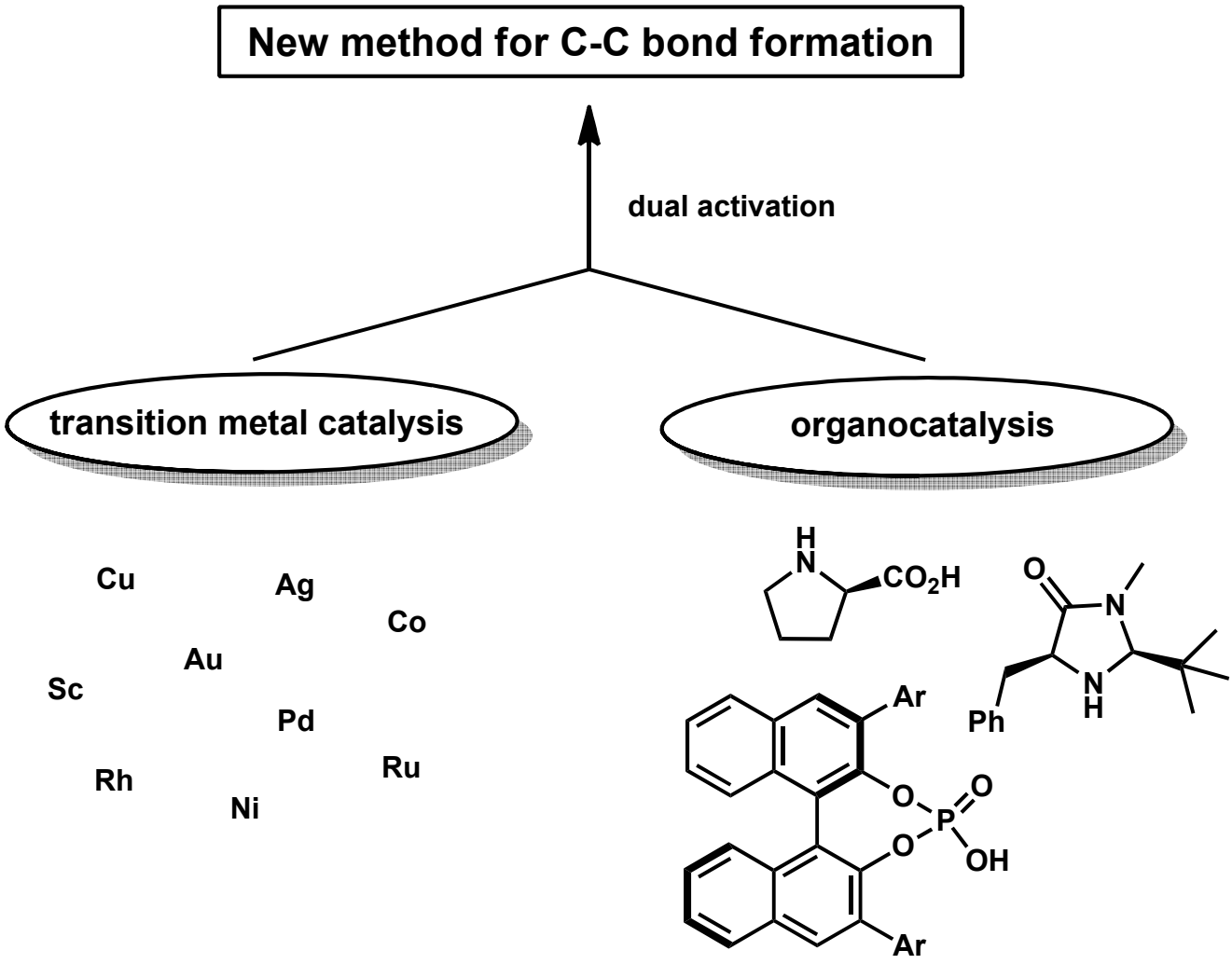
2011.12.20. Yuya Morita (B4)

Combining transition metal catalysis and organocatalysis

~for dual activation of carboxylic acids by transition metal and boron catalysts~



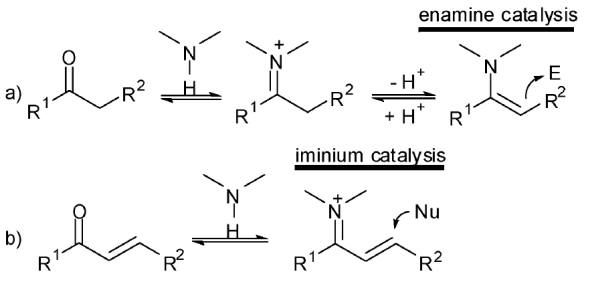
Contents

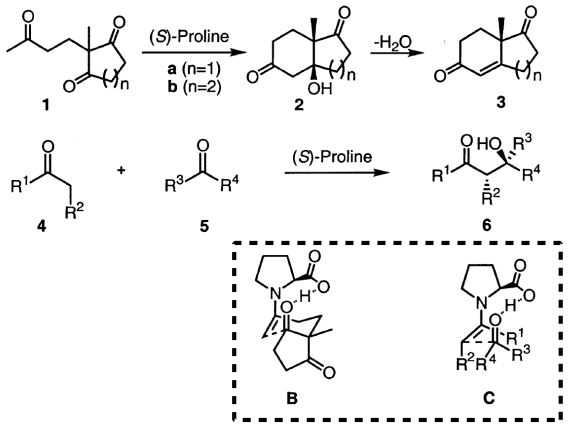
1. Combining transition metal catalysts and aminocatalysts
2. Boron compounds as catalysts
3. Dual activation of carboxylic acids by combining transition metal and boron catalysts

1. Combining transition metal catalysts and aminocatalysts

0. introduction

two types of activation mode by aminocatalysts





enamine - bifunctional catalyst

Proline has been playing a major role in enamine-based catalysis.
In this view, proline can be regarded as a Lewis base/Brønsted acid "bifunctional catalyst".

↓ "replace" the Brønsted acid with a metal Lewis acid

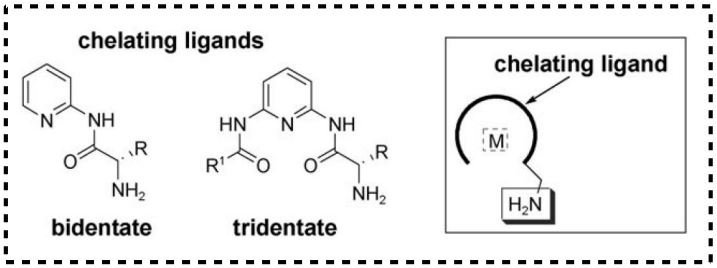
a novel class of metal Lewis acid-enamine bifunctional catalysts with the intention to bridge more traditional transition-metal catalysis with the newly established prosperous area of organocatalysis

the Challenging Problem
the acid-base self-quenching reaction leading to catalyst inactivation

•finetuning the reaction conditions and catalysts
e.g.) using a "soft" Lewis acid (metal such as Cu(I), Ag(I), Au(I), and Pd(0)) and a "hard" Lewis base (amine)

1. combining enamine catalysis and π-allyl palladium complexes
2. combining enamine catalysis and π-activation of C-C triple bond
4. combining enamine catalysis and SOMO photoredox catalysis
5. combining enamine catalysis and Rhodium-catalyzed hydroformylation

•using a tridentate (or bidentate) ligand tethered with a chiral amine (the Lewis acid and Lewis base are incorporated into one molecule)



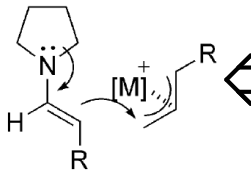
⟹ **A large number of metals can be introduced.**

3. combining enamine catalysis and metal activating carbonyl groups

This new concept aims to achieve organic transformations that cannot be accessed by organocatalysis or metal catalysis alone.

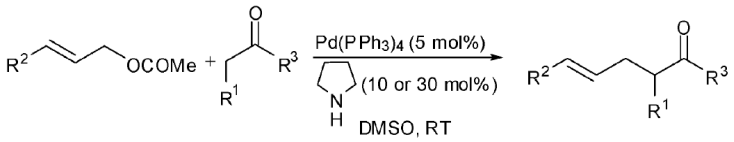
1. combining enamine catalysis and π-allyl palladium complexes

enamine catalysis
nucleophilic activation



π-allyl palladium complexes
electrophilic activation

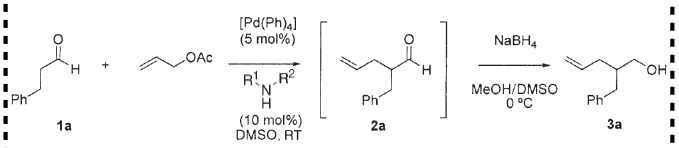
1-1. Direct Intermorecular α-Allylic Alkylation of Aldehydes and Cyclic Ketones



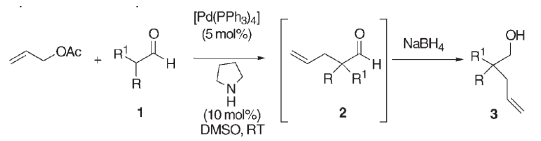
A. Cóldova, et al. Angew. Chem. Int. Ed. 2006, 45, 1952

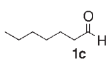
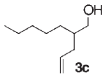
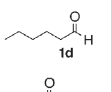
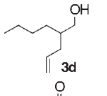
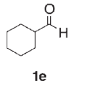
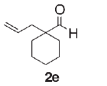
The first example of the one-pot combination of transition metal and enamine catalysis!!

screening of amine catalysts



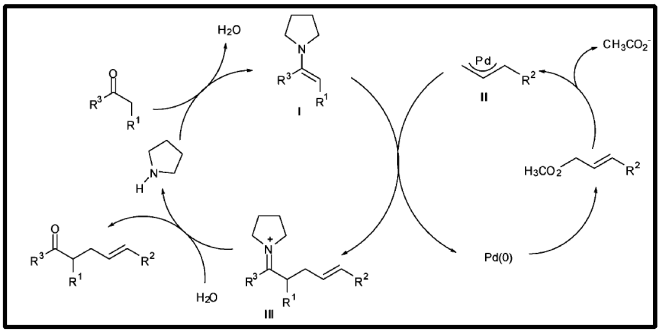
Entry	Amine catalyst	3a t [h]	3a Yield [%][b]
1		16	72
2		16	45
3		16	20
4		16	37

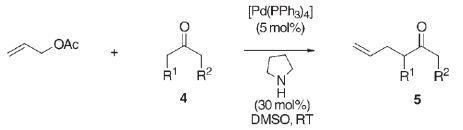


Entry	Aldehyde	Product	t [h]	Yield [%][b]
1	 1a	 3a	16	72
2	 1b	 3b	16	70
3	 1c	 3c	17	76
4	 1d	 3d	17	80
5	 1e	 2e	15	65[c]

[a] See the Experimental Section for the reaction conditions. [b] Yield of the isolated product of the corresponding alcohol **3** after column chromatography on silica gel. [c] The yield of the isolated product of aldehyde **2e**.

mechanism





Entry	Ketone	Product	t [h]	d.r.[b]	Yield [%][c]
1	 4a	 5a	16		95
2	 4b	 5b	16	1:1	90
3	 4c	 5c	16	1:1	85
4	 4d	 5d	16		82
5	 4e	 5e	15	2:1	70
6	 4f	 5f	14		65

[a] See the Experimental Section for the reaction conditions. [b] Determined by NMR spectroscopic analysis. [c] Yield of the isolated product after column chromatography on silica gel.

This is the first direct intermoleculer α-alkylation of aldehydes.

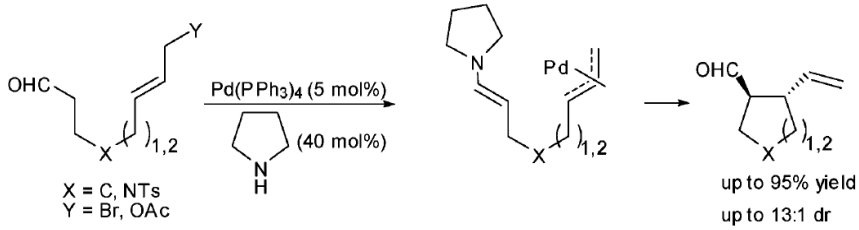
conventional method...

(stoichiometric amounts of metal, preactivated aldehydes...)

But...

