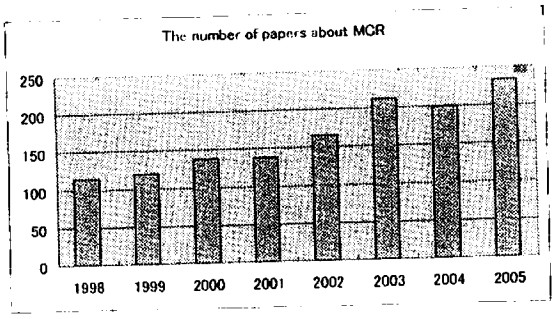
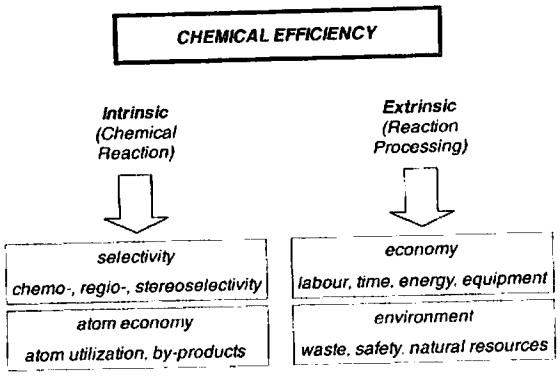
Asymmetric Multicomponent Reaction (AMCR) using Enantioselective Approach

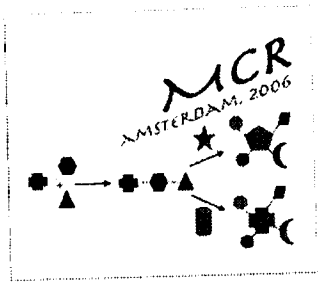
Chen ZhiHua

1. Intruduction:



Scheme 1 Key criteria for chemical efficiency





3rd International Conference on Multi-Component Reactions will be held on July 9 2006 in Amsterdam The Netherlands.

What is Asymmetric Multicomponent Reaction (AMCR)

It should be defined as the reaciton between three or more either achiral reagent in a single vessle which have been added together (or nearly) to form stereoselectively a new chiral compound that contains portions of all the components, forming at least one new stereogenic element.

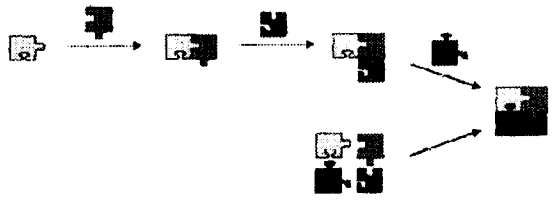
Approach of AMCR

1. Using diastereoselective Approach
2. **Using Enantioselective Approach**

Reviews: *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
Tetrahedron **2006**, 62, 2143.
Chem. Eur. J. **2003**, *9*, 4286.
Chem. Rev. **1996**, *96*, 115.

Moreover, developing of MCR is fit for the needs of Combinatorial Library Synthesis.

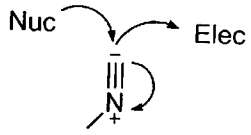
Contents:



Multi-step (top) vs. multicomponent (bottom) assembly of the same compound.

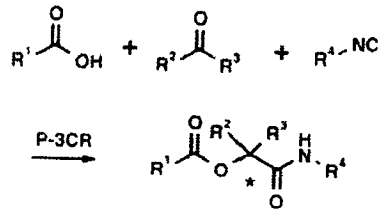
2. AMCR based on Isocyanide

The most important property of isocyanides is the reaction with **nucleophiles** and **electrophiles** at the isocynaide carbon atom.

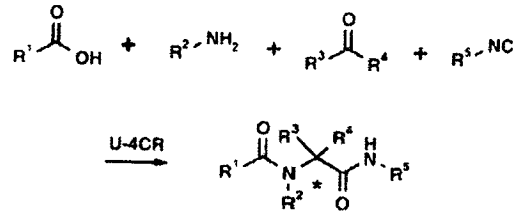


Reviews: *Chem. Rev.* **2006**, *106*, 17.
Angew. Chem. Int. Ed. **2000**, *39*, 3168.

Passerini Reaction

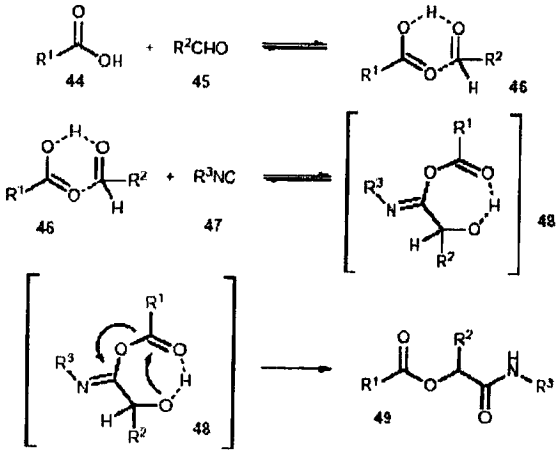


Ugi Reaction



2.1 Passerini Reaction: involving an oxo component, an isocyanide, and a nucleophile.

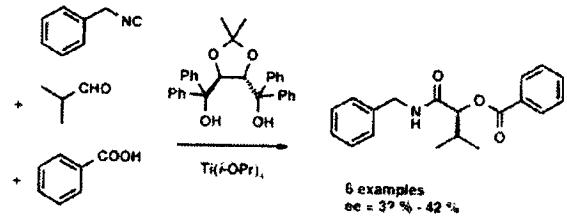
Scheme 2 Suggested mechanism of the P-3CR



Two example of catalytic asymmetric Passerini Reaction

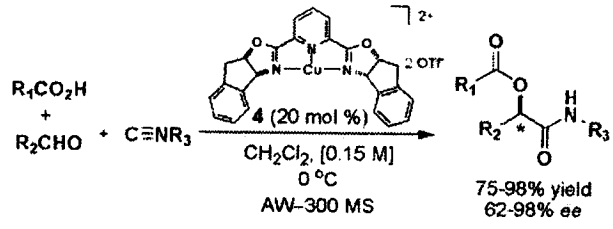
a. Domling Group: Lewis acid/Chiral ligand

