion. The absolute configuration of product enantiomer in excess is noted for each entry.

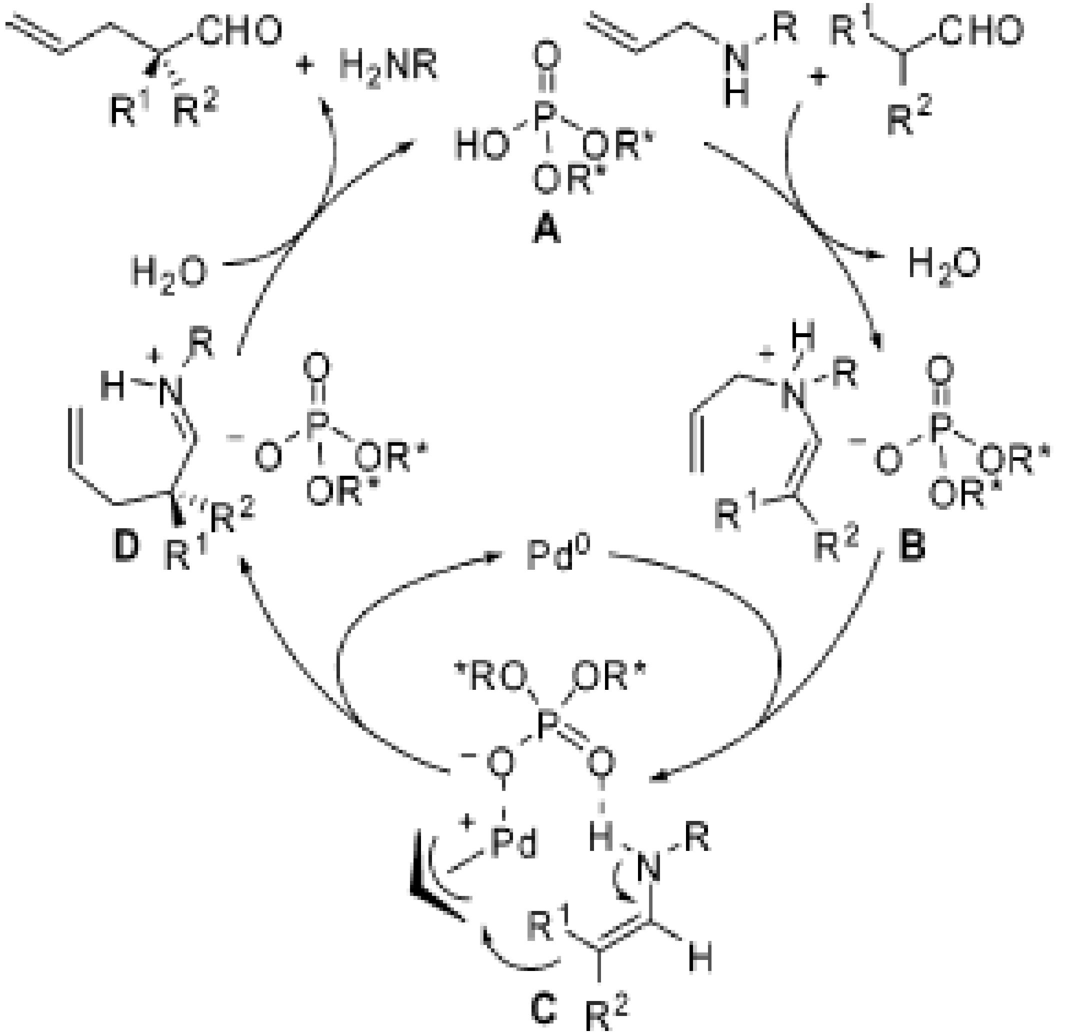


L = (*R*)-**3**, X = 4-(NO_2)-C_6H_3-COO^-	80% yield, 38% ee (*R*)
L = dppm, X = (*R*)-**6**	89% yield, 12% ee (*S*)
L = (*R*)-**3**, X = (*R*)-**6**	91% yield, 3% ee (*R*)
L = (*S*)-**3**, X = (*R*)-**6**	88% yield, 82% ee (*S*)

磷酸与Pd(0)催化的结合

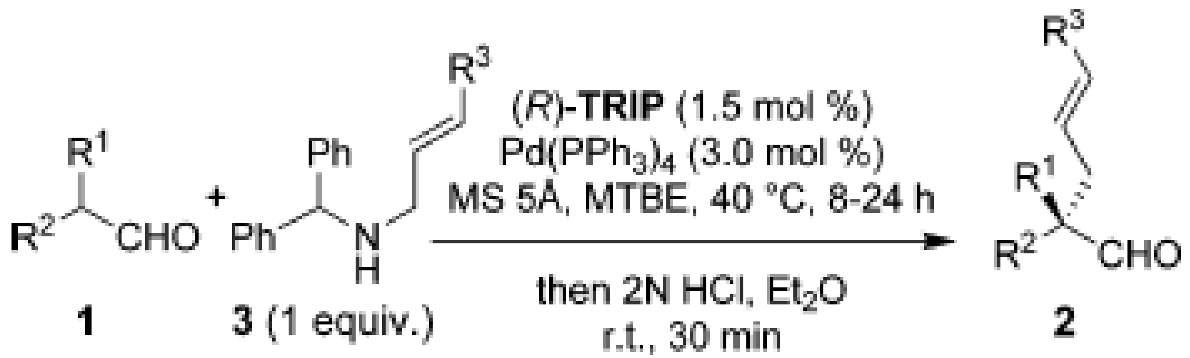


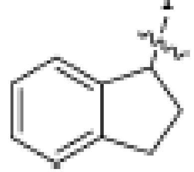
Ref.14: S. Mukherjee; B. List. *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337