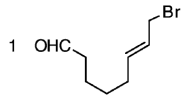
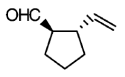
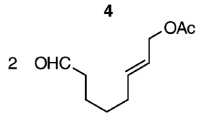
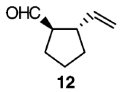
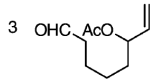
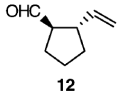
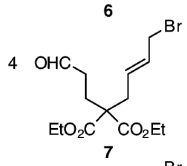
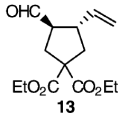
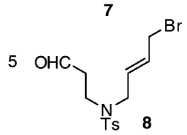
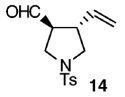
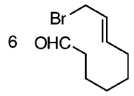
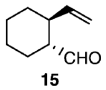
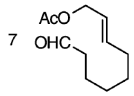
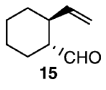
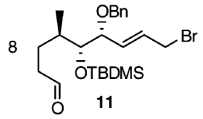
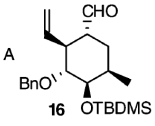
The satisfactory results are not obtained in asymmetric version of this reaction

1-2. Intramorecular α-Allylic Alkylation of Aldehydes



X = C, NTs
Y = Br, OAc

R. N. Saicic, et al. Org. Lett. 2007, 9, 5063

entry	reactant	method[a]	product	yield[b] *trans/cis*
1	 **4**	A	 **12**	72%[c] *11/1*
2	 **5**	B	 **12**	63%[c] *10/1*
3	 **6**	B	 **12**	53% *2/1*
4	 **7**	A	 **13**	75% *13/1*
5	 **8**	A	 **14**	80% *10/1*
6	 **9**	A	 **15**	60% *7/1*
7	 **10**	B	 **15**	65% *10/1*
8	 **11**	A	 **16**	95%[d] *7/1*

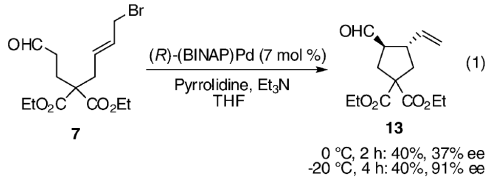
[a] Method A: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), Et_3N (1 equiv), THF, rt, 30 min. Method B: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), DMSO, rt, 30 min. [b] Yield of the isolated, pure compound. [c] Isolated as the corresponding alcohol, after the reduction with $NaBH_4$. [d] 10 mol % of $Pd(PPh_3)_4$.

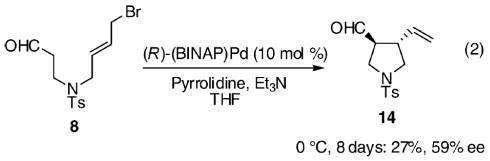
catalytic asymmetric cyclization

•using chiral amine catalysts

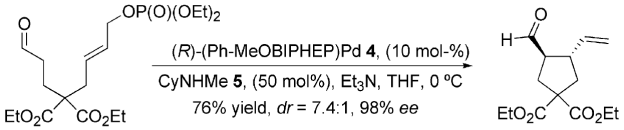
MacMillan's catalyst, (S)-proline, (S)-2-diphenylprolinol did not catalyze the reaction. (S)-2-methoxymethyl pyrrolidine failed to effect the asymmetric induction.

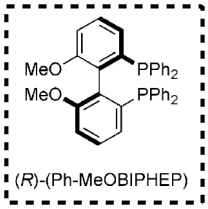
•using the chiral metal complex



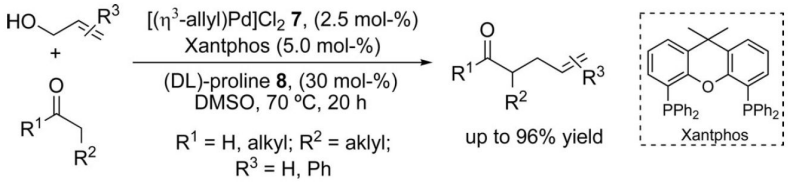


R. N. Saicic, et al. Tetrahedron. 2009, 65, 10485

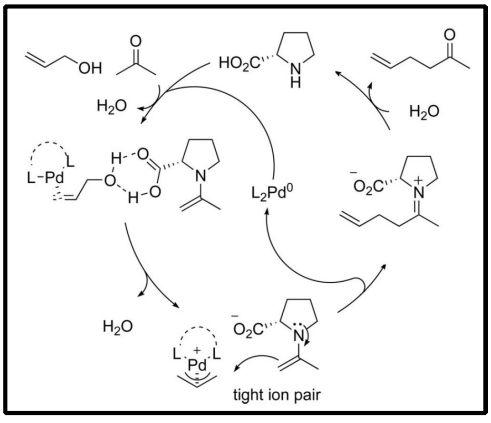




1-3. α-Allylic Alkylation of Aldehydes with Allylic Alcohols



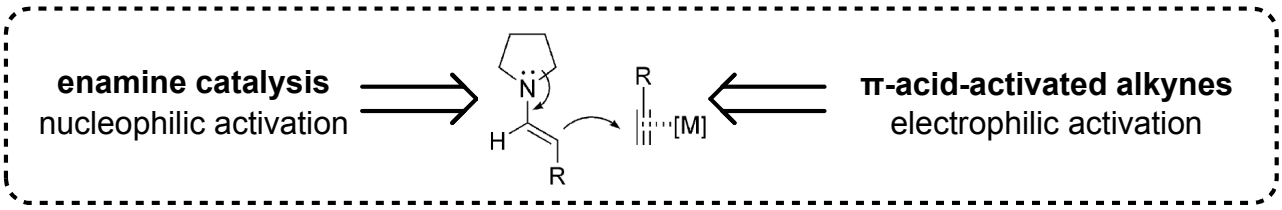
B. Breit, et al. Org. Lett. 2009, 11, 1453



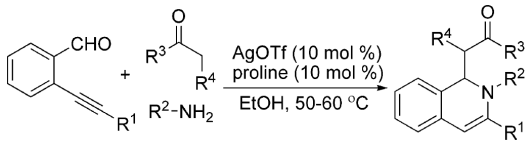
But...

The satisfactory results are not obtained in asymmetric version of this reaction

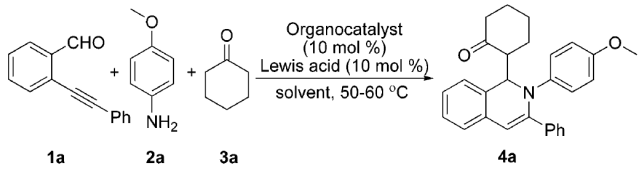
2. combining enamine catalysis and π-activation of C-C triple bond



2-1. 1,2-Dihydroisoquinoline Synthesis



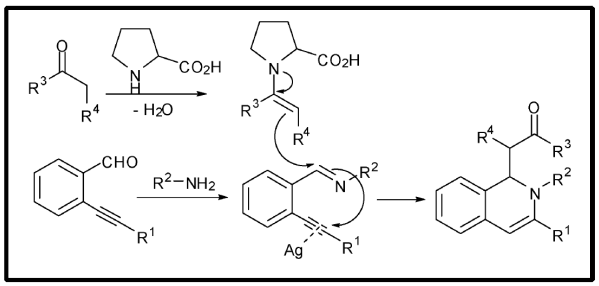
Q. Ding and J. Wu, Org. Lett. 2007, 9, 4959



entry	Lewis acid (10 mol %)	organocatalyst (10 mol %)	solvent	time (h)	yield (%)[b]
1	$PdCl_2$	proline	EtOH	6	10
2	$PdCl_2(PhCN)_2$	proline	EtOH	6	11
3	$Pd(OAc)_2$	proline	EtOH	6	20
4	$Cu(OTf)_2$	proline	EtOH	6	15
5	$CuSO_4$	proline	EtOH	6	27
6	CuI	proline	EtOH	4	59
7	AgOTf	proline	EtOH	4	65
8	AgOTf	proline	MeOH	4	65
9	AgOTf	proline	toluene	24	22
10	AgOTf	proline	THF	24	25
11	AgOTf	proline	DCE	24	13
12	AgOTf	$^{i}Pr_2NH_2$	EtOH	4	52
13	AgOTf	pyrrolidine	EtOH	4	41
14	AgOTf	piperidine	EtOH	4	40
15	AgOTf	proline[c]	EtOH	4	65
16	AgOTf	–	EtOH	24	18
17	AgOTf[d]	proline	EtOH	8	42
18	AgOTf[e]	proline	EtOH	8	32
19[f]	AgOTf	proline	EtOH	4	40

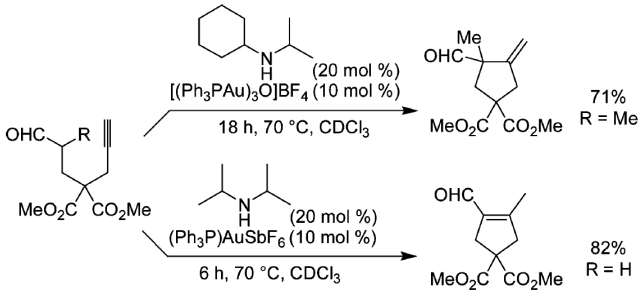
[a] Reaction conditions: 2-alkynylbenzaldehyde **1a** (0.30 mmol), *p*-anisidine **2a** (1.0 equiv), cyclohexanone **3a** (5.0 equiv), Lewis acid (10 mol %), organocatalyst (10 mol %), solvent (2.0 mL), 50−60 °C. [b] Isolated yield based on 2-alkynylbenzaldehyde **1a**. [c] 30 mol % of proline was utilized.[d] 5 mol % of AgOTf. [e] 2.5 mol % of AgOTf. [f] 2.5 equiv of cyclohexanone **3a** was employed.

mechanism



This is the first example of combination of enamine catalysis and π acidic transition metal catalysts.

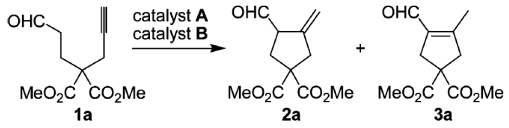
2-2. Direct Carbocyclization of Aldehydes with Alkynes



(α-substituted aldehydes)

(unbranched aldehydes)

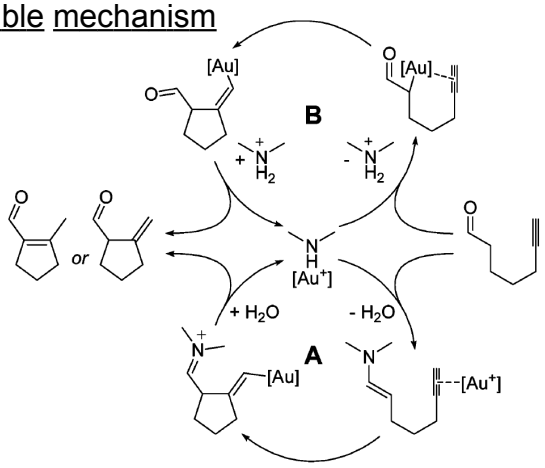
S. F. Kirsch, et al. Org. Lett. 2008, 10, 1025



entry	catalyst **A** (mol %)	catalyst **B** (mol %)	conditions	yield [%][a] **1a**:**2a**:**3a**
1			120 °C, toluene, 24 h	100:0:0[b]
2	$(Ph_3P)AuSbF_6$ (10)		70 °C, $CDCl_3$, 6 h	0:0:0[b]
3	$[(Ph_3PAu)_3O]BF_4$ (10)		70 °C, $CDCl_3$, 6 h	82:0:0
4		$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	100:0:0[b]
5	$(Ph_3P)AuSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	0:0:82
6	$(Ph_3P)AuSbF_6$ (2)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 10 h	0:0:75
7	$(Ph_3P)AuSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, CH_3NO_2, 6 h	0:0:80
8	$[(Ph_3PAu)_3O]BF_4$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 3 h	0:0:86
9	$[(Ph_3PAu)_3O]BF_4$ (10)	$HN(i\text{-}Pr)(c\text{-}Hex)$ (20)	70 °C, $CDCl_3$, 3 h	0:0:83
10	$[(Ph_3PAu)_3O]BF_4$ (10)	$H_2N(i\text{-}Pr)$ (20)	70 °C, $CDCl_3$, 3 h	0:0:74
11	$LAuSbF_6$ (10)[c]	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 6 h	0:0:74
12	$(Ph_3P)AuNTf_2$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 2 h	0:0:13
13	$AgSbF_6$ (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 24 h	0:0:16
14	AgOTf (10)	$HN(i\text{-}Pr)_2$ (20)	70 °C, $CDCl_3$, 2 h	0:0:59
15	$PtCl_2$ (10)	$HN(i\text{-}Pr)_2$ (20)	120 °C, toluene, 24 h	0:0:50

[a] Yield of pure product after column chromatography unless otherwise indicated. [b] The ratios were determined by ^1H NMR spectroscopy. [c] L = 2-(biphenyl)di-*tert*-butylphosphine. [d] Traces of **3a** (<5%) were detected by capillary gas chromatography in the absence of $HN(i\text{-}Pr)_2$.

possible mechanism



•AgOTf

$EtN(i\text{-}Pr)_2$ gave TM is 73% isolated yield.

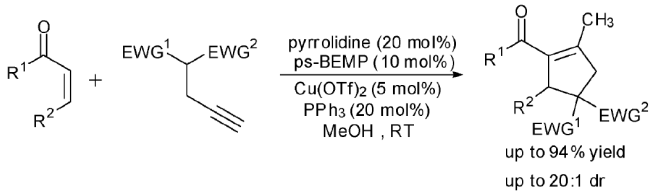
→ mechanism B

•$[(Ph_3PAu)_3O]BF_4$

$EtN(i\text{-}Pr)_2$ failed to give significant amount of TM.