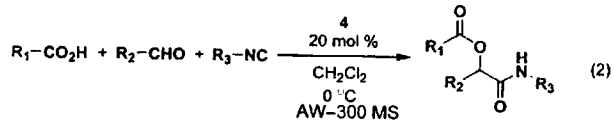
Org. Lett. **2003**, *5*, 4021



b. Schreiber Group: Cu (II)-pybox complex

Org. Lett. **2004**, *6*, 4231





entry[a]	R_1	R_2	R_3	product	% yield[b]	% ee[c]
1	$PhCH_2$ (9)	2-furyl (10)	$PhCH_2$ (11)	16	83	62 (*R*)[d]
2	$PhCH_2$ (9)	$BnOCH_2$ (6)	$PhCH_2$ (11)	17	87	72
3	Ph (5)	2-thiophenecarboxyl (12)	*t*-butyl (13)	18	95	82 (*R*)
4	Ph (5)	$BnOCH_2$ (6)	*n*-butyl (14)	19	87	88
5	Ph (5)	$BnOCH_2$ (6)	*n*-pentyl (15)	20	83	89
6	Ph (5)	$BnOCH_2$ (6)	$PhCH_2$ (11)	21	89	93
7	Ph (5)	$BnOCH_2$ (6)	*t*-butyl (13)	22	95	98
8	Ph (5)	2-furyl (10)	*p*-MeOPh (7)	23	98	91 (*R*)
9	Ph (5)	2-furyl (10)	$PhCH_2$ (11)	24	90	75 (*R*)
10	Ph (5)	2-furyl (10)	*t*-butyl (13)	25	97	89 (*R*)
11	Ph (5)	2-furyl (10)	*n*-butyl (14)	26	82	78 (*R*)
12	Ph (5)	2-furyl (10)	*n*-pentyl (15)	27	82	78 (*R*)
13	Ph (5)	2-thiophenecarboxyl (12)	*p*-MeOPh (7)	28	95	89 (*R*)
14	Ph (5)	2-thiophenecarboxyl (12)	$PhCH_2$ (11)	29	87	75 (*R*)
15	Ph (5)	2-thiophenecarboxyl (12)	*n*-butyl (14)	30	76	64 (*R*)
16	Ph (5)	2-thiophenecarboxyl (12)	*n*-pentyl (15)	31	75	60 (*R*)

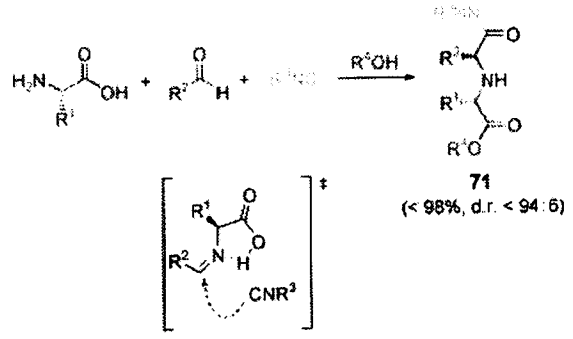
[a] [0.15 M] final. [b] Isolated yield. [c] See the Supporting Information for HPLC conditions. [d] Inferred absolute stereochemistry based on X-ray crystal analysis with 5-bromo-2-furaldehyde as the substrate.

2.2 Ugi Reaction: involved a schiff base or an enamine with a nucleophile and an isocyanide

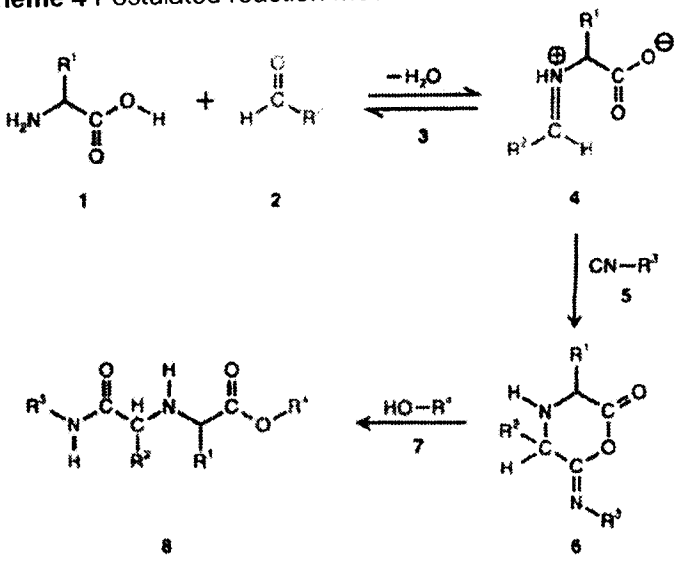
Angew. Chem. Int. Ed. **1996**, *35*, 173.

*** high degree of diversity**
*** two possible amide bonds**

Scheme 3 Diastereoselective Ugi four-component reaction with a chiral α-amino acid

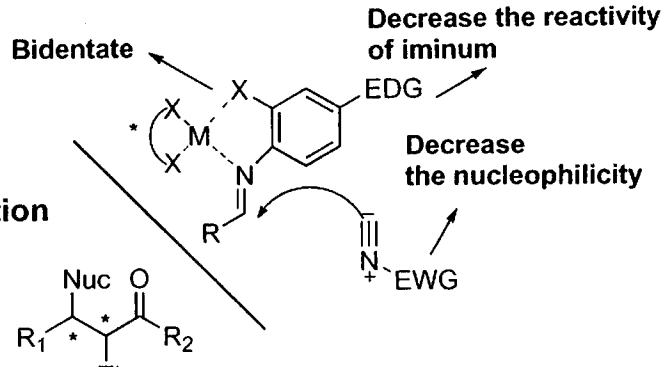


Scheme 4 Postulated reaction mechanism for the U-4CR



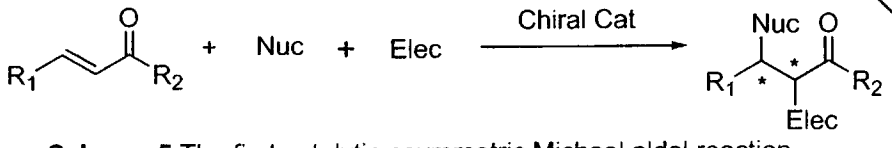
Why enantioselective approach is difficult:

1. **high reactivity**
2. **the amide bonds of product**

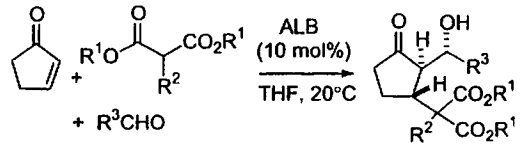


3. AMCR based on Tandem Conjugate

3.1 Tandem Enantioselective Conjugate Addition

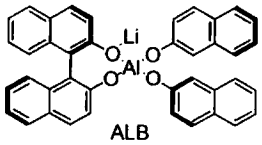


Scheme 5 The first catalytic asymmetric Michael aldol reaction



R^1 = Et, R^2 = Me, R^3 = $Ph(CH_2)_2$: 64% ee = 91%

R^1 = Et, R^2 = Me, R^3 = Ph: 82% ee = 89%



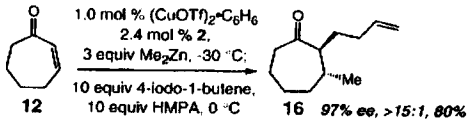
Angew. Chem. Int. Ed. **1996**, *35*, 104
Angew. Chem. Int. Ed. **1997**, *36*, 1236
J. Org. Chem. **1998**, *63*, 3666

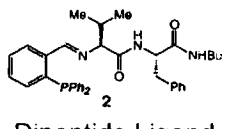
a. Hayashi Tamio Group: Rh catalyst

J. Am. Chem. Soc. **2001**, *123*, 755.

Hoveyda Group: Cu-dipeptide catalyst

Scheme 6 Cu-catalyzed conjugate addition to seven-menbered cyclic enones





Dipeptide Ligand

This type of catalyst works for the first step (1,4 addition) but has nothing to do with the second step.