(2)

α-Allylation of Aldehydes

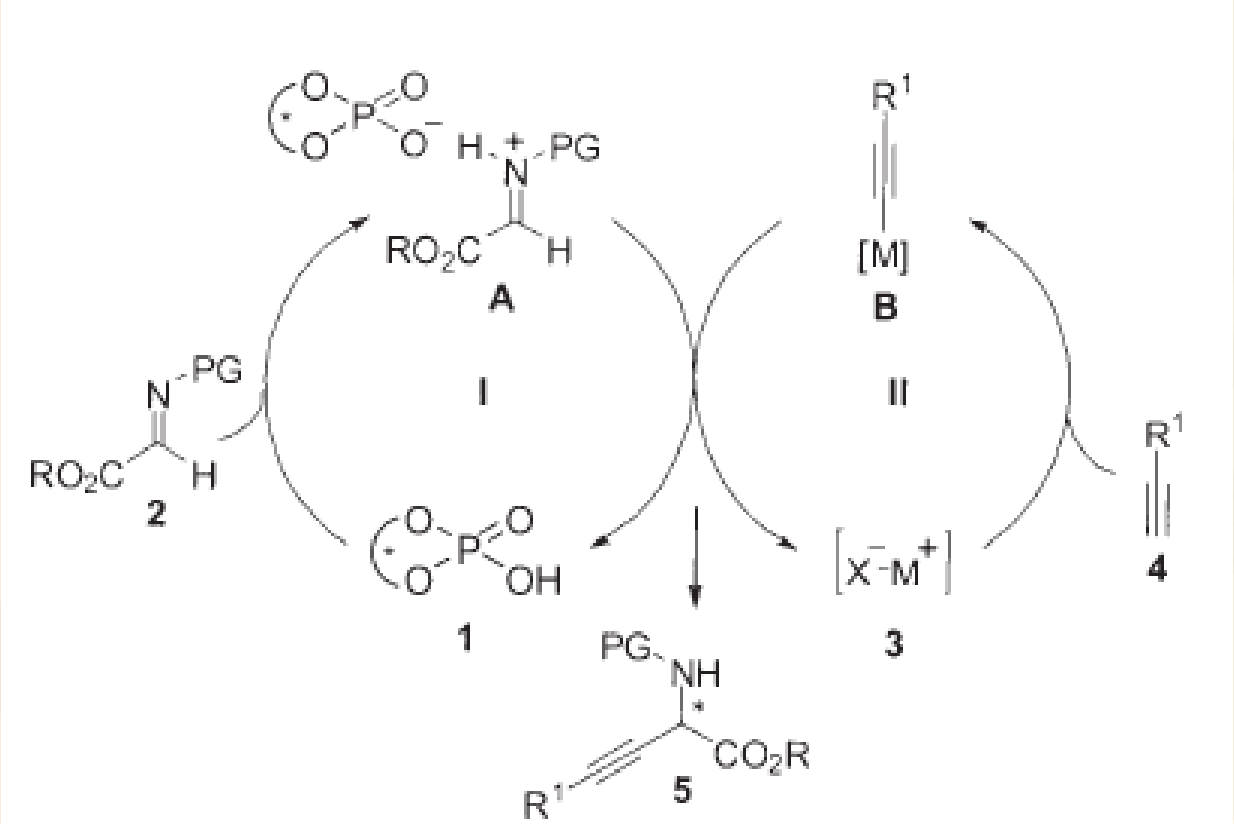


entry	R¹	R²	R³		yield (%)	er[a]
1	Me	Ph	H	**2a**	85	98.5:1.5
2	Me	4-Me-C_6H_4	H	**2b**	89	97:3
3	Me	3-Me-C_6H_4	H	**2c**	84	98:2
4	Me	3-F-C_6H_4	H	**2d**	85	98:2
5[b]	Me	2-F-C_6H_4	H	**2e**	74	97:3
6	Me	4-*i*-Bu-C_6H_4	H	**2f**	76	97.5:2.5
7	Me	2-naph	H	**2g**	71	97:3
8	Me	2-thiophenyl	H	**2h**	80	93:7
9			H	**2i**	45	95:5
10[c]	Me	*c*-hex	H	**2j**	65	85:15
11[d,e]	Me	Ph	Me	**2k**	40	96:4
12[d,e]	Me	Ph	Ph	**2l**	82	91:9

[a] From GC or HPLC. [b] Reaction run at 50 °C. [c] Reaction run at 110 °C in toluene. [d] Reaction run at 60 °C. [e] Reaction run for 72 h.