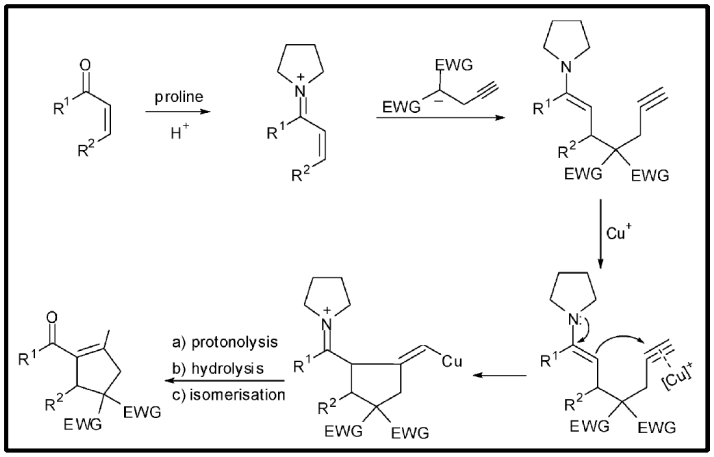
→ mechanism A

2-3. A Carboannulation for the Synthesis of Cyclopentene



D. J. Dixon, et al. Chem. Commun. 2008, 2923

mechanism

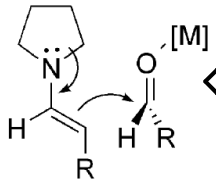


But...

Good enantioselectivity was not observed in this type of reaction.

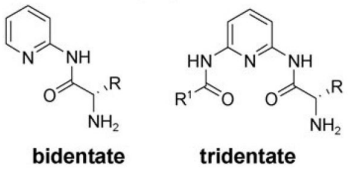
3. combining enamine catalysis and metal activating carbonyl groups

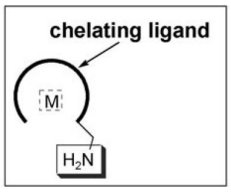
enamine catalysis
nucleophilic activation



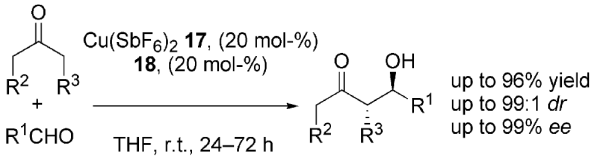
metal activating calbonyl groups
electrophilic activation

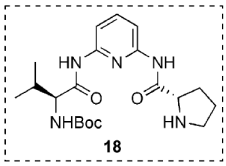
chelating ligands





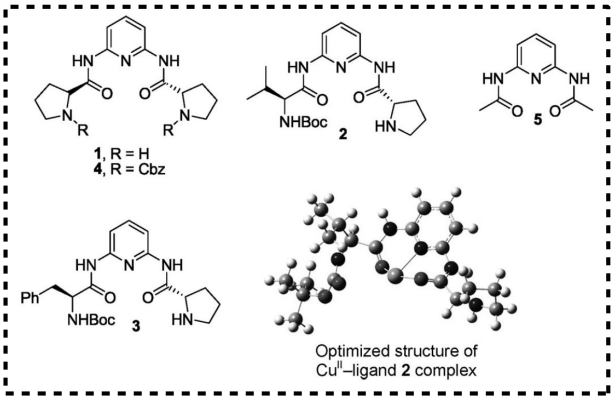
3-1. Direct Asymmetric Aldol Reaction of Ketones

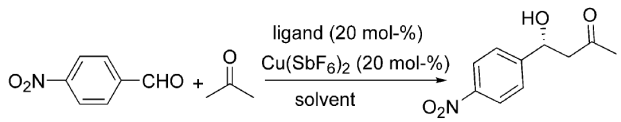




H. Wang, et al. Eur. J. Org. Chem. 2009, 4581

tridentate ligands

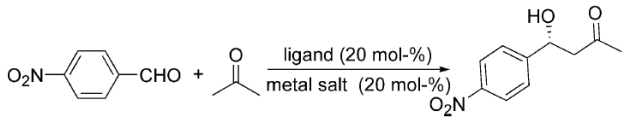




Entry	Ligand	THF [mL]	Acetone [mL]	Time [h]	Yield [%][c]	*ee* [%][f]
1	**1**	2	0.5	72	31	83
2	**1**	2	1	60	51	82
3[b]	**1**	2	1	60	61	79
4	**1**	0.6	0.3	48	84	75
5	**2**	2	1	48	93	88
6	**2**	0.6	0.3	24	93	87
7[c]	**2**	0.6	0.3	48	75	90
8	**3**	0.6	0.3	48	92	85
9[d]	**2**	0.6	0.3	72	95	83

[a] Reactions were performed with 0.2 mmol aldehyde. [b] H_2O (0.3 mL) was added. [c] At 0 °C. [d] 10 mol-% of catalyst. [e] Isolated yield. [f] Determined by chiral HPLC.

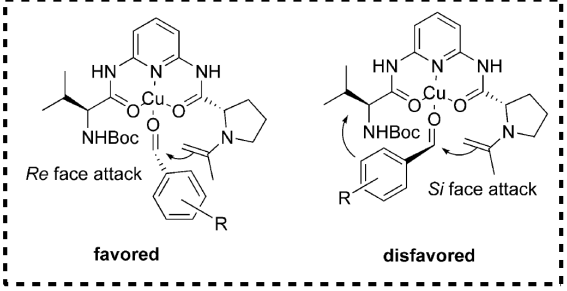
*the catalysts were prepared by stirring the ligand and the metal salt in solvent for 2-4 hours at room temperature before addition of the substrates



Entry	Metal	Ligand	Time [h]	Yield [%][c]	*ee* [%][d]
1[8]	–	**1**	48	74	43
2	$Zn(OAc)_2$	**1**	24	73	53
3	$Zn(ClO_4)_2$	**1**	36	45	28
4[b]	$Ni(OAc)_2$	**1**	48	84	38
5[b]	$Ni(ClO_4)_2$	**1**	48	63	58
6	$Co(ClO_4)_2$	**1**	24	83	42
7	$Cu(OTf)_2$	**1**	48	85	48
8	$Cu(ClO_4)_2$	**1**	72	81	47
9[b]	$Cu(NO_3)_2$	**1**	48	48	70
10	$Cu(SbF_6)_2$	**1**	48	58	75
11	$Cu(SbF_6)_2$	**4**	72	0	≈
12	$Cu(SbF_6)_2$	**5**	72	0	≈
13[e]	$Cu(SbF_6)_2$	**5**	60	20	≈

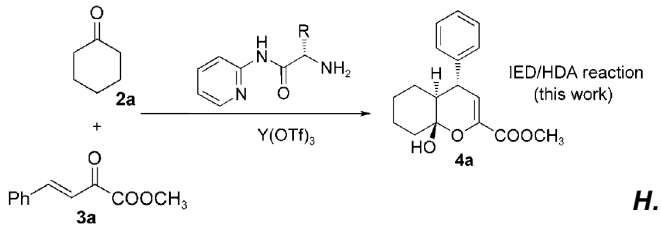
[a] Reactions were carried out with acetone (2 mL) and aldehyde (0.2 mmol). [b] DMSO (1 mL) was added. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Pyrrolidine (20 mol-%) was added.

proposed trasition state



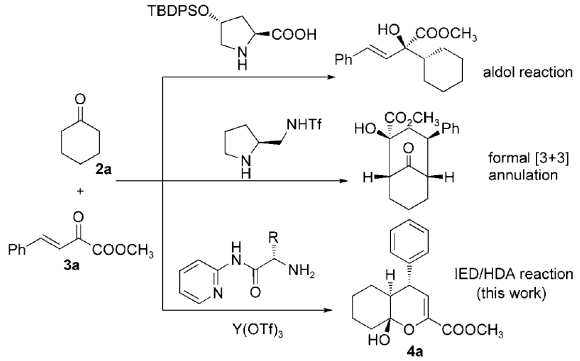
The tethered pyrrolidine moiety in the ligand did not participate in the coordination to the metal and the acid-base self-quenching reaction did not happen as expected!!

3-2. Asymmetric Inverse-Erectron-Demand Hetero-Diels-Alder Reaction



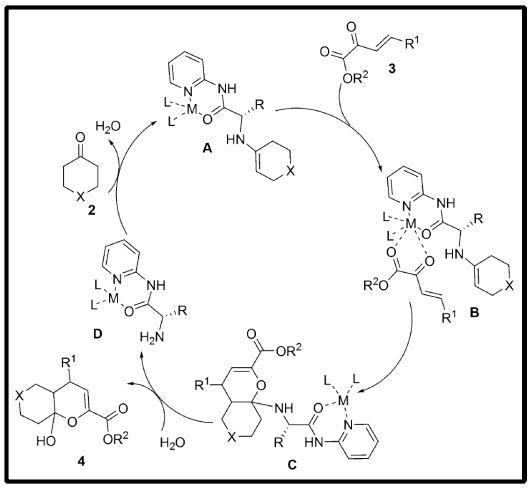
H. Wang, et al. Angew. Chem. Int. Ed. 2011, 50, 3484

The competing reactions of cyclohexanone with enone **3a** in the presence of an amine catalyst

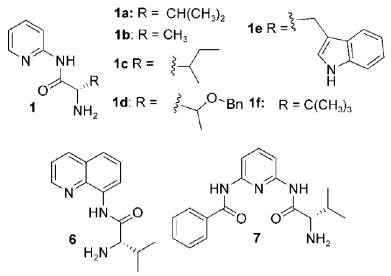


- a highly enantioselective aldol reaction occurs in the presence of a proline-derived catalyst
- a novel asymmetric formal [3+3] annulation reaction occurs in the presence of another proline-derived catalyst

proposed catalytic cycle



ligand screening

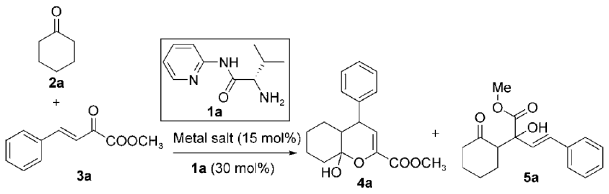


Entry	Ligand	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	**4a/5a**[c]	*ee* [%][d]
1	**1a**	CH_3CN	36	70	4:1	92:8	85
2	**1b**	CH_3CN	36	21	13:1	50:50	66
3	**1c**	CH_3CN	36	72	4:1	95:5	80
4	**1d**	CH_3CN	48	48	4:1	75:25	48
5	**1e**	CH_3CN	36	64	6:1	88:12	71
6	**6**	CH_3CN	72	51	–	10:90	–
7	**7**	CH_3CN	36	54	6:1	85:15	67
8	**1f**	CH_3CN	36	91	3:1	98:2	92
9	**1f**[e]	CH_3CN	72	86	2.5:1	>99:1	>99
10	**1f**[e]	**THF**	**84**	**81**	**9:1**	**>99:1**	**>99**

[a] Reaction conditions: enone **3a** (0.2 mmol) and cyclohexanone (0.5 mL) at room temperature in 1 mL of solvent. [b] Yield of the isoalted HDA products. [c] Determined by ^{1}H NMR spectroscopy.[10] [d] Determined by HPLC analysis using a chiral stationary phase. [e] Run at 4 °C. Bn = benzyl.

optimization of HDA reaction[a]

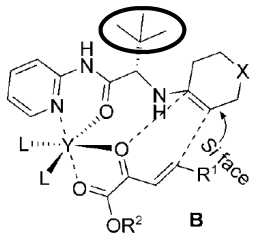
*the catalysts were prepared by stirring the ligand and the metal salt in solvent for 1-4 hours before addition of the substrates



Entry	Metal	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	**4a/5a**[c]	*ee* [%][d]
1	$Cu(SbF_6)_2$	THF	72	72	–	0:100	–
2	$La(OTf)_3$	THF	16	95	4:1	95:5	49
3	$Yb(OTf)_3$	THF	36	61	3:1	70:30	70
4	$Sc(OTf)_3$	THF	60	60	–	0:100	–
5	$Eu(fod)_3$	THF	60	37	–	0:100	–
6	**$Y(OTf)_3$**	**THF**	**16**	**61**	**7:1**	**92:8**	**83**
7	$Y(OTf)_3$	CH_2Cl_2	36	75	4:1	96:4	75
8	$Y(OTf)_3$	Toluene	36	74	4:1	>99:1	67
9	**$Y(OTf)_3$**	**CH_3CN**	**36**	**70**	**4:1**	**92:8**	**85**
10	$Y(OTf)_3$	Neat	36	76	4:1	58:42	82
11	$Y(OTf)_3$	MeOH	72	31	–	<1:99	–
12[e]	$Y(OTf)_3$	CH_3CN	36	50	5:1	91:9	82
13[f]	$Y(OTf)_3$	CH_3CN	72	20	–	8:92	–
14[g]	$Y(OTf)_3$	CH_3CN	72	20	–	4:96	–
15[h]	$Y(OTf)_3$	CH_3CN	72	38	4:1	83:17	80

[a] Reaction conditions: enone **3** (0.2 mmol) and cyclohexanone (0.5 mL), room temperature in 1 mL of solvent. [b] Yield of the isolated HDA products. [c] Determined by ^{1}H NMR spectroscopy.[10] [d] Determined by HPLC analysis using a chiral stationary phase. [e] 50 mg of silica gel was added. [f] 5 equivalents of H_2O was added. [g] 10 equivalents of H_2O was added. [h] 100 mg of 4 Å M.S. was added. fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadiene, M.S. = molecular sieves, THF = tetrahydrofuran.

proposed transition state

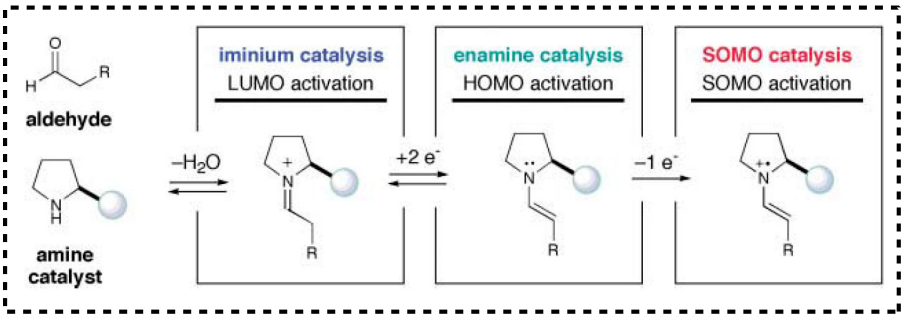


The big R (tert-butyl) group shields the *Re* face of the enamine, thus the activated enone attacks from the *Si* face.