For others this type examples

J. Am. Chem. Soc. **2001**, *123*, 4358.
J. Am. Chem. Soc. **2001**, *123*, 5841.

Hayashi Tamio Group: Rh catalyst

J. Am. Chem. Soc. **2002**, *124*, 10984.

Both 1,4 addition and the aldol reactions are catalyzed by a rhodium complex.

Table 1 Tandem 1,4-Addition-Aldol Reaction

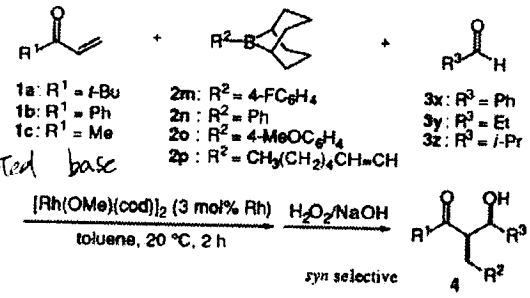
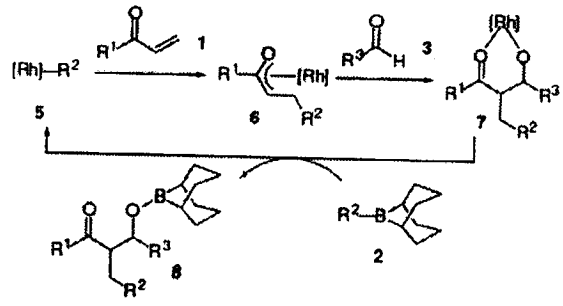


Table 1. Rhodium-Catalyzed Tandem Conjugate Addition–Aldol Reaction of Enone **1**, *B*-*R*-9BBN **2**, and Aldehyde **3**[a]

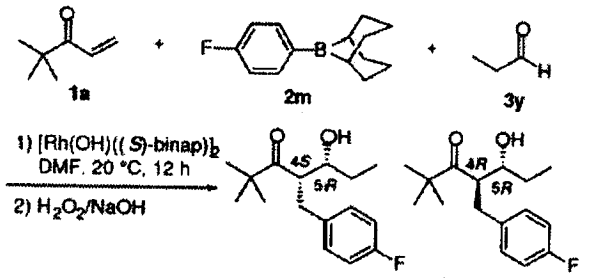
entry	enone 1	*B*-*R*-9BBN 2	aldehyde 3	product 4	yield (%)[b]	syn/anti[c]
1	1a	2m	3x	4amx	96	9.6/1
2	1a	2n	3x	4anx	97	10.7/1
3	1a	2o	3x	4aox	99	8.9/1
4[d]	1a	2p	3x	4apx	85	21.4/1
5	1a	2m	3y	4amy	72	12.4/1
6	1b	2m	3x	4bmx	88	9.0/1
7	1b	2m	3z	4bmz	93	9.0/1
8	1c	2m	3x	4cmx	99	5.7/1

Scheme 7

Mechanism: through (Oxa-π-allyl) rhodium intermediate



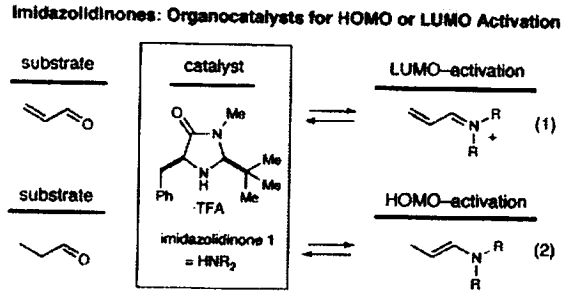
Scheme 8 Enantioselective 1,4-Addition-Aldol Reaction



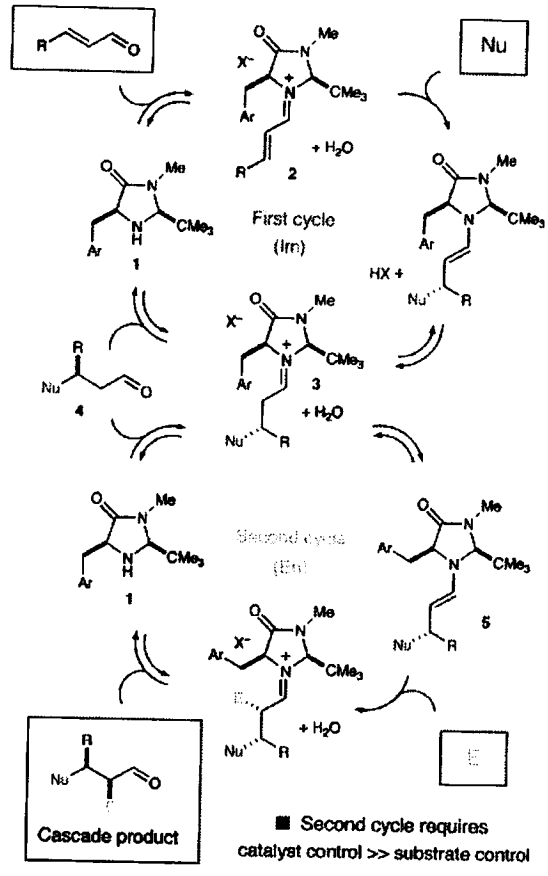
syn-**4amy** (41% ee) *anti*-**4amy** (94% ee)
syn/*anti* = 0.8/1

b. MacMillan Group: Cascade catalyst

Scheme 9 *J. Am. Chem. Soc.* **2005**, *127*, 15051.



Scheme 10 Concept



Scheme 11 Catalysts

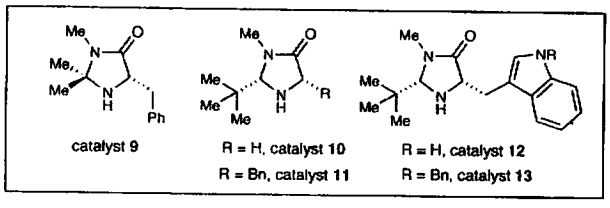
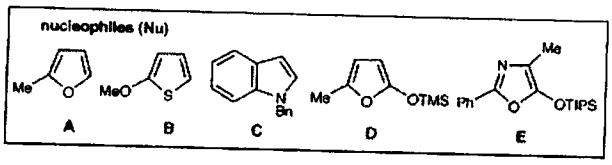
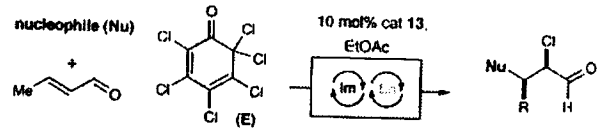
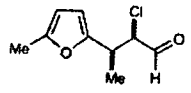
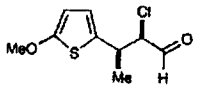
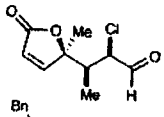
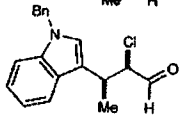
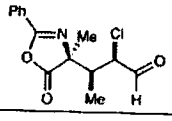


Table 2 Scope of Representative Nucleophiles





entry	nucleophile	product	temp (°C)	% yield	dr[a]	% ee
1	A		−50	86	14:1	99
2	B		−50	77	11:1	99
3[b]	D		−55	71	>25:1	>99
4	C		−60	75	12:1	>99
5	E		−40	97	9:1	>99

[a] Absolute and relative configuration assigned by chemical correlation. [b] Superior yields were obtained when the electrophile was added after consumption of the silyloxy furan.