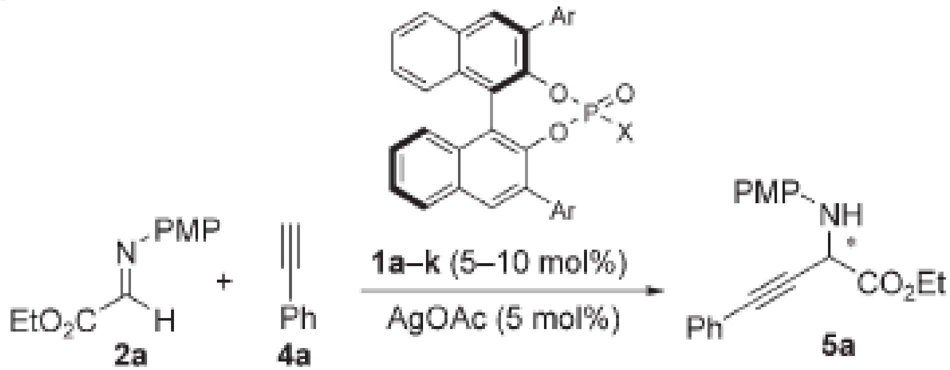
α-支链的醛酮做亲核剂发生烯丙位取代生成季碳是有挑战性的工作。

磷酸与Ag(I)催化的结合

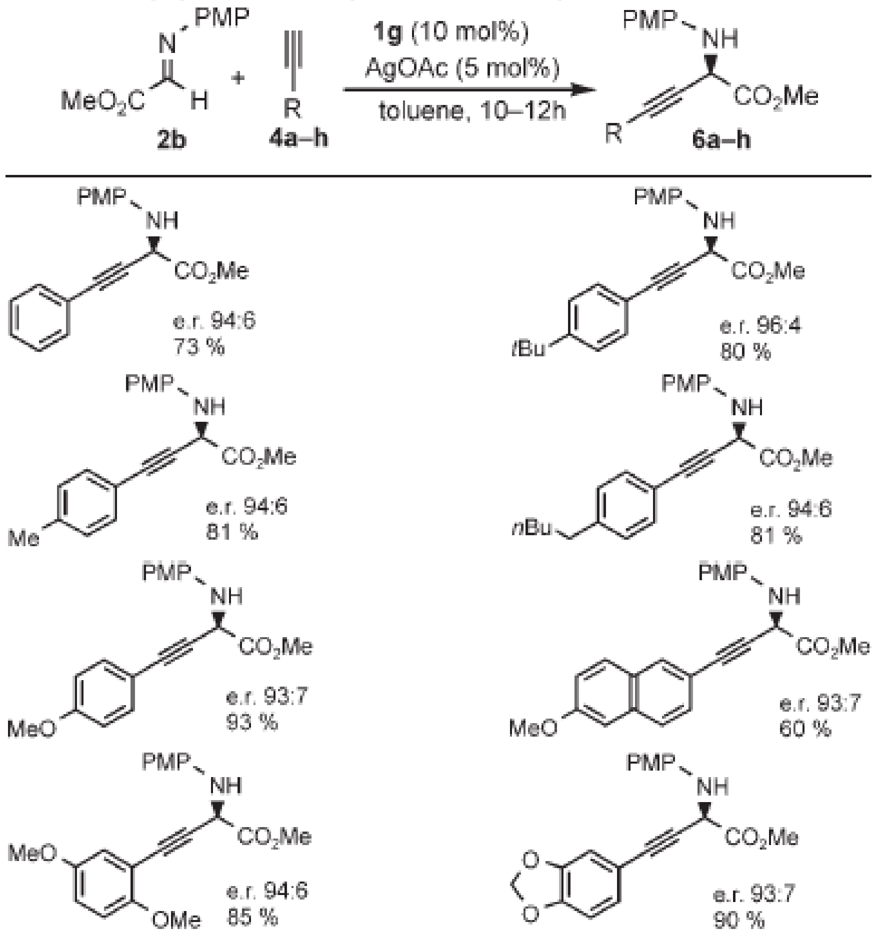


Ref.15：M. Rueping; A. P. Antonchick; C. Brinkmann. *Angew. Chem. Int. Ed.* **2007**, *46*, 6903 –6906