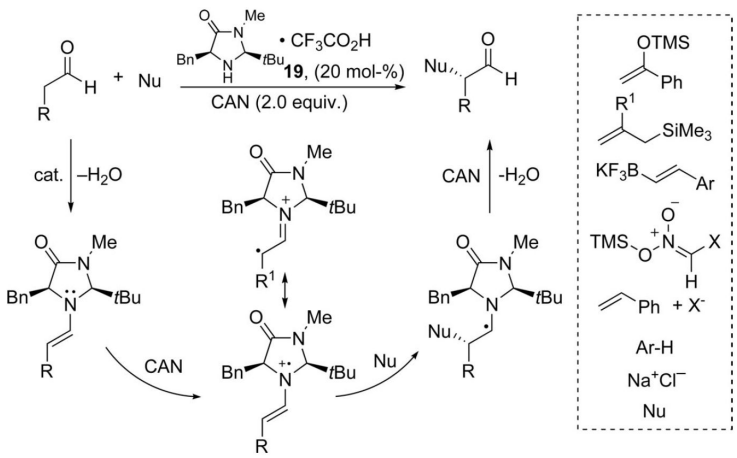
4. combining enamine catalysis and SOMO photoredox catalysis

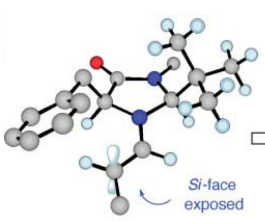
SOMO activation strategy

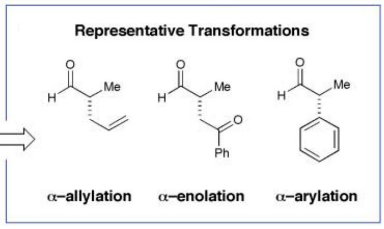
- single-electron oxidation of a transient chiral enamine intermediate was achieved on treatment of enamines with suitable metal oxidants (such as CAN) CAN=$Ce(NH_4)_2(NO_3)_6$
- the enamine nucleophiles were transformed into radical cationic electrophiles



4-1. Direct Asymmetric Alkylation of Aldehydes





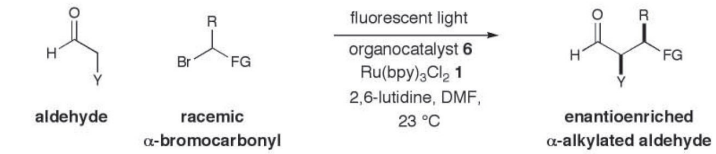


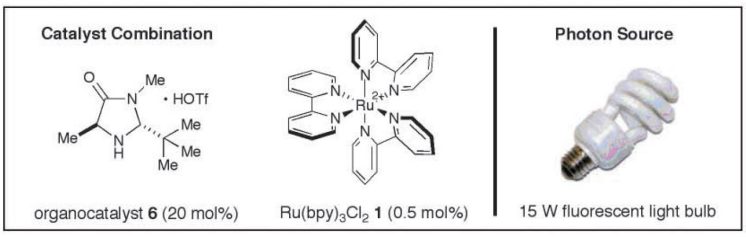
radical-cation intermediate

- reactivity to unactivated olefins
- experiments of the radical clock

D. W. C. MacMillan, et al. Science, 2007, 316, 582

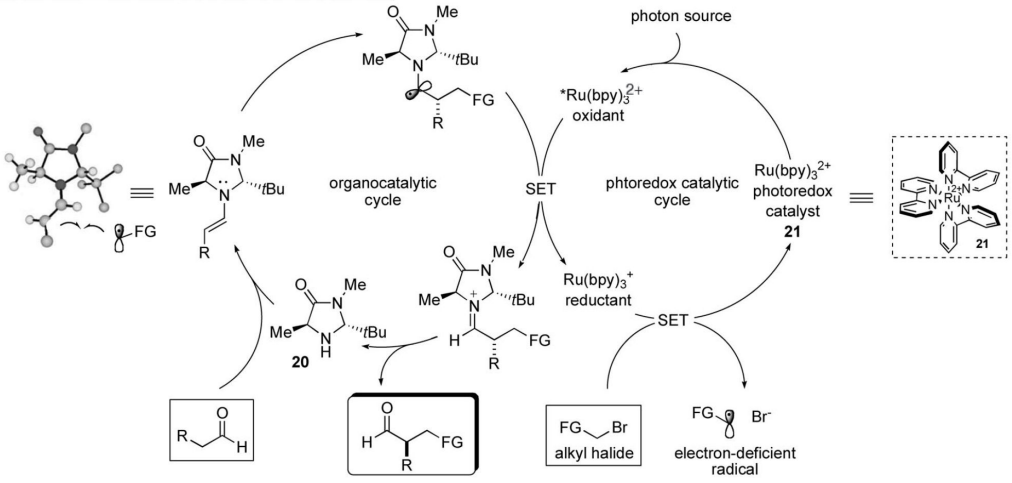
4-2. combining enamine catalysis and photoredox catalysis





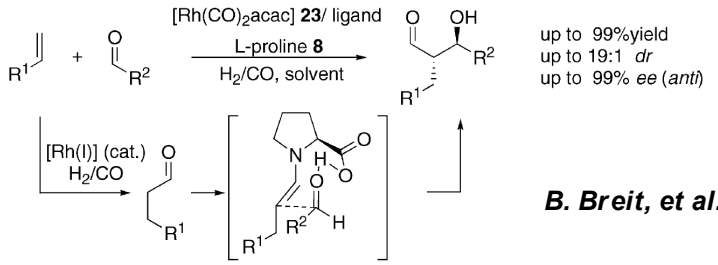
The experiment of radical clock indicates that a 3π electron SOMO activated intermediate is not operative in the organocatalytic cycle.

D. W. C. MacMillan, et al. Science, 2008, 322, 77



5. combining enamine catalysis and Rhodium-catalyzed hydroformylation

5-1. Tandem Hydroformylation/Enantioselective Aldol Reactions



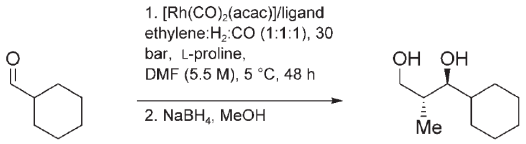
B. Breit, et al. Adv. Synth. Catal. 2007, 349, 1891

The difficulty of this cross-aldol reaction between two non-equivaent aldehydes

- two aldehyde have to show significant rate differences in enamine formation
- the homo-aldol of the aldehyde component has to be suppressed

tandem hydroformylation/organocatalytic aldol reaction

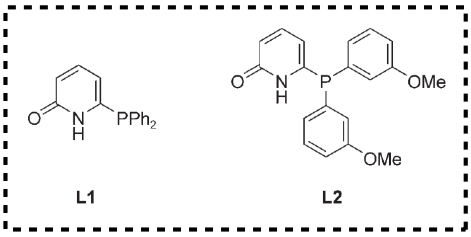
generate the donor aldehyde in a low stationary concentration by the hydroformylation of alkenes



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]

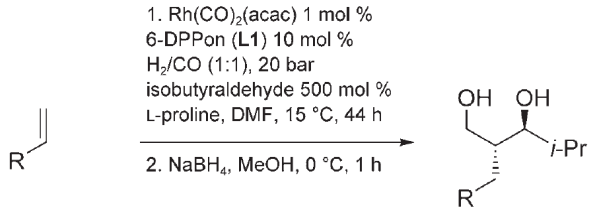
ligands

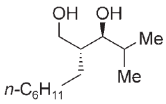
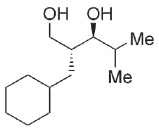


A crucial factor for success of this reaction is the correct adjustment of the hydroformylation rate to the rate of proline-catalyzed aldol addition since accumulation of the donor aldehyde would facilitate undesired homodimerization.

*In case of the more electrophilic aryl aldehydes, the more reactive hydroformylation catalyst based on **L1** gave optimal results.

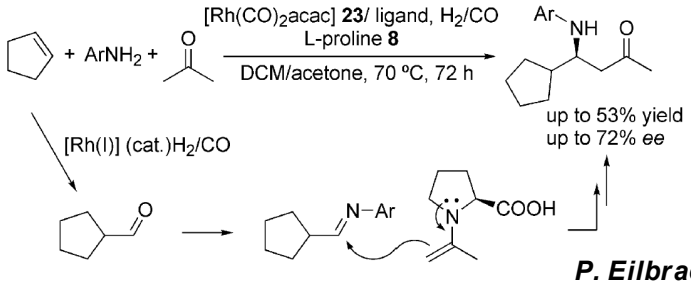
Application to terminal alkenes



Entry	Product	Yield [%][a]	*dr*[b]	*ee* [%][c]
1		86	19:1	97
2		50	10:1	99

[a] Isolated yields of purified cross aldol products (two steps).
[b] Determined by GC after conversion to the corresponding acetonide.
[c] Determined by chiral GC (Chiraldex (G-TA)).

5-2. Tandem Hydroformylation/Enantioselective Mannich Reactions



P. Eilbracht, et al. Adv. Synth. Catal. 2009, 351, 339

2. Boron compounds as catalysts

1. combined acid catalysis

combined acids system (Lewis acid and Brønsted acid)

an effective asymmetric environment by more-organized structures

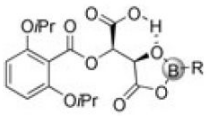
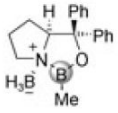
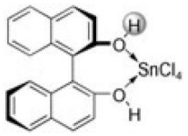
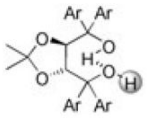
more reactivity by associative interaction

e.g.) $HSO_3F•SbF_5$ (magic acid)

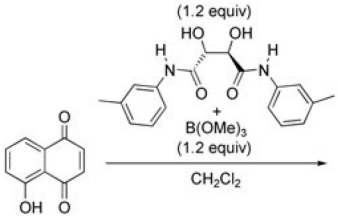
The concept of combined acids can be a particularly useful tool for the design of asymmetric catalysis.

H. Yamamoto, K. Futatsugi, Angew. Chem. Int. Ed. 2008, 47, 2876

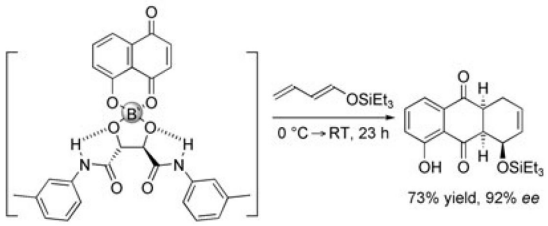
Table 1: General classifications of combined acid catalysis.