Scheme 12 Scope of Electrophiles

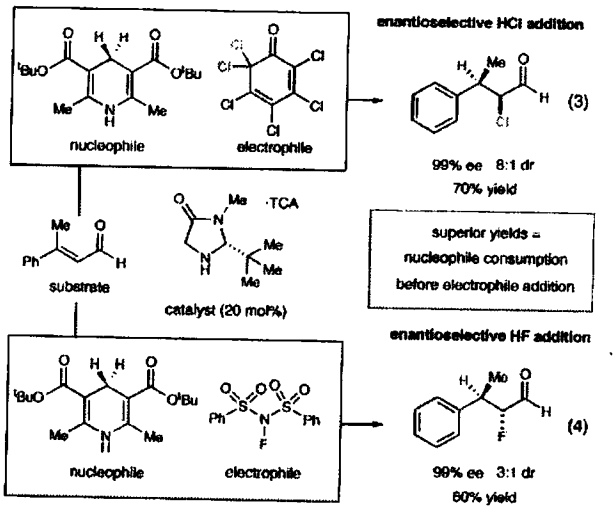
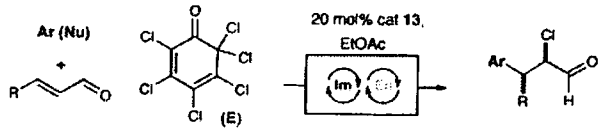
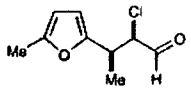
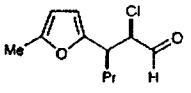
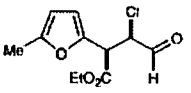
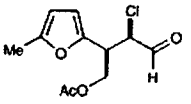
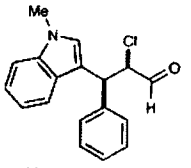
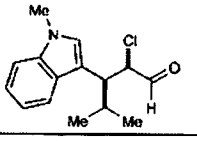


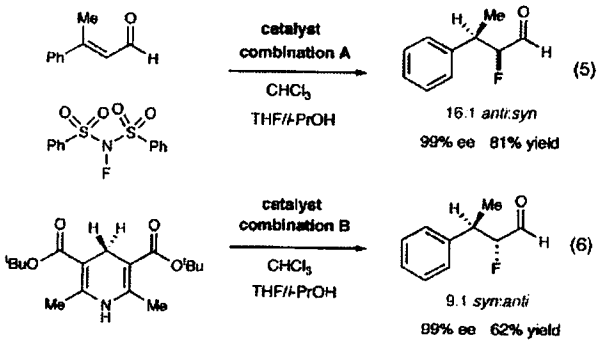
Table 3 Scope of Enal Component

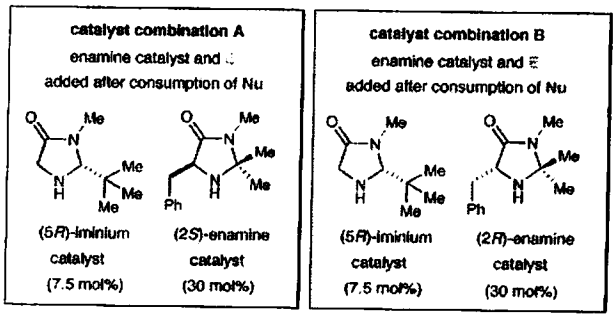


entry	R =	product	temp (°C)	% yield	dr[a]	% ee[b]
1	Me		−50	86	14:1	99
2	Pr		−50	74	13:1	99
3	CO_2Et		−60	80	22:1	99
4	CH_2OAc		−40	82	11:1	>99
5	Ph		−40	83	9:1	99
6	*i*-Pr		−40	67	12:1	>99

[a] Absolute and relative configuration assigned by chemical correlation. [b] Enantiomeric excess determined by chiral GLC analysis.

Scheme 13 Diastereoselectivity control





Similar studies:
List Group:*J. Am. Chem. Soc.* **2005**, *127*, 15036.
Jorgensen:*J. Am. Chem. Soc.* **2005**, *127*, 15710.

2.2 Knoevenagel/Diels-Alder Reaction and Wittig/Knoevenagel/Diels-Alder Reaction

Barbas Group: Amino acid Catalyst

Angew. Chem. Int. Ed. **2003**, *42*, 4233

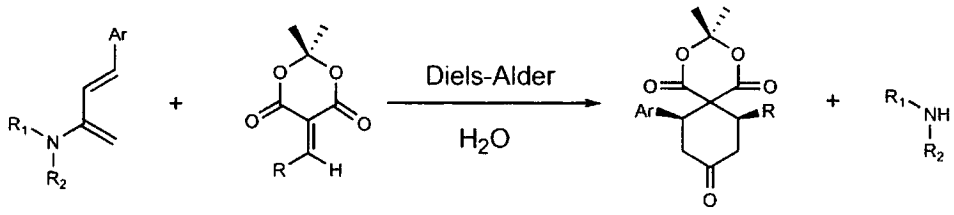
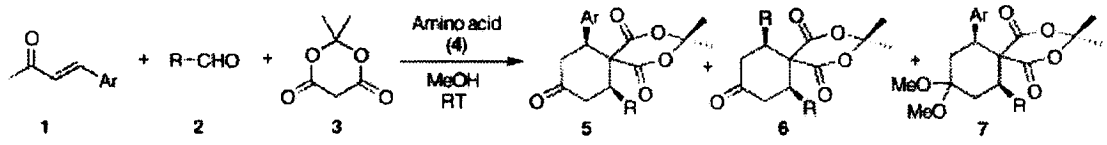
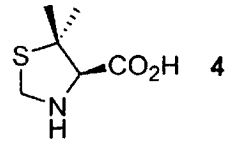


Table 4 Amino acid catalyzed asymmetric three component knoevenagel/Diels- Alder Reactions



1a: Ar = Phenyl
1b: Ar = Piperonyl
1c: Ar = 1-Naphthalenyl
1d: Ar = 2-Furanyl
1e: Ar = 2-Thiophenyl