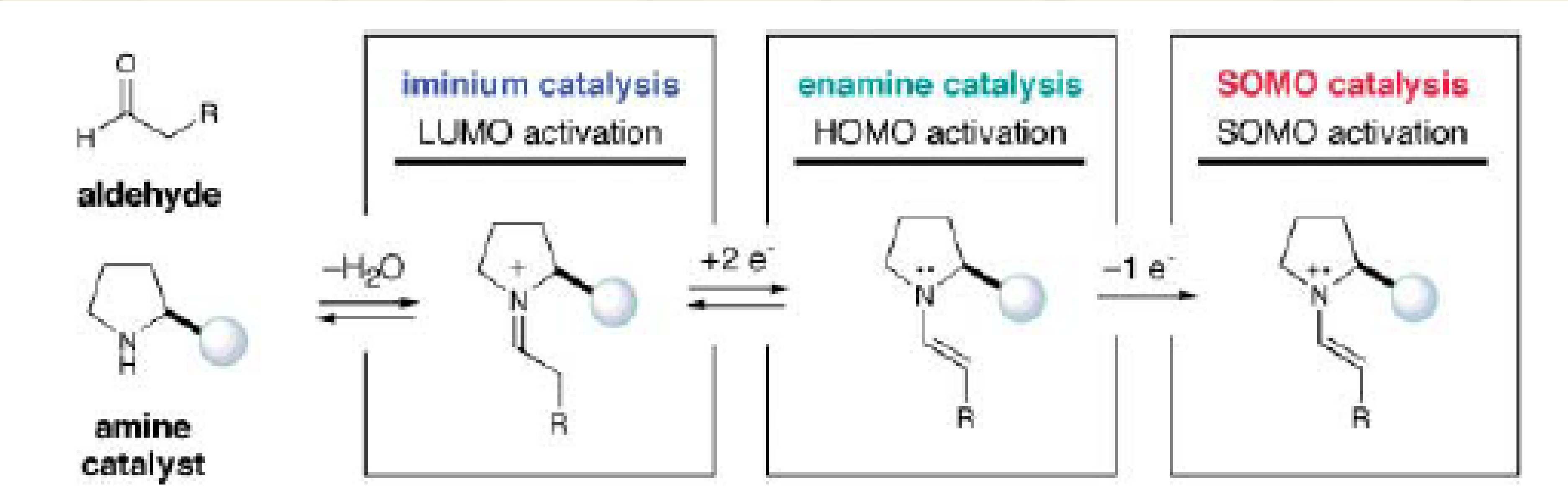
alkyne addition.