	Catalyst system	General structure	Examples
*	Brønsted acid assisted Lewis acid catalyst (BLA) Enhancement of Lewis acidity by the combination with Brønsted acid		
*	Lewis acid assisted Lewis acid catalyst (LLA) Enhancement of Lewis acidity by the combination with Lewis acid		
	Lewis acid assisted Brønsted acid catalyst (LBA) Enhancement of Brønsted acidity by the combination with Lewis acid		
	Brønsted acid assisted Brønsted acid catalyst (BBA) Enhancement of Brønsted acidity by the combination with Brønsted acid		

1-1. a chiral boron reagnet (BLA)



Yamamoto, H. et al. Tetrahedron Lett. 1986, 27, 4895

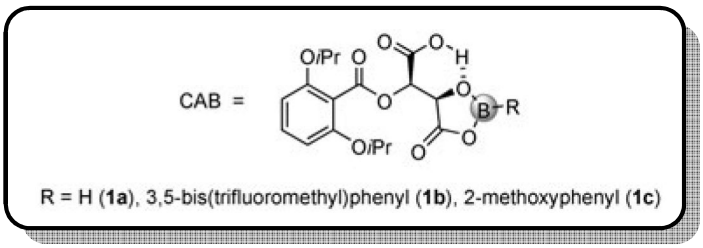


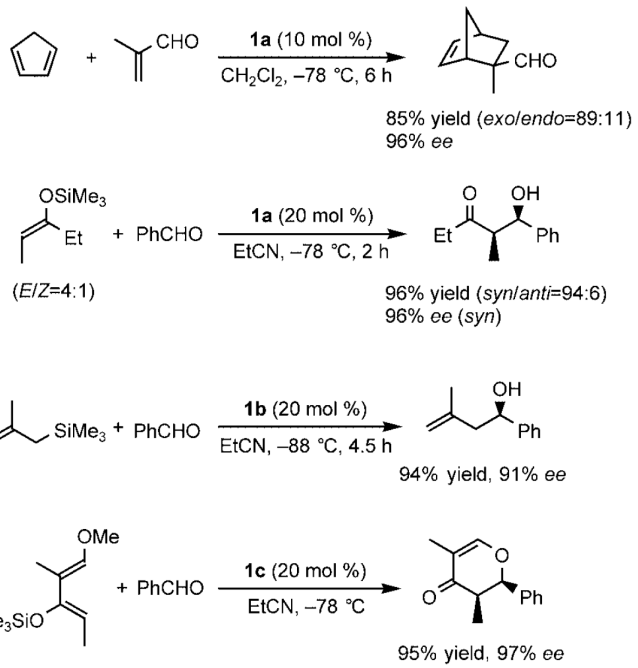
The intramolecular **hydrogen bonding** between the hydrogen atom on the amide and the oxygen atom attached to the boron center increases the Lewis acidity of boron.

But...

1.2 equiv of boron reagent is required in this reaction.

1-2. CAB (chiral acyloxyborane) catalysts (BLA)



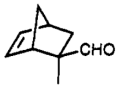
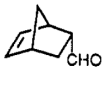


Scheme 2. Asymmetric reactions promoted by CAB catalysts.

Mechanism studies of a CAB-catalyzed asymmetric diel-Alder reactions

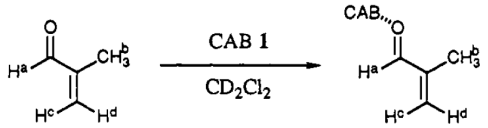
Yamamoto, H. et al. J. Am. Chem. Soc. 1993, 115, 10412

Table I. Asymmetric Diels-Alder Reaction of α,β-Enal with Cyclopentadiene Catalyzed by **1**[a]

	% ee (config)		
CAB **1** R			
1-hexynyl	64 (*R*)	58 (*R*)	42 (*R*)
PhC≡C	62 (*R*)	48 (*R*)	40 (*R*)
H	87 (*R*) [96 (*R*)][b,c]	47 (*R*) [84 (*R*)][b,c]	2 (*S*) [2 (*S*)][b,c]
Me		2 (*S*)	14 (*S*)
Ph	80 (*R*)	10 (*S*) [3 (*S*)][b]	37 (*S*)
3,5-$(CF_3)_2C_6H_3$		3 (*S*)	59 (*S*)
o-$PhOC_6H_4$	93 (*R*)	57 (*S*)	67 (*S*)
o-$NpOC_6H_4$[d]		53 (*S*)	77 (*S*)

[a] Unless otherwise noted, the reaction was carried out in propionitrile for several hours using 10–20 mol % of **1** and cyclopentadiene (3 equiv) at –78 °C. [b] Dichloromethane was used in place of propionitrile. [c] (2*R*,3*R*)-2-*O*-(2,6-Dimethoxybenzoyl)tartaric acid was used as a chiral ligand.[1b] [d] *o*-Naphthoxyphenyl.

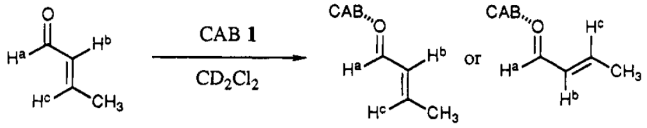
Table II. Summary of NOE Data for Methacrolein



		NOE (saturated/observed, %)			
complex	*t* (°C)	H^a/H^b	H^a/H^c	H^a/H^d	H^c/H^a
methacrolein only	–95	0	6.3	0	18
methacrolein–**1**, R = H[b]	–95	0	–10	0	6.3
methacrolein–**1**, R = *o*-$PhOC_6H_4$[b]	–75	0	–22	0	–33

[a] Calibrated probe temperature. [b] Complexed formed by addition of 0.72 equiv of the aldehyde to **1**.

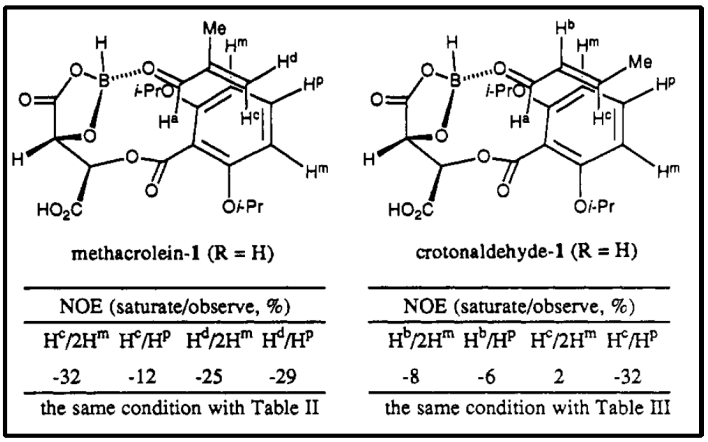
Table III. Summary of the NOE Data for Crotonaldehyde



		NOE (saturated/observed, %)			
complex	*t* (°C)	H^a/H^b	H^a/H^c	H^b/H^a	H^c/H^a
crotonaldehyde only	–95	0	5.4		
crotonaldehyde–**1**, R = $C_4H_9C{\equiv}C$[b]	–75	0	6		13
crotonaldehyde–**1**, R = H[b]	–95	0	18		
crotonaldehyde–**1**, R = 3,5-$(CF_3)_2C_6H_3$[b]	–75	–32	0	–48	
crotonaldehyde–**1**, R = *o*-$PhOC_6H_4$[b]	–75	–14	0	–18	

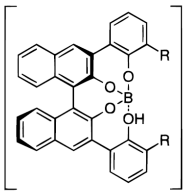
[a] Calibrated probe temperature. [b] Complex formed by addition of 0.72 equiv of the aldehyde to **1**.

CAB-methacrolein and CAB-crotonaldehyde complex

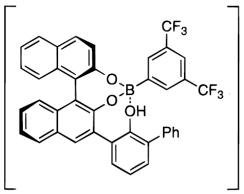


Based on the NOE experiments, it was established that the effective shielding of the CAB-coordinated aldehydes arises from **π stacking** of 2,6-diisopropoxybanzaldehyde ring and the coordinated aldehyde.

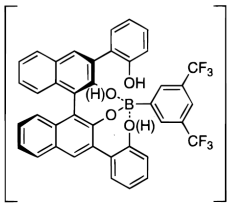
1-3. π-π donor-acceptor interaction (BLA)



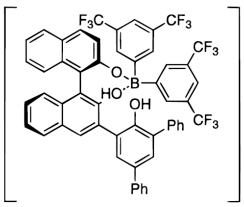
BLAs **1a** (R=H), **1b** (R=Ph)



BLA **2a**



BLA **3**



BLA **4a**

Yamamoto, H. et al. J. Am. Chem. Soc. 1998, 120, 6920

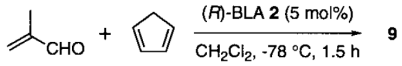
The coordination of a proton of the 2-hydroxyphenyl group with an oxygen of the adjacent B-O bond in complex plays an important role.

hydrogen bonding interaction *via* a Brønsted acid

↓

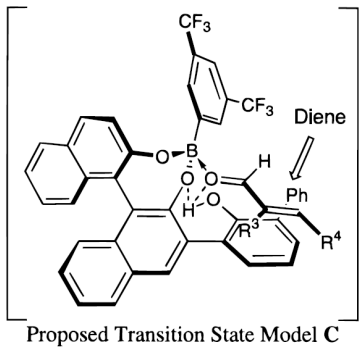
•increase the Lewis acidity of boron
•increase the π-basicity of the phenoxy moiety

Asymmetric Diels-Alder reactions catalyzed by BLA 2



entry	chiral ligand	method[b]	yield[c] (%)	ee (%)[d] [config]
1	(*R*)-**18a**	A	96	99 [*S*]
2		B	94	98 [*S*]
3		A[e]	95	48 [*S*]
4	(*R*)-**18b**	B	89	50 [*S*]
5	(*R*)-**18c**	B	97	77 [*S*]
6	(*R*)-**18d**	B	63	60 [*S*]
7	(*R*)-**18a** (MeO)[f]	B	9	45 [*S*]
8	(*R*)-Binaphthol	B	22	46 [*S*]

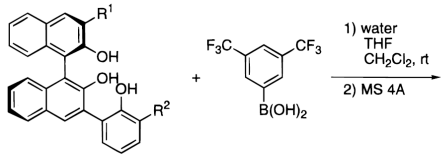
[a] The reactions were conducted in dichloromethane using aldehyde (1 equiv, 0.25 M) and diene (4 equiv) in the presence of 5 mol % of **2** at −78 °C for 1.5 h. [b] See text. [c] Isolated yield. [d] The ee of major isomer and the absolute configuration of its carbonyl α-carbon are indicated. The absolute configuration was assigned by comparison with data in the literature. For the determination method, see Experimental Section. [e] No THF was added. [f] (*R*)-3-(2-Methoxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl was used.



Proposed Transition State Model **C**

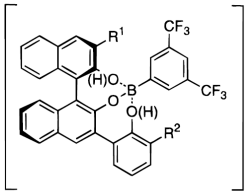
The attractive π-π donor-acceptor interaction between a dienophile and a chiral ligand is highly effective for inducing asymmetry.

synthesis of BLA catalysts



18a: R^1=H, R^2=Ph
18b: R^1=H, R^2=Me
18c: R^1, R^2=H
18d: R^1=Ph, R^2=H

17



BLA **2a-d**

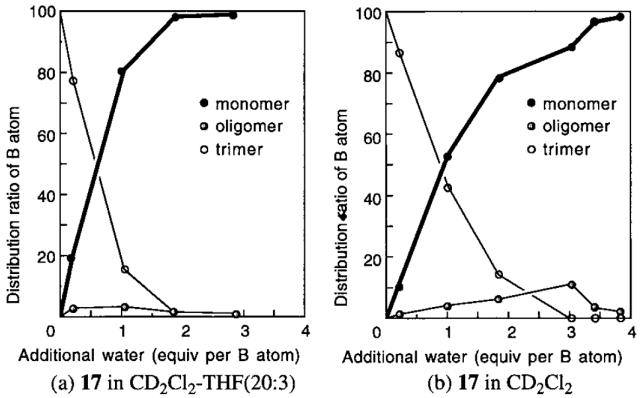
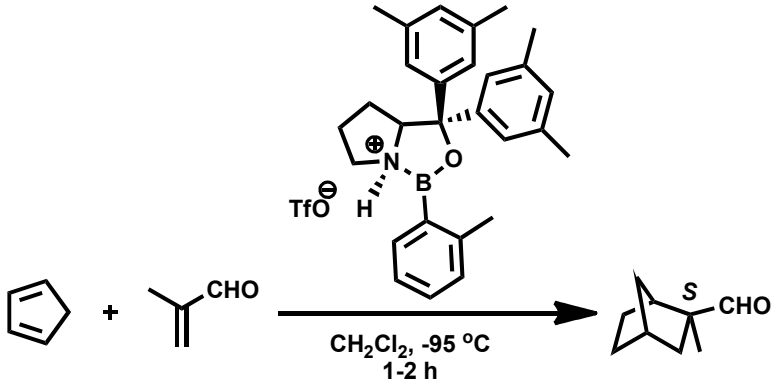


Figure 1. Plot of the distribution ratio of boron atom in a solution of **17** versus additional water.

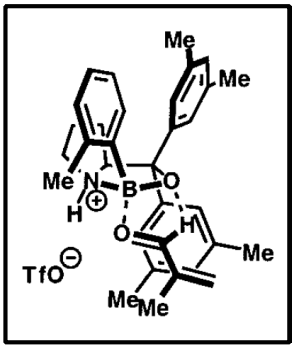
*THF and additional water are required for the preparation of a sufficient amount of BLA2.