2a: R = 4-$NO_2C_6H_4$
2b: R = 4-CNC_6H_4
2c: R = C_6H_5
2d: R = 3,4-$(OCH_2O)C_6H_3$

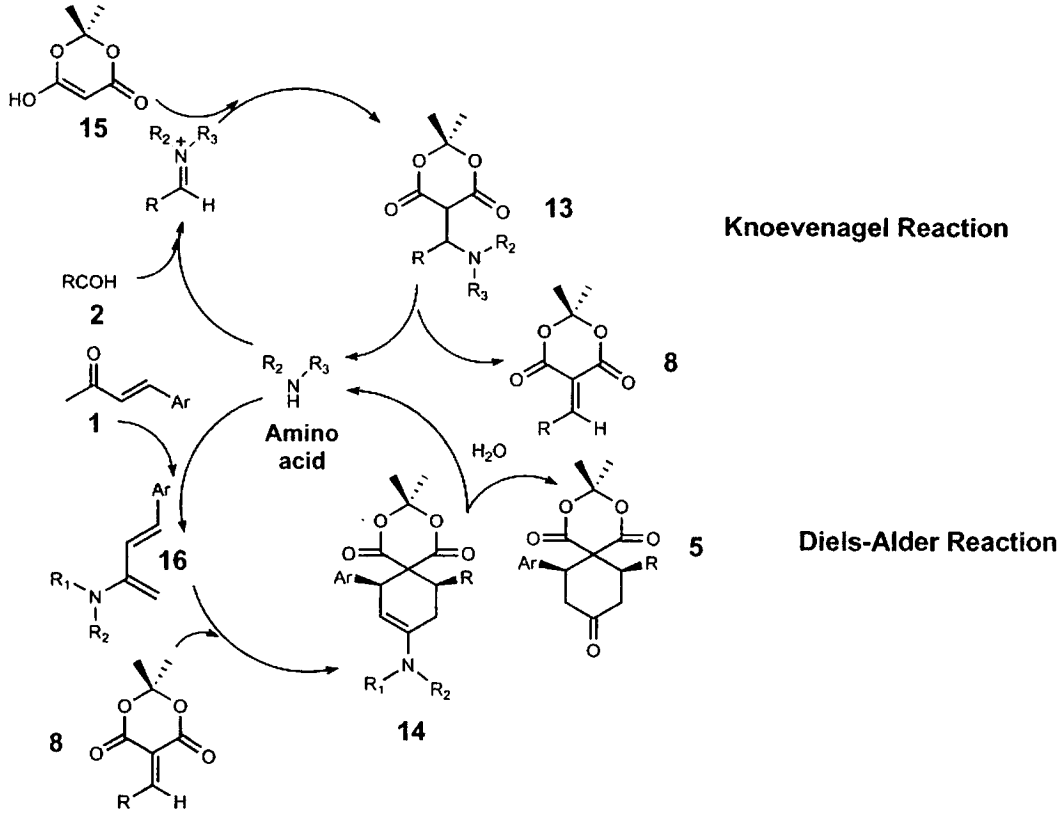


5,5-dimethyl thiazolidinium-4-carboxylate (**DMTC**)

Entry	Enone	Aldehyde	t [h]	Products	Yield [%][b]	Ratio 5:7	*ee* for 5 [%][c]
1[d]	1a	2c	96	5ac, 7ac	85	16:1	prochiral
2[d]	1b	2d	96	5bd	99	>100:1	prochiral
3	1a	2a	72	5aa, 7aa	95	13:1	86
4	1a	2b	96	5ab, 7ab	85	16:1	84
5	1c	2a	72	5ca	93	>100:1	99
6	1d	2a	72	5da, 7da	92	12:1	88
7	1e	2a	72	5ea, 7ea	80	15:1	99

[a] See Supporting Information. [b] Yield of the combined isolated products. [c] Enantiomeric excesses were determined using chiral-phase HPLC. [d] Reaction catalyzed by L-proline (0.1 mmol).

Scheme 14 Proposed reaction mechanism for the formation of the product.



Scheme 15 Proposed reaction mechanism for the formation of the unexpected product.

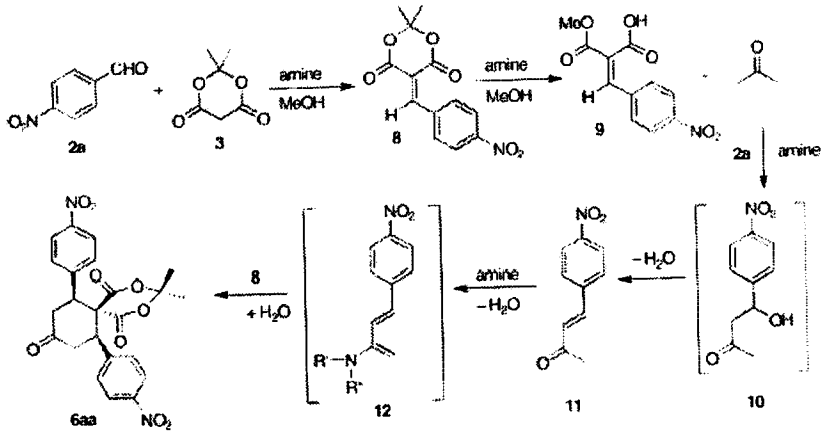
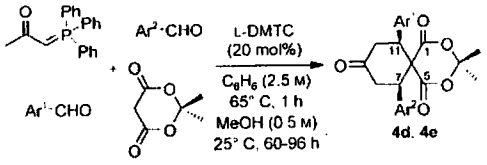


Table 5 Amino acid catalyzed asymmetric four component Wittig/Knoevenagel/Diels- Alder Reactions



Chem. Eur. J. **2004**, *10*, 5323.

Entry	Ar^1	Ar^2	Yield[%]	d.r.	er[b]	Absolute[c] configuration
1[d]	C_6H_5	4-$NO_2C_6H_4$	83	>100:1	69	(7*R*,11*S*)-**4d**
2[d]	4-$NO_2C_6H_4$	C_6H_5	80	>100:1	42	(7*S*,11*R*)-**4d**
3[e]	C_6H_5	4-CNC_6H_4	85	>100:1	70	(7*R*,11*S*)-**4e**
4[e]	4-CNC_6H_4	C_6H_5	80	>100:1	42	(7*S*,11*R*)-**4e**

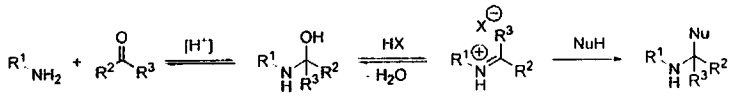
[a] Experimental conditions: aldehyde, Ar1-CHO (0.5 mmol), and 1-(triphenylphosphanylidene)-propan-2-one (0.5 mmol) in benzene (0.2 mL) were stirred at 65 °C for 1 h, then L-DMTC (0.1 mmol), aldehyde, Ar2-CHO (0.5 mmol), Meldrum's acid (0.5 mmol), and methanol (1.0 mL) were added and stirred at 25 °C (see Experimental Section). [b] Enantiomeric excesses were determined using chiral-phase HPLC. [c] Absolute configuration determined based on HPLC analysis and comparison to earlier reports. [d] Spirotriones **4a** and **4b** are formed in 2:1 ratio with 10% yield. [e] Spirotrione **4f** is formed in 10% yield.