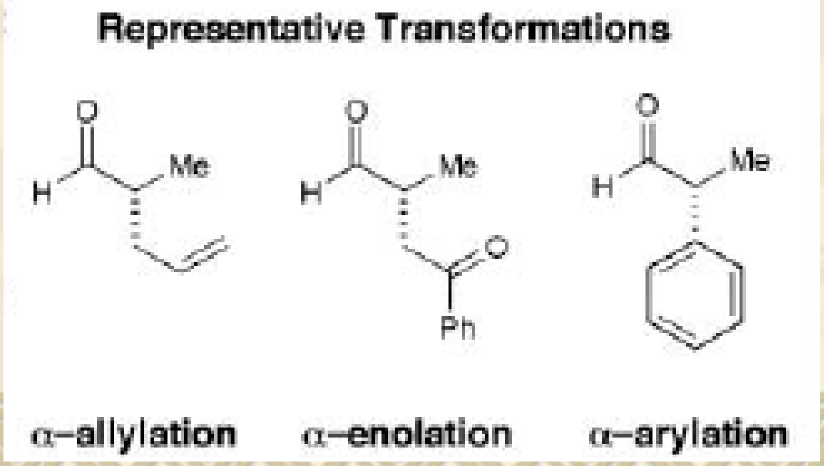


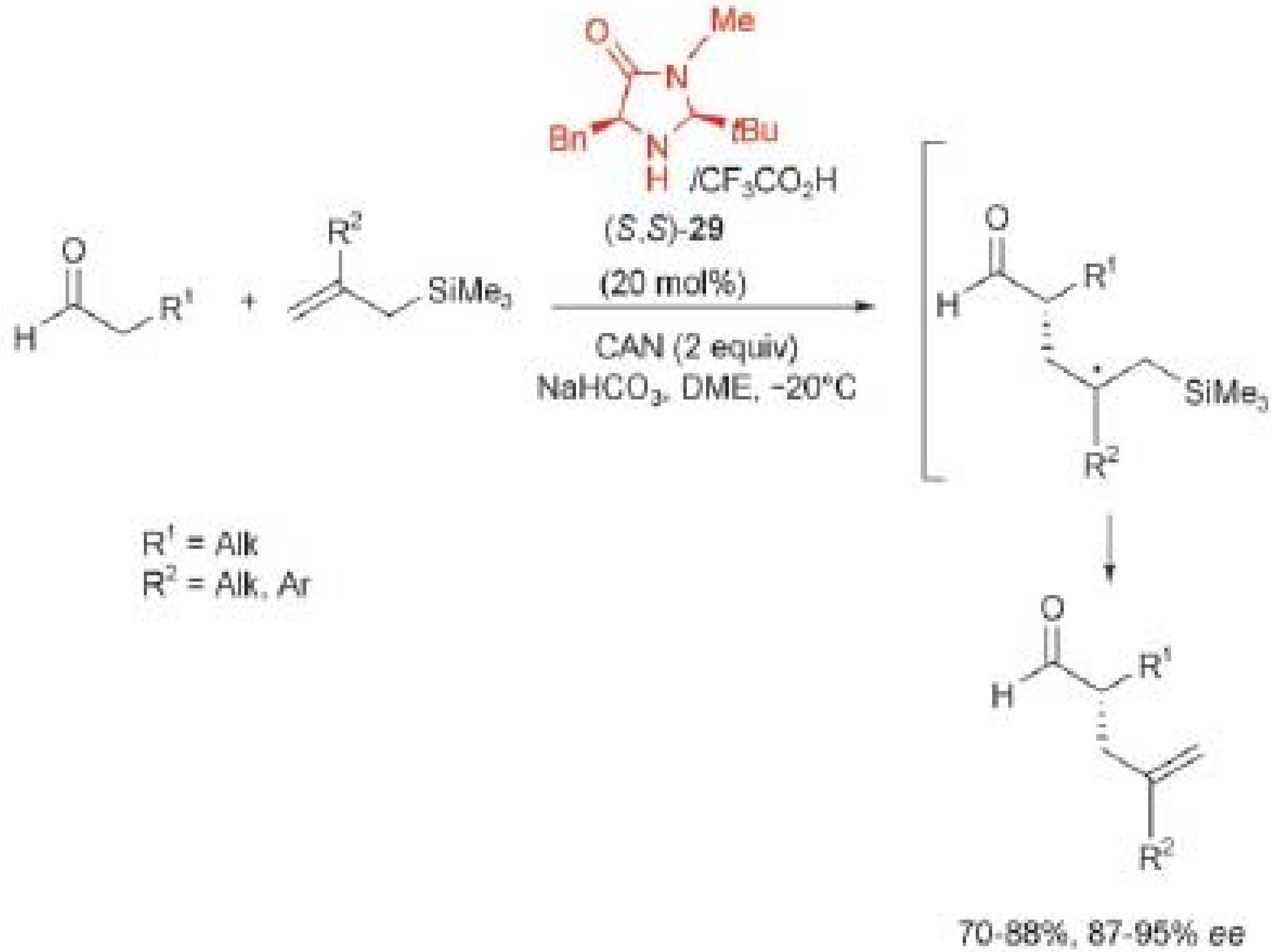
Entry[a]	MX	MX [mol%]	1g [mol%]	R	e.r.[b]
1	–	–	10	Et	n.d.[c]
2	AcOAc	10	–	Et	n.d.
3	AgOAc	5	2	Et	76:24
4	AgOAc	5	5	Et	86:14
5	AgOAc	5	10	Et	91:9
6	AgOAc	5	10	Me	94:6
7	AgOAc	5	20	Et	87:13
8	AgOBz	5	5	Et	65:35
9	Ag_2O	2.5	5	Et	55:45
10	Ag_2CO_3	2.5	5	Et	73:27
11	$AgCO_2CF_3$	5	10	Et	85:15
12	$AgSO_3CF_3$	5	10	Et	72:28
13	$AgNO_3$	5	10	Et	81:19
14	$AgBF_4$	5	10	Et	79:21
15	CuOAc	5	10	Et	92:8
16	$Cu(OAc)_2$	5	10	Et	93:7