1-4. oxazaborolidine (BLA)

asymmetric Diels-Alder reaction



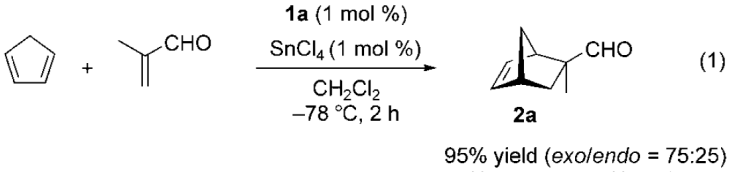
transition state



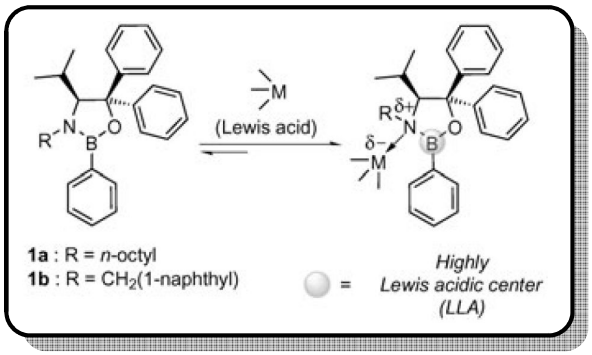
E. J. Corey, et al. J. Am. Chem. Soc. 2002, 124, 3808

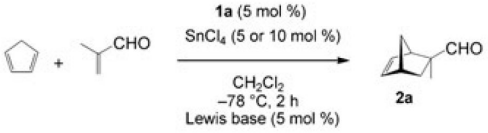
1-5. oxazaborolidine (LLA)

asymmetric Diels-Alder reaction

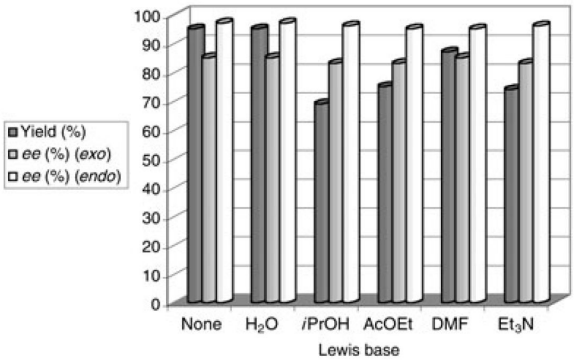


95% yield (*exo*/*endo* = 75:25)
84% *ee* (*exo*), 96% *ee* (*endo*)



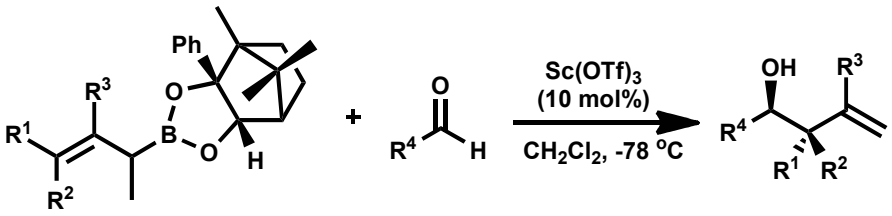


H. Yamamoto, et al., Angew. Chem. Int. Ed. 2005, 44, 1484

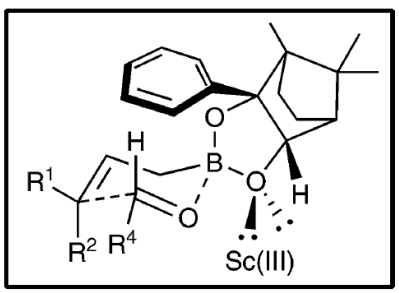


The reactivity and asymmetric induction ability can be maintainted **even in the presence of a small amount of water as well as other Lewis bases** by adding a slightly larger amount of $SnCl_4$.

1-6. dioxaborolane (LLA)



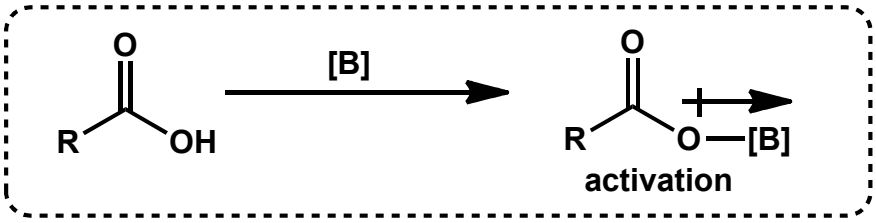
transition state



A close investigation pointed to electrophilic activation by **coordination of the metal ion to one of the boronate oxygens** in a closed bimolecular transition state.

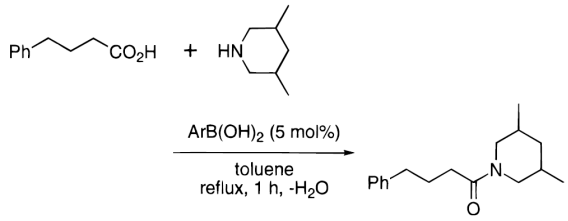
D. G. Hall, et al. J. Am. Chem. Soc. 2004, 126, 4518

2. activation of carboxylic acid



2-1. boron compound-catalyzed amide condensation

1. arylboronic acid



Yamamoto, H. et al. J. Org. Chem. 1996, 61, 4196

entry	Ar	yield[b] (%)	entry	Ar	yield[b] (%)
1	3,4,5-$F_3C_6H_2$	74	5	C_6H_5	23
2	3-$NO_2C_6H_4$	60	6	2,4,6-$(CF_3)_3C_6H_2$	21
3	3,5-$(CF_3)_2C_6H_3$	56	7	2,3,4,5-F_4C_6H	11
4	4-$CF_3C_6H_4$	54	8	c	<2

[a] In the presence of 5 mol % of arylboronic acid, a mixed solution of 1 equiv of 4-phenylbutyric acid (0.2 M) and 1 equiv of 3,5-dimethylpiperidine (0.2 M) in toluene was refluxed with removal of water (4-Å molecular sieves in a Soxhlet thimble). [b] Isolated yield. [c] No catalyst was added.

proposed catalytic cycle

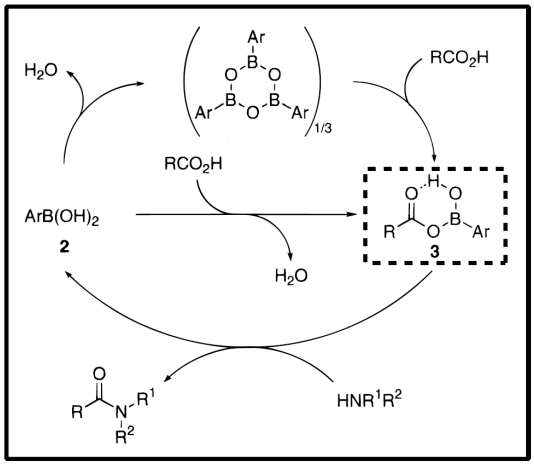


Table 2. Amidation Reaction between Carboxylic Acids and Amines Catalyzed by 1[a]

carboxylic acid	amine	solvent	time (h)	yield[b] (%)
PhCO_2H	PhNH_2	toluene	18	96
	HN	toluene	16	>99
	Bu_2NH	xylene	20	56
		mesitylene	14.5	99
	$PhNH_2$	mesitylene[c]	4	99
CO_2H	PhNH_2	xylene	18	96
CO_2H	PhNH_2	mesitylene[c]	2	92
PhCO_2H	HN	xylene	29	99
$PhCO_2H$		mesitylene	20	95

[a] Unless otherwise noted, in the presence of 1 mol % of **1**, a mixed solution of 1 equiv of carboxylic acid (0.2 M) and 1 equiv of amine (0.2 M) in toluene, xylene, or mesitylene was refluxed with removal of water (4-Å molecular sieves in a Soxhlet thimble). [b] Isolated yield by column chromatography on silica gel. [c] A mixed solution of 1 equiv of carboxylic acid (2 M) and 1 equiv of amine (2 M) in mesitylene was used.

arylboronic acids with electron-withdrawing substituents at the aryl group

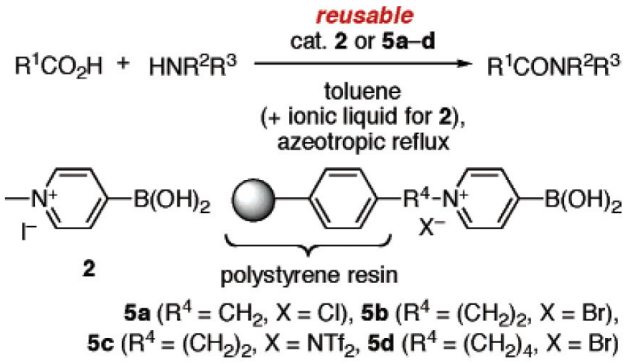
- •water-, acid-, and base-torelant
- •thermally stable and can be readily handled in air
- •strong Lewis acidity enhances the rate of the generation of acyloxyborane species and their reactivity with amines

→ **only catalytic amount of boronic acids are required!!**

But...

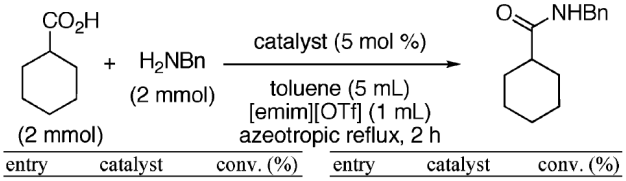
Catalytic activities of these neutral boronic acids are greatly diminished in polar solvents. This solvent limitation restricts the scope of substrates.

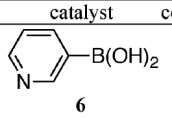
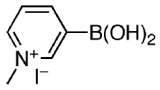
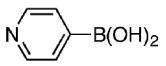
2. *N*-Alkyl-2-boronopyridinium Salt



Yamamoto, H. et al. Org. Lett. 2005, 7, 5043

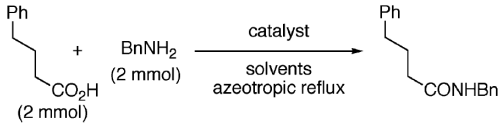
- 4-borono-N-methylpyridinium iodide (2) is effective **in polar solvents**.
- A catalyst **2** can be reused through the use of ionic liquid-toluene biphasic solvents.
- Catalysts **5** are reusable without the need for ionic liquids.



entry	catalyst	conv. (%)	entry	catalyst	conv. (%)
1	**2**	59	3	 **6**	43
2	 **3**	54	4[a]	 **7**	8

[a] **7** did not dissolve under these conditions.

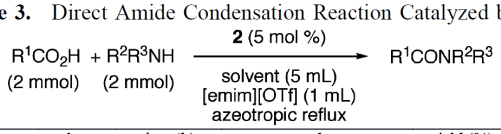
Table 2. Catalytic Activities of **2** and $[\mathbf{2}]_{12}$ for Amide Condensation

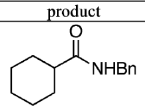
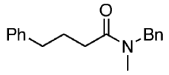
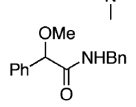
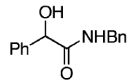
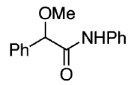
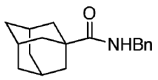
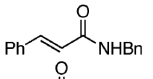
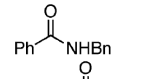
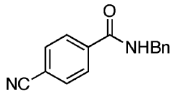


entry	catalyst (mol %)	solvents (mL)	time (h)	yield (%)
1	**2** (5)	toluene (5)	1	41
2	$[\mathbf{2}]_{12}$ (10)[a]	toluene (5)	1	15
3	**2** (5)	toluene (5)−[emim][OTf] (1)	1	74
4	$[\mathbf{2}]_{12}$ (5)[b]	toluene (5)−[emim][OTf] (1)	1	75
5	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
6[c]	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
7[d]	**2** (5)	toluene (5)−[emim][OTf] (1)	5	>99
8	**1** (5)	toluene (5)−[emim][OTf] (1)	1	88
9[e]	**1** (5)	toluene (5)−[emim][OTf] (1)	1	7

[a] $[\mathbf{2}]_{12}$ (10 mol % for B-atom) was used. [b] $[\mathbf{2}]_{12}$ (5 mol % for B-atom) was used. [c] **2** used in entry 5 was recovered and reused in entry 6. [d] **2** used in entry 6 was recovered and reused in entry 7. [e] A solution of **1** in [emim][OTf] used in entry 8 was recovered and reused in entry 9.

Table 3. Direct Amide Condensation Reaction Catalyzed by **2**



entry	solvent	time (h)	product	yield (%)
1	toluene	6		92
2	toluene	18		95
3[a]	toluene	5 (1st) 5 (2nd) 5 (3rd)		98 (1st) 93 (2nd) 95 (3rd)
4	*o*-xylene	18		91
5	*o*-xylene	18		80
6	*o*-xylene	10		91
7	*o*-xylene	3		90
8	*o*-xylene	6		98
9[a]	*o*-xylene	5 (1st) 5 (2nd) 5 (3rd)		99 (1st) 98 (2nd) 99 (3rd)

[a] A solution of **2** in [emim][OTf] was reused three times.