Our Group 's paper about preparation α,β-Unsaturated N-Acylpyrroles in situ. *J. Am. Chem. Soc.* **2004**, *126*, 7559

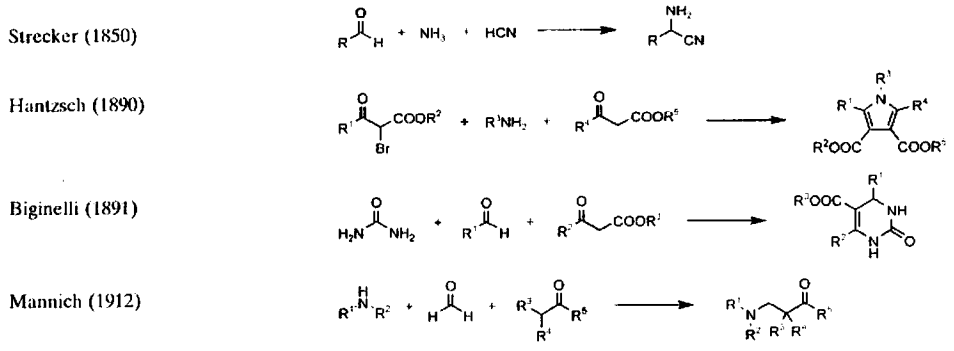
4. AMCR based on Nucleophilic addition to Imine.

Introduction:

Scheme 16 Iminium intermediate

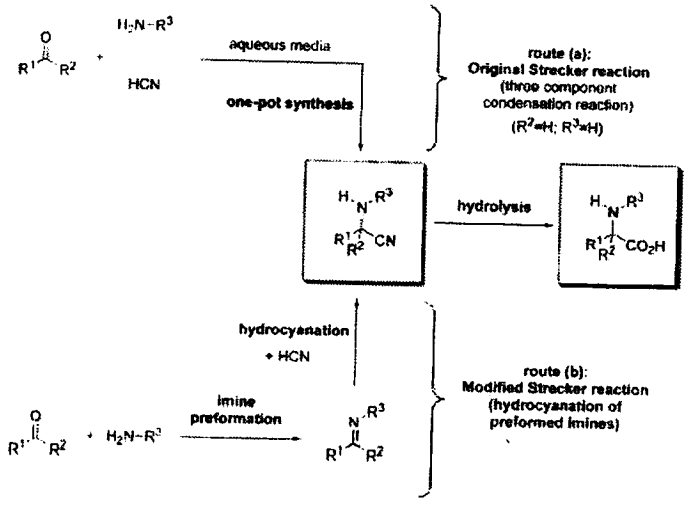


Scheme 17 Historical significant multicomponent reaction based on the α aminoalkylation of carbonyl compounds



4.1 Strecker Reaction

Scheme 18 Principles of Different Type of Strecker Reations



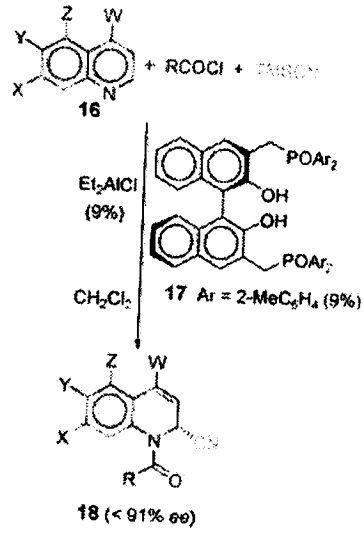
Developments in Catalytic Asymmetric Strecker-Type Reaction:

Reviews: *Chem. Rev.* **2003**, *103*, 2795.
Angew. Chem. Int. Ed. **2001**, *40*, 85.

Lipton Group: diketopiperzine-based organcatalyst
Jacobsen Group: Al(III) - salen based catalyst
Hoveyda Group: Titanium-peptide-based catalyst
Jacobsen Group: Thiourea / Urea -type organcatalyst
and so on...

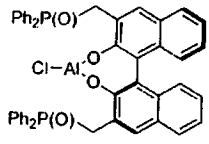
Scheme 20 Enantioselective Reissert-Henze MCR (a variant of the Strecker reation)

J. Am. Chem. Soc. **2000**, *122*, 6327
J. Am. Chem. Soc. **2001**, *123*, 6801
J. Am. Chem. Soc. **2004**, *126*, 11808

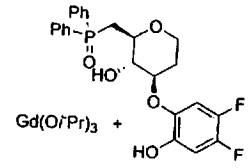


Our lab's work: Bifuntional Lewis acid - Lewis base catalyst

Scheme 19



33
aluminium-binaphthol-based catalyst
(developed by the Shibasaki group)



gadolinium-carbohydrate-based catalyst
(developed by the Shibasaki group)

J. Am. Chem. Soc. **1999**, *121*, 2641
Angew. Chem. Int. Ed. **2000**, *39*, 1650.
Chem. Pharm. Bull. **2000**, *48*, 1586

J. Am. Chem. Soc. **2003**, *125*, 5634

Catalytic Asymmetric Strecker Reaction: (Kobayashi Group)

Angew. Chem. Int. Ed. **1998**, *37*, 3186.
J. Am. Chem. Soc. **2000**, *122*, 762.

Scheme 21 Preparation of Chiral Zirconium Catalyst

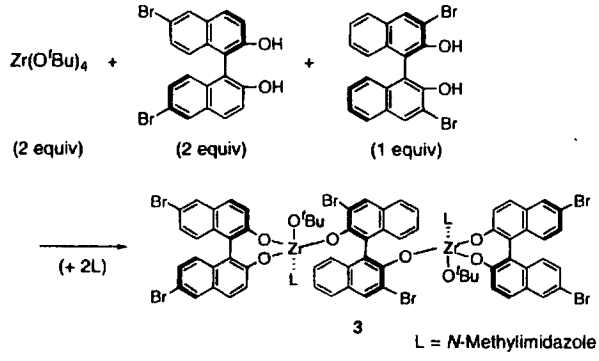
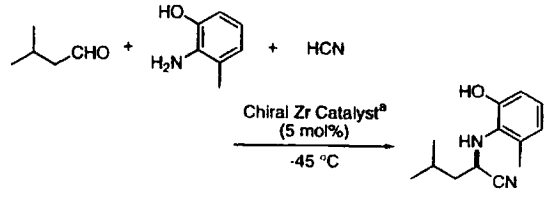


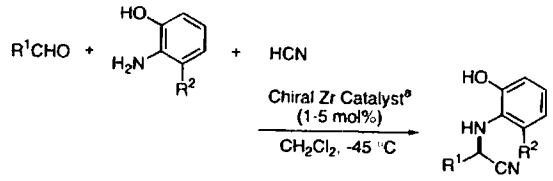
Table 6 Effect of Solvents and Concentration



entry	solvent	additive	concn (M)	yield (%)	ee (%)
1[b]	toluene	MS 4A	0.04	63	65
2[c]	toluene	MS 4A	0.04	49	79
3[c]	CH_2Cl_2	MS 4A	0.04	63	85
4[c]	CH_2Cl_2	none	0.01	99	94

[a] See text. [b] Aldehyde, amine, and HCN were added to catalyst 3. [c] HCN was added to catalyst 3 first and this catalyst solution was added to the mixture of aldehyde and amine.