4. SOMO Strategy

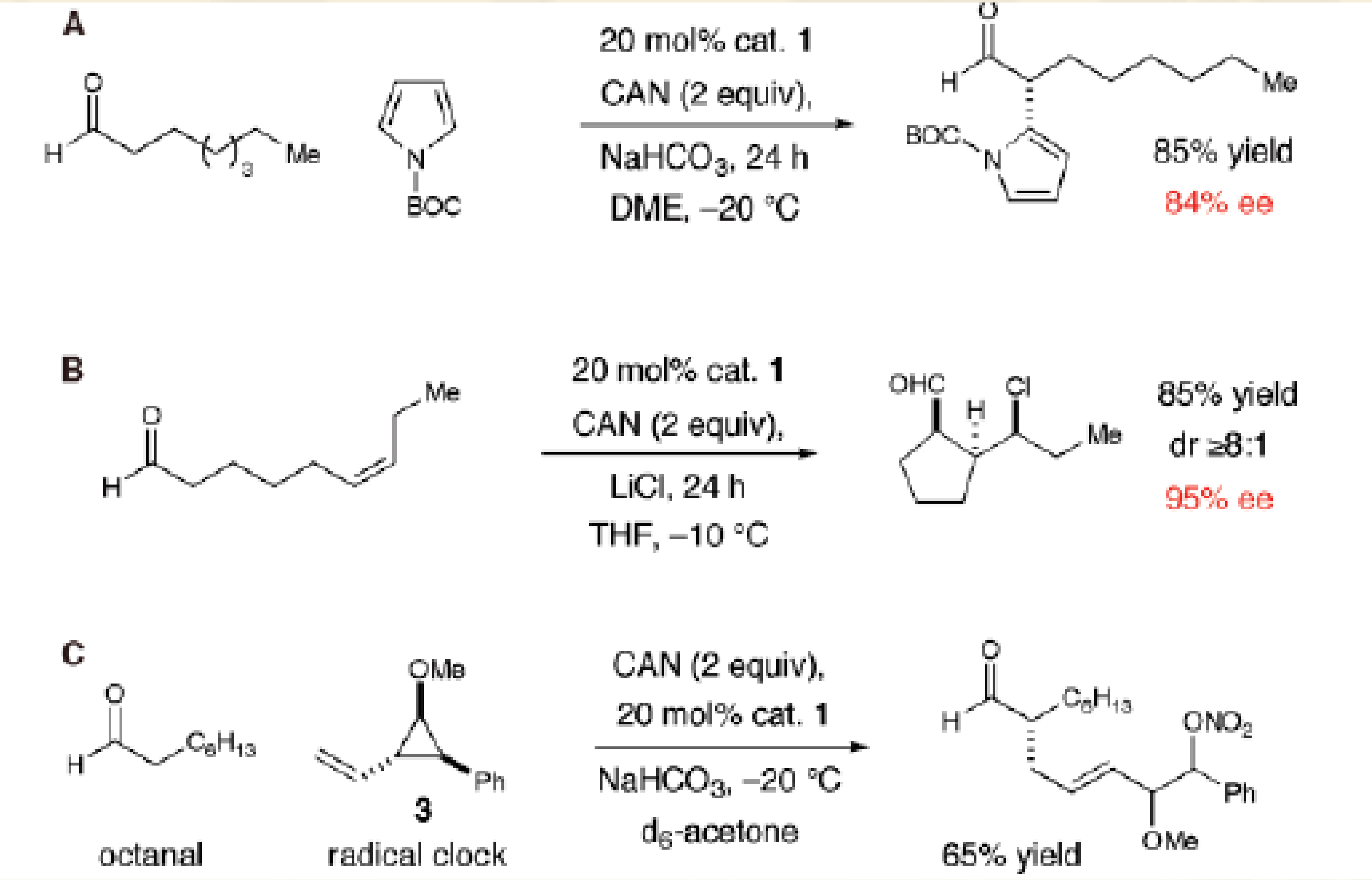


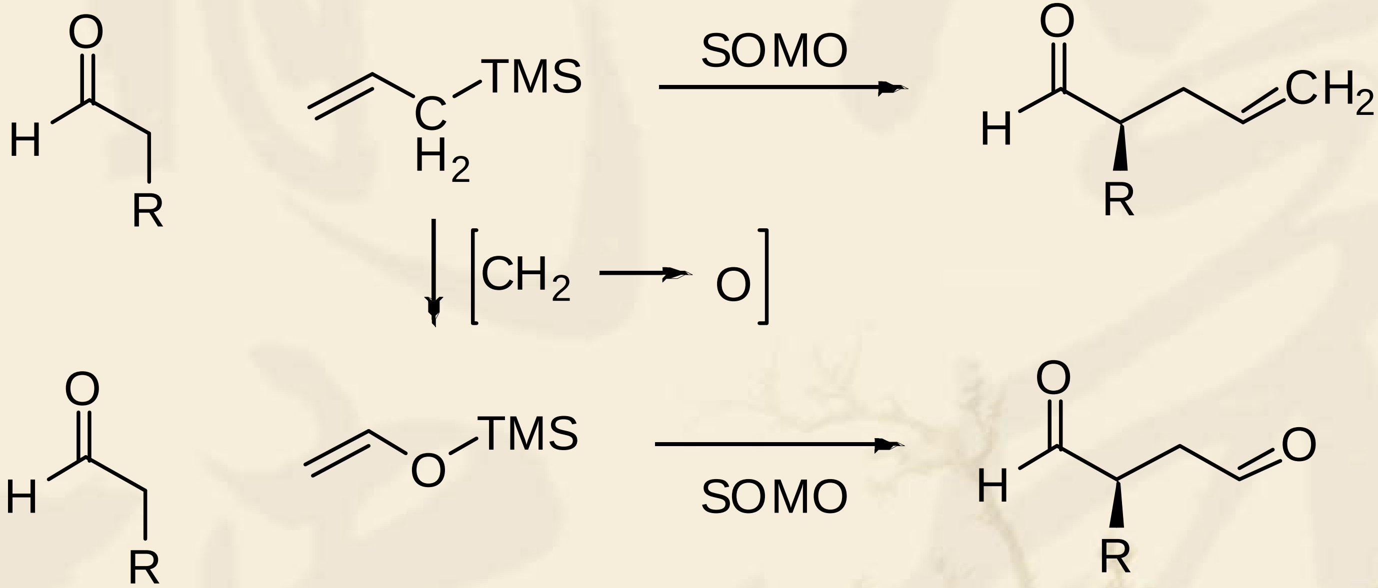




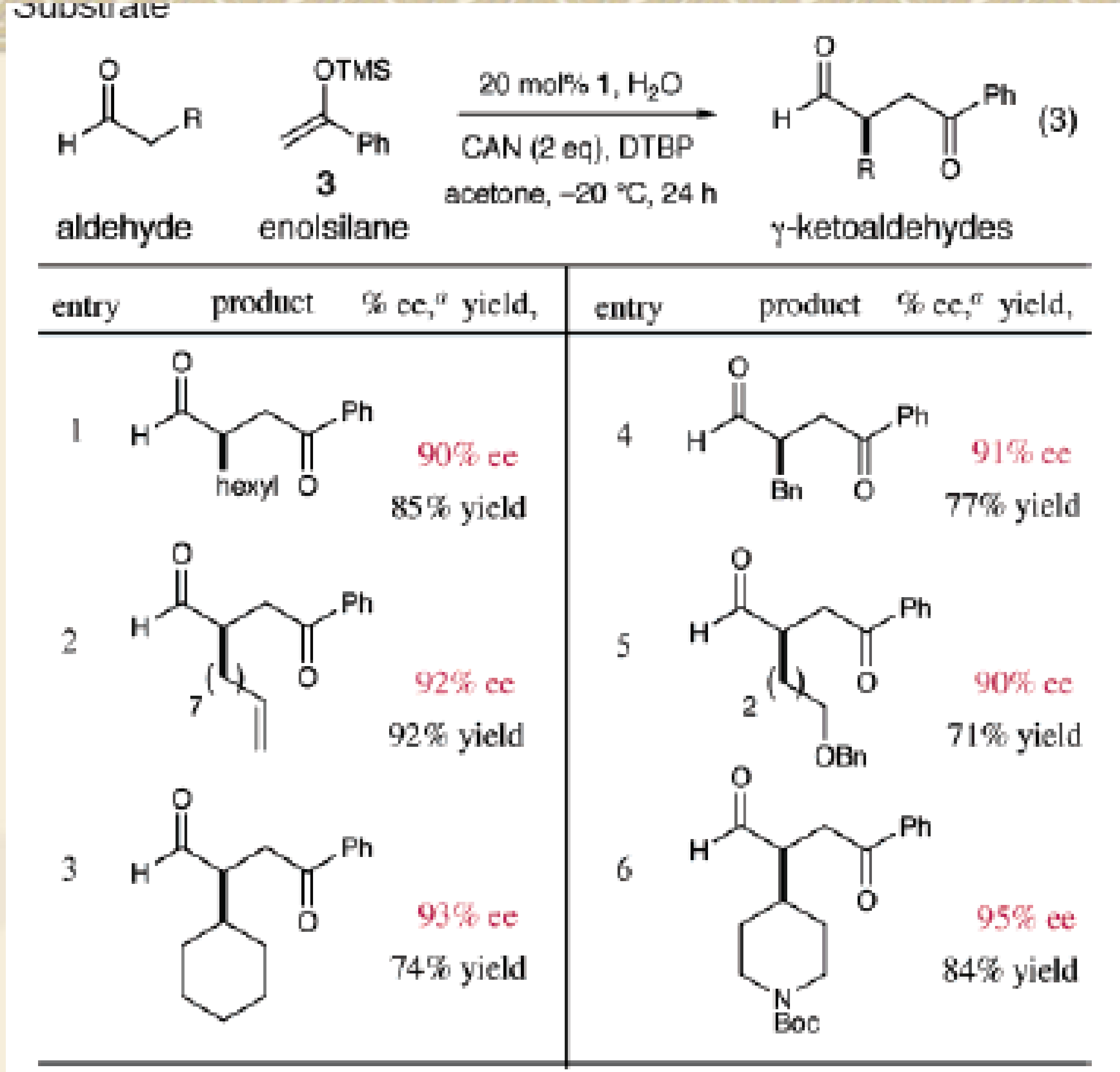
Ref.16: T. D. Beeson; A. Mastracchio; J.-B. Hong; K. Ashton; D. W. C. MacMillan.

Science. 2007, *316*, 582 – 585


A
20 mol% cat. 1
CAN (2 equiv),
NaHCO3, 24 h
DME, –20 °C
85% yield
84% ee
B
20 mol% cat. 1
CAN (2 equiv),
LiCl, 24 h
THF, –10 °C
85% yield
dr ≥8:1
95% ee
C
CAN (2 equiv),
20 mol% cat. 1
NaHCO3, –20 °C
d6-acetone
octanal
3
radical clock
65% yield