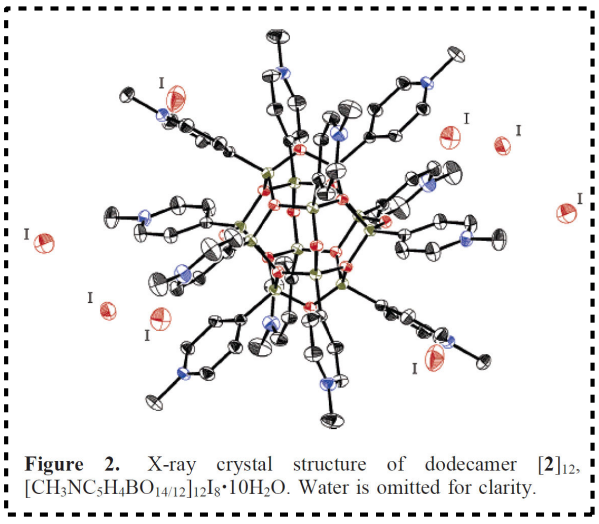
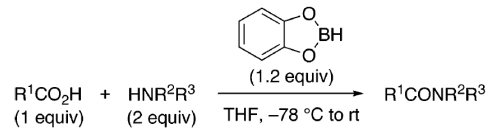


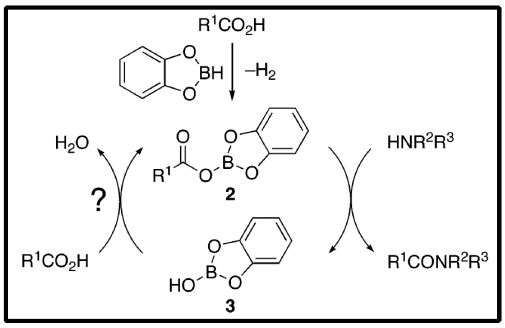
Figure 2. X-ray crystal structure of dodecamer $[\mathbf{2}]_{12}$, $[CH_3NC_5H_4BO_{14/12}]_{12}I_8 \cdot 10H_2O$. Water is omitted for clarity.

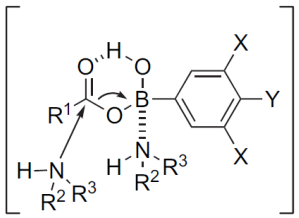
1-ethyl-3-methylimidazolium trifluoromethanesulfonate [emim][OTf] plays an important role in suppressing the condensation of **2** to $[\mathbf{2}]_{12}$.

3. catecholborane

Ganem's amide condensation







Ganem, B. et al. J. Org. Chem. 1978, 43, 4393

Under this condition, benzo[*d*][1,3,2]dioxaborol-2-ol (**3**) is inert as a condensing reagent.

How can we use 3 as a condensing reagent??

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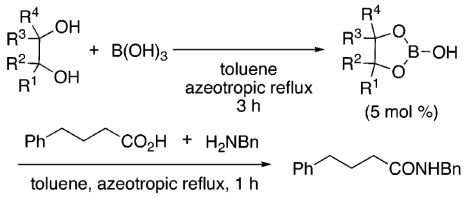
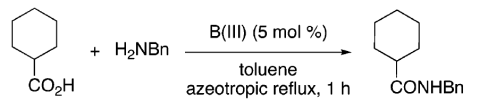
3 serves as a dehydrative catalyst under azeotropic reflux conditions with the removal of water in less polar solvents!!

Yamamoto, H. et al. Org. Lett. 2006, 8, 1431



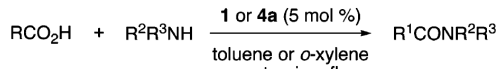
entry	B(III) catalyst	conv (%)	entry	B(III) catalyst	conv (%)
1	**3**	61	3		64
			4		74
2	**4b**	93	5[a]	$B(OH)_3$	31
			6[a]	$B(OH)_2$	96

[a] $B(OH)_3$ and **1** were used instead of 1,3,2-dioxaborolan-2-ol derivatives.



entry	B(III) catalyst[a]	conv (%)	entry	B(III) catalyst[a]	conv (%)
1	**4a**	62	5		3
2	**4b**	52			
3	**1**	32			
4	$B(OH)_3$	2			

[a] **4b** and **4c** were prepared from $B(OH)_3$ and tetrachlorocatechol in situ before the addition of carboxylic acids and amines.



entry	product (**5**–**18**)	solvent, time (h)	yield (%) **1**	yield (%) **4a**
1	PhCONHBn **5**	toluene, 0.25	60	41
2	PhCONMeBn **6**	toluene, 1	42	26
3	PhCONHBn **7**	*o*-xylene, 0.5	59	51
4	PhCONMeBn **8**	*o*-xylene, 1	37	16
5	CONHBn **9**	toluene, 1	32	62
		toluene, 5	–	**94**
6	CONHBn **10**	**toluene, 24**	8	**93**
7	CONHBn **11**	toluene, 19	11	55
		***o*-xylene, 24**	–	**99**
8	*t*-BuCONHBn **12**	toluene, 20	5	55
		***o*-xylene, 15**	–	**94**
9	CONHBn **13**	toluene, 2	25	77
		toluene, 5	–	**95**
10	CONHBn **14**	toluene, 24	15	22
		***o*-xylene, 20**	20	**99**
11	$Ph_2CHCONHBn$ **15**	toluene, 2	30	32
		toluene, 11	–	**93**
12	CONMeBn **16**	*o*-xylene, 5	47	53
		***o*-xylene, 19**		**93**
13	CONHBn NHBoc **17**	toluene, 5	35	42
		toluene, 20	–	**91**[a]
14	CONHBn **18**	*o*-xylene, 1	32	62
		***o*-xylene, 9**	–	**92**

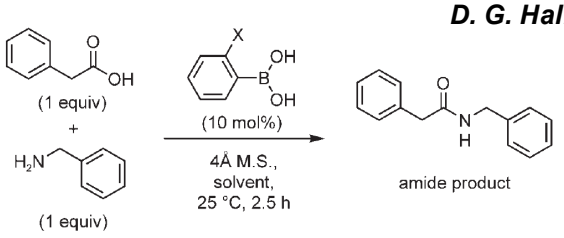
[a] Optical purity of the amide was reduced from >99% ee to 86% ee through amide condensation.

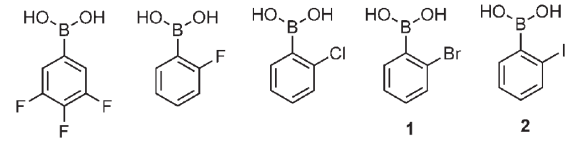
But...

These catalysts(1~3) required heating at reflux in solvent at temperatures over 110 °C.

4. *o*-halophenylboronic acid

D. G. Hall, et al. Angew. Chem. Int. Ed. 2008, 47, 2876





				1	2
THF	22%	27%	47%	49%	71%
CH_2Cl_2	42%	41%	64%	76%	91%

Scheme 2. Comparison of product yields between the most promising *ortho*-substituted arylboronic acid catalysts in a model amidation reaction.

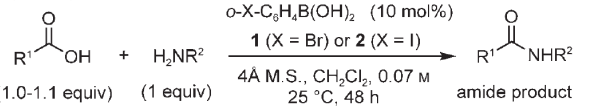
*MS4Å is essential to scavenge the water by-product of the reaction.

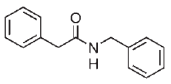
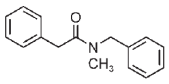
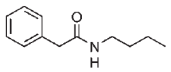
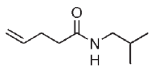
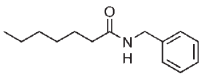
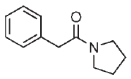
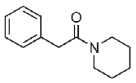
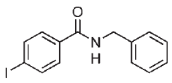
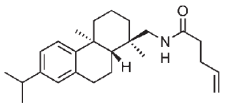
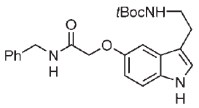
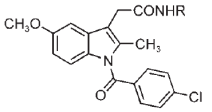
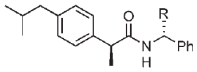
Why is the catalyst 2 so effective?

- *para* isomer is significantly less effective
- *o,o'*-dihaloarylboronic acids are less reactive
- inductive effects alone cannot account for

The reason is unclear at present...

Table 1: Direct amidations between carboxylic acids and amines catalyzed by boronic acids **1** and **2** at room temperature.[a]



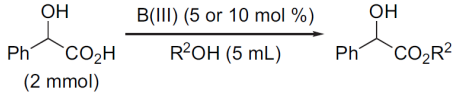
1		99%
2		0%
3		66% (87% in THF)
4		80%
5		99%
6		41% 76% (with **2**)
7		52% (with **2**) 97% (with **2** in THF)
8		24% (with 20 mol% **2** in toluene at 50°C)
9		74% (with **2**)
10		95% (with 20 mol% **2**)
11		R = $(CH_3)_2CHCH_2$ 73% R = $PhCH_2$ 93%
12		R = H 73% (with **2** in THF) R = CH_3 70% (with 20 mol% **2**, THF, 16 h)

[a] The boronic acid (0.05 mmol), carboxylic acid (0.50-0.55 mmol), and the amine (0.5 mmol) were stirred at 24–25 °C for 48 h in solvent containing powdered activated 4Å molecular sieves (1 g). Unless indicated otherwise, amidations took place in CH_2Cl_2 with catalyst **1** (10 mol%). Product purity was greater than 95% according to ^{1}H NMR spectroscopic analysis. Boc = butoxycarbonyl.

Catalyst 2 functions under practical and mild conditions at room temperature!!

2-2. boron compound-catalyzed ester condensation

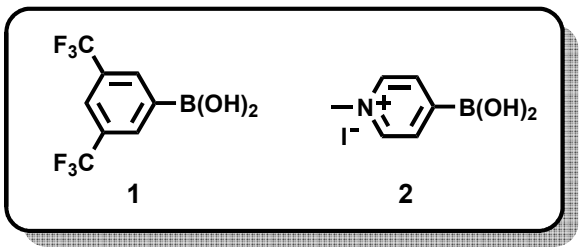
ester condensation of α-hydroxycarboxylic acids

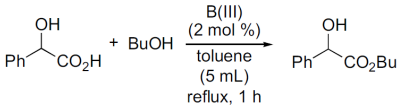


Yamamoto, H. et al. Tetrahedron. 2007, 63, 8645

Entry	R^2OH	Temp, time (h)	Conv. (%)		
			$B(OH)_3$	**1**	**2**
1[a]	MeOH	rt, 2	28	48	77
2[a]	EtOH	rt, 5	24	19	43
3[b]	*i*-BuOH	Reflux, 1	36	32	83
4[a]	*i*-PrOH	Reflux, 5	29	14	52
5[b]	$(CH_2OH)_2$	80 °C, 1.5	48[c]	29[c]	83[c]

[a] Catalyst (10 mol %) was used.
[b] Catalyst (5 mol %) was used.
[c] 2-Hydroxyethyl mandelate was produced.





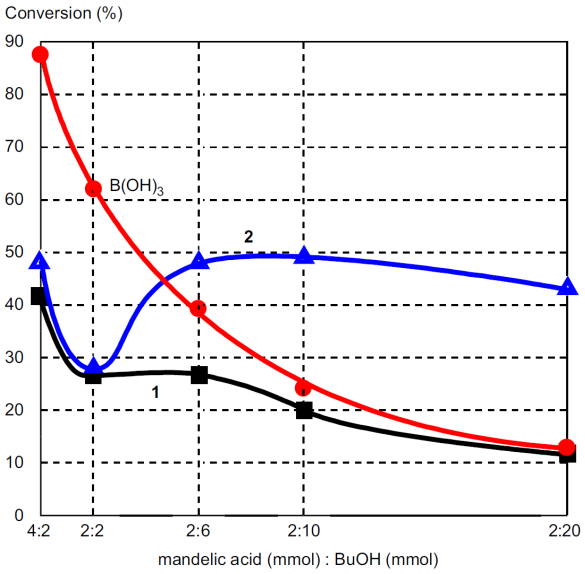
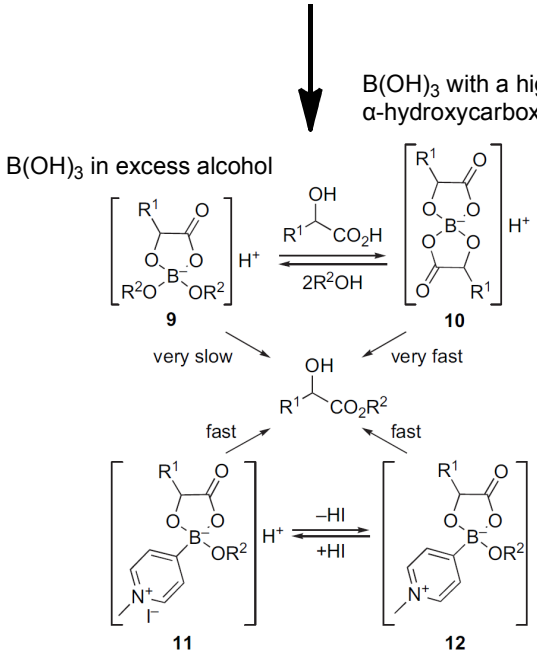
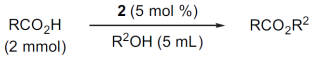


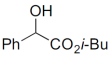
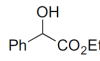
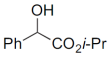
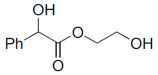
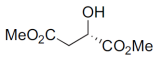
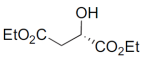
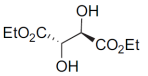
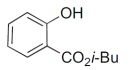
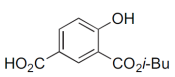
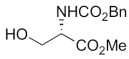
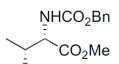
Figure 3. Correlation between the catalytic activity of boron(III) compounds and the molar ratio of mandelic acid and butanol.