Table 7 Catalytic Asymmetric Strecker Reactions Using HCN



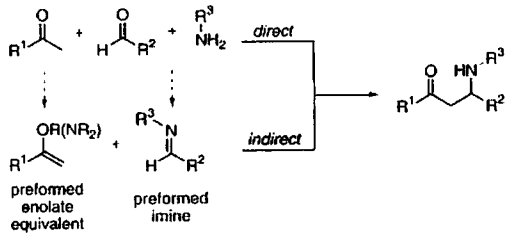
R^1	R^2	catalyst (mol %)	yield (%)	ee (%)
Ph	H	5	80	86
α-Nap	H	5	83	85
$Ph(CH_2)_2$	CH_3	2.5	85	94
$Ph(CH_2)_2$	CH_3	2.5	76	93 (*S*)[b]
C_8H_{17}	CH_3	2.5	83	90
C_8H_{17}	CH_3	1	86	84
C_8H_{17}	CH_3	2.5	93	91[c]
^{t}Bu	CH_3	5	99	94
^{t}Bu	CH_3	2.5	94	91
c-C_6H_{11}	CH_3	5	95	94
^{t}Bu	CH_3	5	quant	86
^{t}Bu	CH_3	2.5	quant	88[c]

[a] See text. [b] (*S*)-3-Br-BINOL and (*S*)-6-Br-BINOL were used. [c] $Zr(O^nPr)_4$ was used instead of $Zr(O^tBu)_4$.

4.2 Mannich Reaction (a classic method for the preparation of β-amino carbonyl compounds)

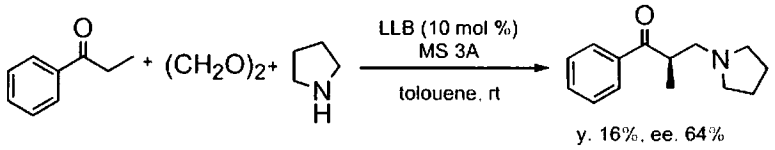
Scheme 22 Direct and Indirect

Review: *Acc. Chem. Res.* **2004**, *37*, 102



Our group: The first report of a direct catalytic asymmetric Mannich

Tetrahedron Lett. **1999**, *40*, 307

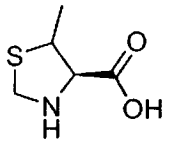


y. 16%, ee. 64%

Developments in Direct Catalytic Asymmetric Mannich-Type Reaction:

Trost group: Dinuclear zinc catalyst

Barbas group: 5,5-dimethylthiazolidine-4-carboxylic acid

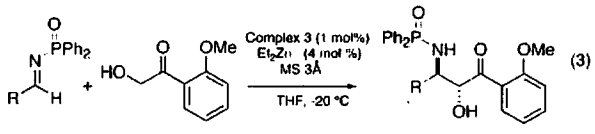


Jorgensen group: Chiral copper (II) bisoxazoline (BOX) catalyst

Our group: Et_2Zn/linked-BINOL complex

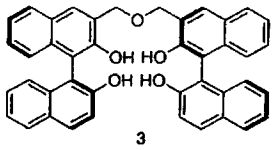
Scheme 23 Mannich-type reaction using Et_2Zn/linked-BINOL complex

J. Am. Chem. Soc. **2003**, *125*, 2582

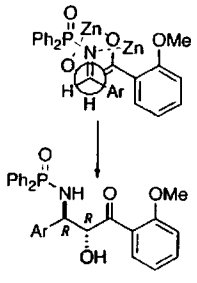


R
4-MeC_6H_4
2-MeC_6H_4
C_6H_4
4-$NO_2C_6H_4$
4-$MeOC_6H_4$
4-ClC_8H_4
1-Naphtyl
2-furyl
E-cinnam
cyclo-propyl

96-98% yield
3:1- >49:1 dr
98->99.5% ee



3

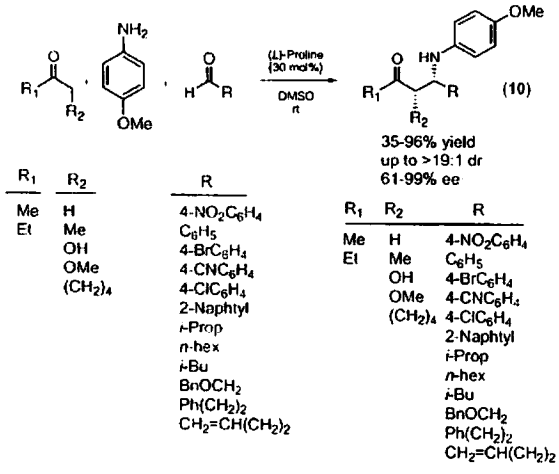


The Direct Catalytic Asymmetric Three-Component Mannich Reaction

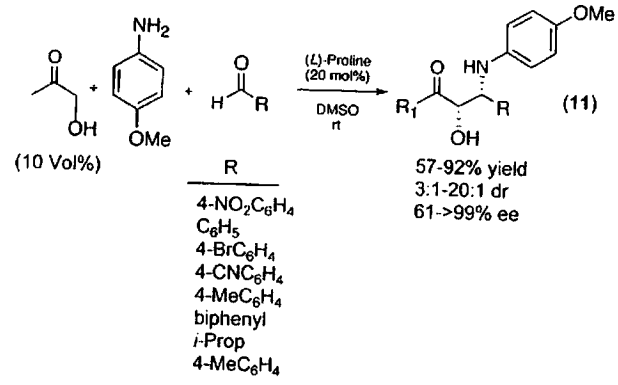
a. List Group

Acc. Chem. Res. **2004**, *37*, 548
J. Am. Chem. Soc. **2000**, *122*, 9336.
J. Am. Chem. Soc. **2002**, *124*, 827.

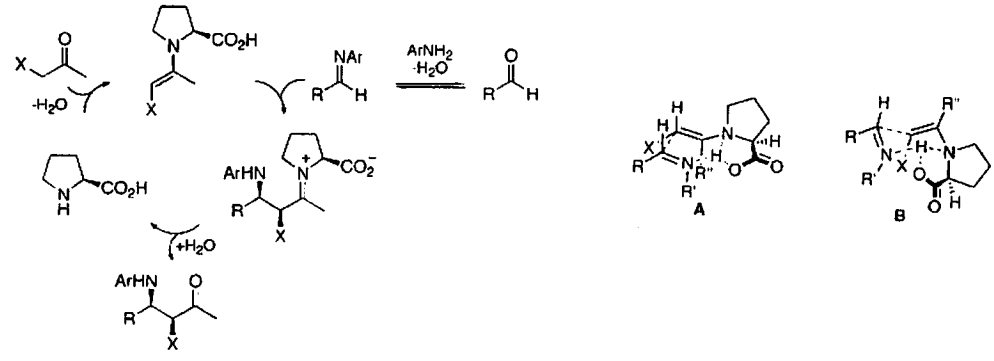
Scheme 24 The proline-catalyzed Mannich one-pot three-component reaction.