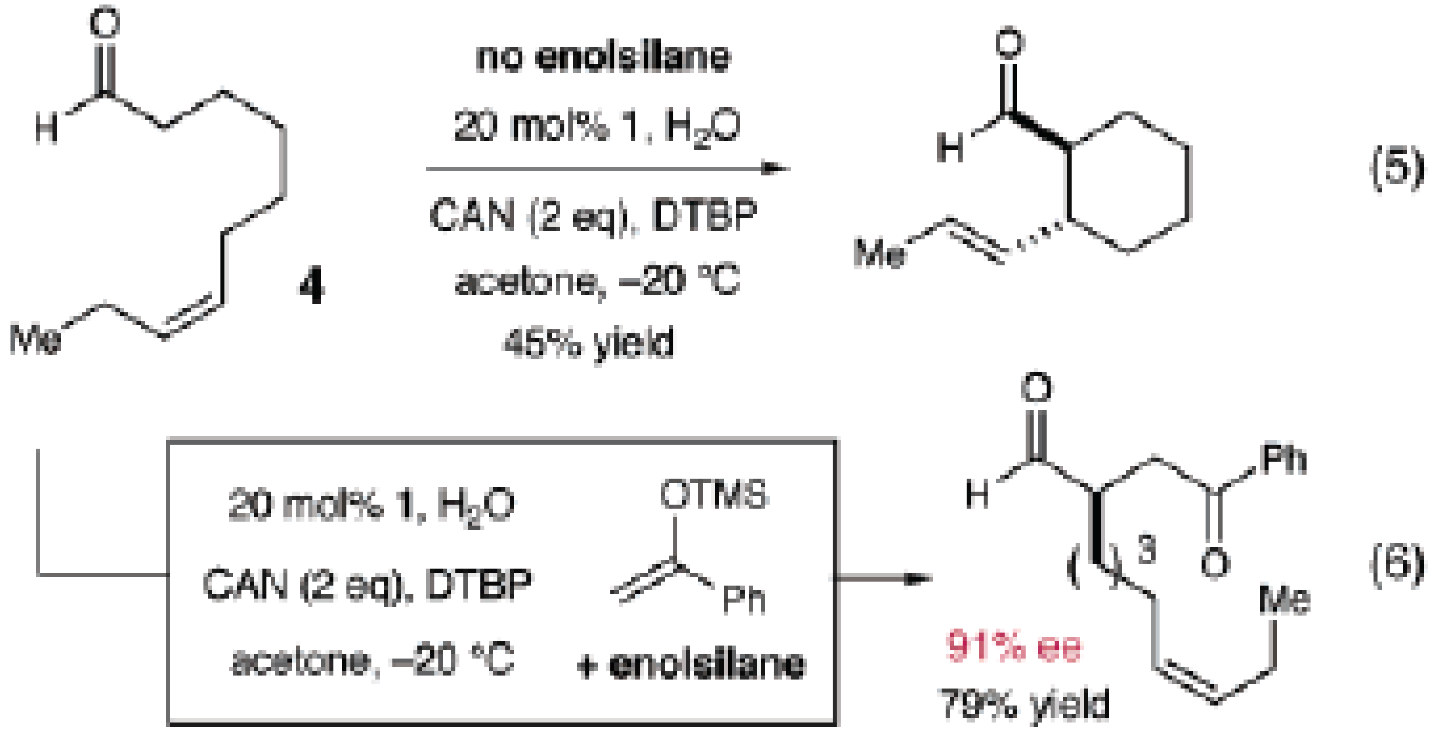


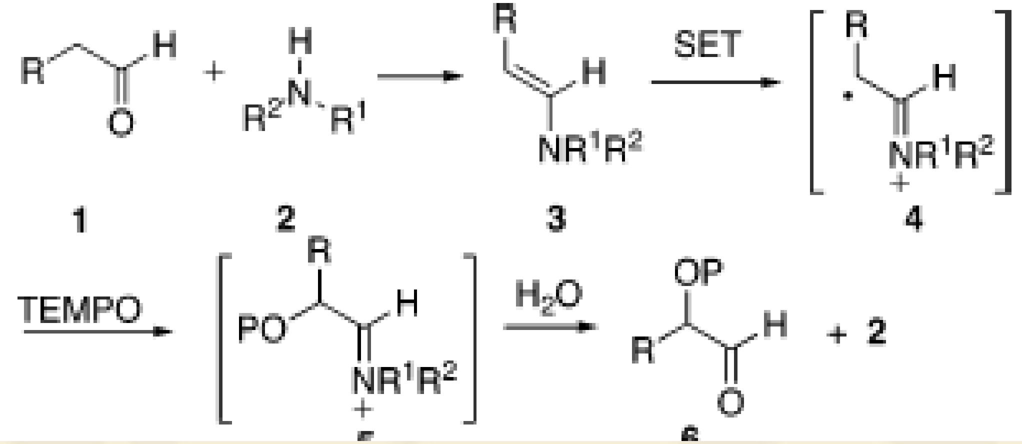
O
H
R
TMS
C
H_2
SOMO
O
H
CH_2
R
CH_2
O
O
H
R
TMS
O
SOMO
O
H
O
R

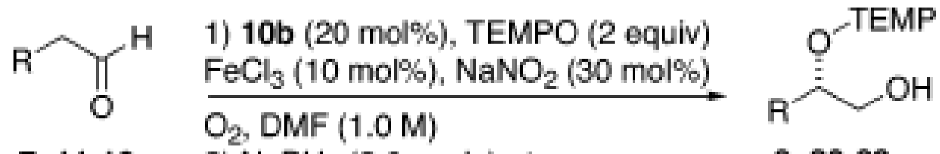


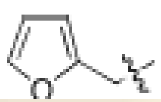
Ref.17: H.-Y. Jang; J.-B. Hong; D.W. C. MacMillan. *J. Am. Chem. Soc*. 2007, *129*, 7004 – 7005.

Intramolecular Radical Cyclization versus Intermolecular Enolation







entry	R	temp, °C	time h	yield (%)[b]	ee (%)[c]
1	C_6H_5 **11**	room temp	2	74	32
2	$C_6H_5CH_2$ **7**	room temp	2	80	71
3[d]		−10	24	68	82
4	$C_6H_5CH_2CH_2$ **12**	room temp	2	78	60
5		−10	24	64	84
6	4-$MeOC_6H_4CH_2CH_2$ **13**	room temp	2	77	81
7		−10	24	64	86
8	3,4-$(MeO)_2C_6H_3CH_2$ **14**	room temp	2	76	72
9[d]		−10	24	68	84
10	4-$NO_2C_6H_4CH_2CH_2$ **15**	room temp	2	74	75
11		−10	24	75	82
12	 **16**	room temp	2	65	84
13		−10	24	66	90

Ref.17: M. P. Sibi; M. Hasegawa; *J. Am. Chem. Soc.* **2007**, *129*, 4124 – 4125.

- Thank you!