- Boric acid was the most active catalyst with a molar ratio of mandelic acid/butanol of >1:2.
- **2** was the most active catalyst with a molar ratio of mandelic acid/butanol of <1:3.



Not only α-hydroxycarboxylic acids but also β-hydroxycarboxylic acids were condensed.



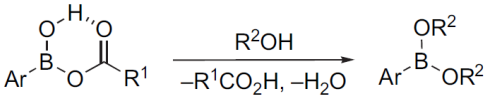
Entry	Temp, time (h)	Product	Yield (%)
1	rt, 10		93
2	Reflux, 6		99
3	rt, 10		96
4	Reflux, 15		92
5	Reflux, 4		95
6[a]	Reflux, 21		81
7	80 °C, 5		97
8[a]	Reflux, 15		95
9[a]	Reflux, 23		86
10[a]	Reflux, 18		92
11	Reflux, 17		85
12[b,c]	Reflux, 20		84
13	Reflux, 20		93
14	Reflux, 22		89

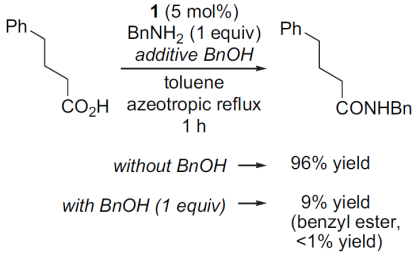
[a] Dicarboxylic acid was used as a substrate.
[b] Compound **2** (10 mol %) was used.
[c] Diisobutyl 4-hydroxyisophthalate and 2-hydroxy-5-(isobutoxycarbonyl)-benzoic acid were produced in respective yields of 5 and 2%.

limitation of this reaction

Boron(III) compounds were much less effective for the esterification of simple carboxylic acids.

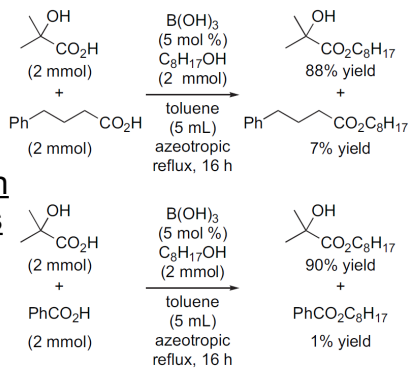
This is because an alkoxyborane species is preferentially produced rather than the desired acyloxyborane species.





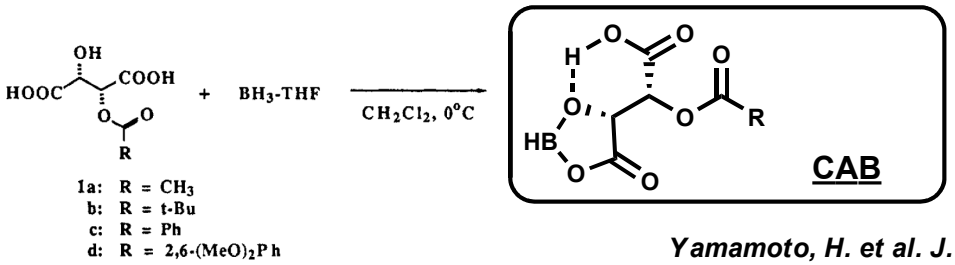
Amide condensation is suppressed in the presence of alcohol.

chemoselective esterification of α-hydroxycarboxylic acids



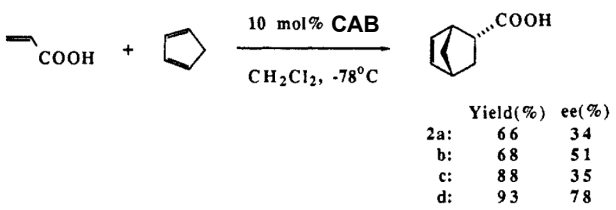
2-3. boron compound-catalyzed Diels-Alder reaction

1. CAB (chiral acyloxyborane) catalysts



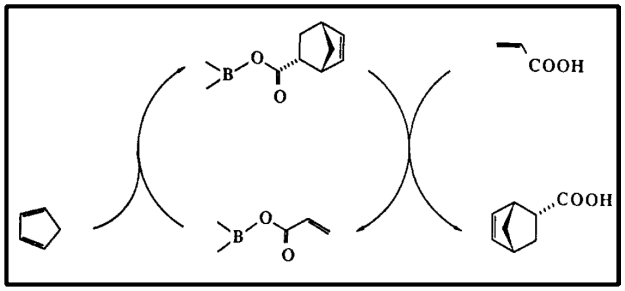
1a: R = CH_3
b: R = t-Bu
c: R = Ph
d: R = 2,6-$(MeO)_2$Ph

Yamamoto, H. et al. J. Am. Chem. Soc. 1988, 110, 6254

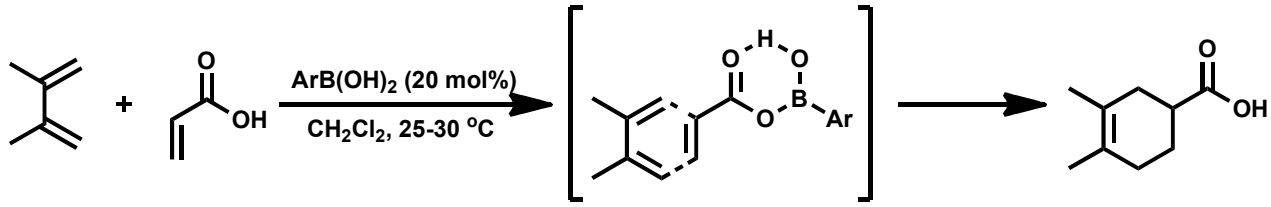


	Yield(%)	ee(%)
2a:	66	34
b:	68	51
c:	88	35
d:	93	78

catalytic cycle



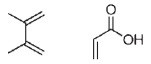
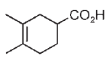
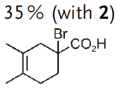
2. boronic acid



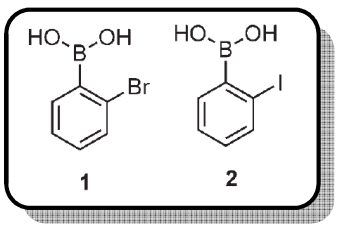
D. G. Hall, et al. Angew. Chem. Int. Ed. 2008, 47, 2876

Table 2: Diels–Alder cycloadditions of free α,β-unsaturated carboxylic acids catalyzed by boronic acids **1** and **2**.[a]

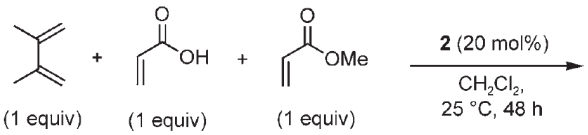
diene (2 equiv) + dienophile (1 equiv) —*o*-Br-$C_6H_4B(OH)_2$ (**1**) (20 mol%), CH_2Cl_2 1.0 M, 25-30 °C, 48 h→ cycloadduct

1				
			no catalyst	5%
			1 with 1.0 equiv water	25%
			1 with 0.1 equiv water	76%
			1 with no water added	90%
			1 with 4Å M.S.	20%
2				
				99% (24 h)
3				
				35% (with **2**)
4				
				71%

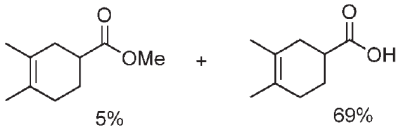
[a] The boronic acid (0.28 mmol), carboxylic acid (1.4 mmol), and diene (2.78 mmol) were stirred at 25 °C in dichloromethane. Unless indicated, the mixture was stirred for 48 h with catalyst **1** (20 mol%). Yields are for purified products.



selective activation of carboxylic acid



(1 equiv) (1 equiv) (1 equiv)

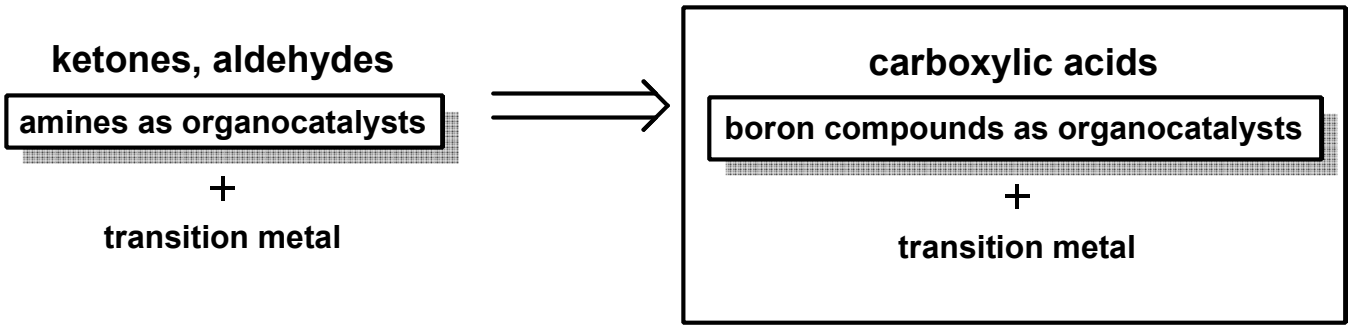


5% 69%

A remarkable selectivity of carboxylic acids over the corresponding esters!!

3. Dual activation of carboxylic acids by combining transition metal and boron catalysts

0. concept



1. motivation

Some boron compounds-catalyzed reactions using carboxylic acids as substrates were reported.

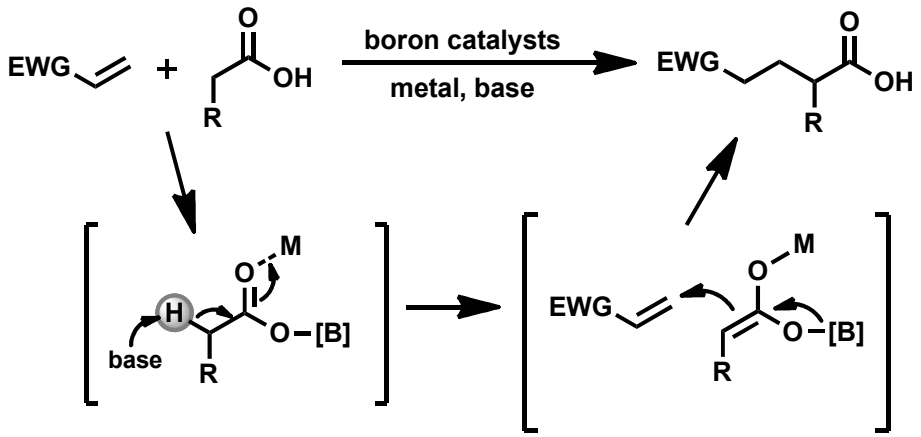
- •amide condensation
- •ester condensation
- •Diels-Alder reaction

(see Chapter 2-2)

But the reaction using carboxylic acids as nucleophiles seemed to be difficult so far.

dual activation by transition metal and boron catalysts

These reactions (such as Michael addition, aldol reaction...) will be possible.



*boron catalysts, metal, and base(NEt_3 etc.) can coexist (see p.14)

2. advantage

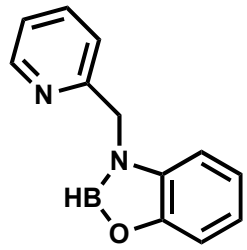
Boron compounds can selectively activate carboxylic acids. (see p.20)

carboxylic acids are activated enough to be deprotonated the α-proton by weak base

Chemoselective nucleophilic addition of carboxylic acids will be possible.

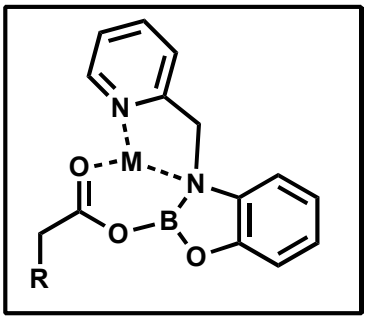
3. catalyst design

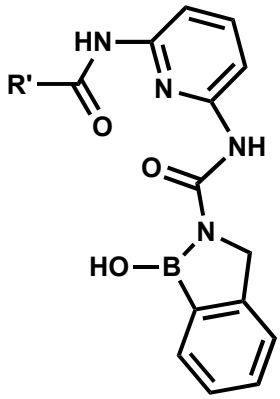
•using a bidentate (or tridentate) ligand tethered with a boron compound



catalyst

active species





catalyst