Scheme 25 Catalytic enantioselective synthesis of syn- 1,2-amino alcohols



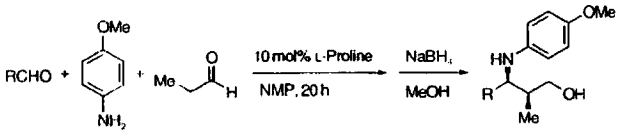
Scheme 26 Proposed Mechanism



b. Hayashi Yujiro Group:

Angew. Chem. Int. Ed. **2003**, *42*, 3677.

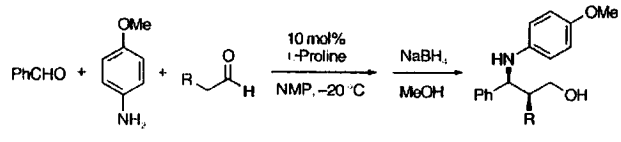
Table 8 Three-component Mannich reaction with various acceptor aldehydes



Entry	Aldehyde	T [°C]	Yield [%][b]	*syn*:*anti*	*ee* [%][c]
1	benzaldehyde	23	<10	n.d[d]	n.d
2	benzaldehyde	0	15	>95:5	n.d
3	benzaldehyde	−10	50	>95:5	90
4	benzaldehyde	−20	90	>95:5	98
5	benzaldehyde[e]	−20	71	>95:5	96
6	*p*-nitrobenzaldehyde	23	<10	n.d	n.d
7	*p*-nitrobenzaldehyde	0	89	>95:5	95
8	*p*-nitrobenzaldehyde	−10	93	>95:5	99
9	*p*-bromobenzaldehyde	−10	85	>95:5	95
10	*p*-bromobenzaldehyde	−20	33	>95:5	98
11	*p*-chlorobenzaldehyde	−20	91	>95:5	98
12	2-naphthaldehyde	−20	59	>95:5	96
13	*p*-tolualdehyde[e]	−20	95	>95:5	86
14	furfural	−20	87	>95:5	84
15	*p*-pyridinecarbaldehyde	−20	84[f]	>95:5	>99

[a] Reaction conditions: aldehyde:4-methoxyaniline:propanal:proline = 1.0:1.1:3.0:0.1. NMP was used as the solvent except in entries 5 and 13. Reaction time: 20 h. [b] Yield of the isolated amino alcohol. [c] The *ee* values were determined by chiral HPLC analysis (CHIRAPAK AD-H or AS-H). [d] Not determined. [e] DMF was used as the solvent. [f] Yield of the corresponding amino *tert*-butyldimethylsilyl ether, see text.

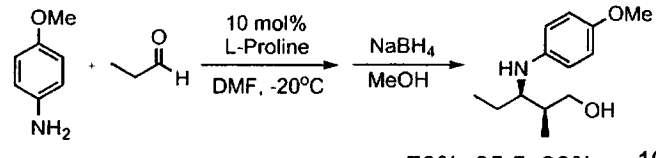
Table 9 Three-component Mannich reaction with various donor aldehydes



Entry	R	Yield [%][b]	*syn*:*anti*	*ee* [%][c]
1	Me	90	>95:5	98
2	Et	85	>95:5	97
3	*n*Pr	55	>95:5	71

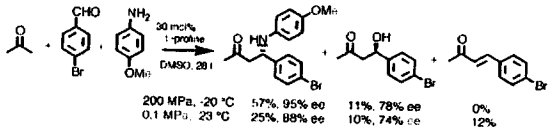
[a] Reaction conditions: benzaldehyde:4-methoxyaniline:aldehyde:proline = 1.0:1.1:3.0:0.1 [b] Yield of the isolated amino alcohol. [c] *ee* values were determined by chiral HPLC analysis (CHIRAPAK AD-H).

Scheme 27 The self-Mannich reaction of propanal



70%, 95:5, 96%ee

Scheme 28 Application of High pressure Induced by water-freezing to the Three-component Mannich Reaction



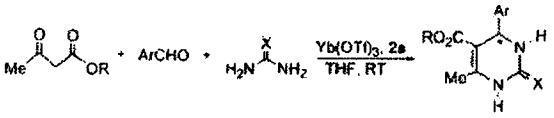
J. Am. Chem. Soc. **2003**, *125*, 11208.

4.3 Biginelli Reaction

(Asymmetric synthesis of Dihydropyrimidines)

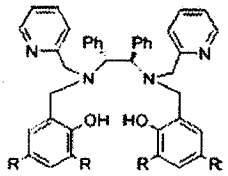
Scheme 29 Enantioselective Three -component Biginelli Reaction catalyzed by Yb-hexadentate complex

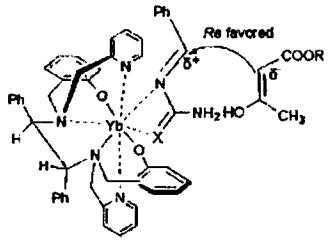
J. Am. Chem. Soc. **2005**, *127*, 16386.



R = Et, ^{i}Pr X = O, S

y. 73% to 90%, ee. 80% to 99%





For further imformation, ref to Mr Noda`s report

4.4 Organometallic 1,2-Addition Processes (Preparation of Progargylamines)

Aliphatic imine is difficlut to be isolated, so one of solution is to generate it in situ.
Very recently, the preparation of the Dpp imine and Boc imine was reported

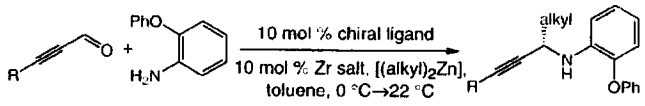
Tetrahedron Lett. **2006**, *47*, 3985
J. Am. Chem. Soc. **2006**, *128*, 6048.

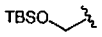
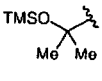
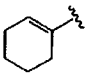
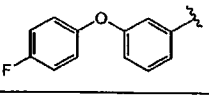
Three-component enantioselective synthesis of Progargylamines

a. Hoveyda Group

Angew. Chem. Int. Ed. **2003**, *42*, 4244

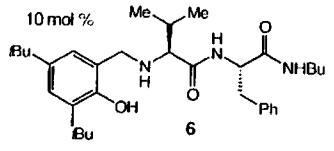
Table 10 Zr-dipeptide complex catalyzed enantioselective alkylation of alkynylamines.

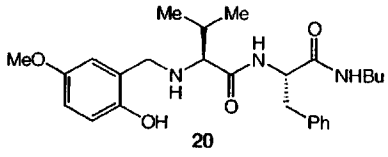


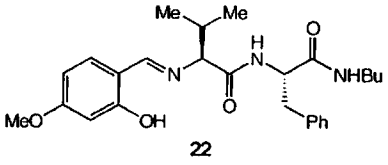
Entry	R	[(alkyl)$_2$Zn]	Zr salt	Product	Chiral ligand	Yield [%]	*ee* [%]
1	*n*Pent	3 [Me_2Zn]	[Zr(O*t*Bu)$_4$]	15	6	87	82
2	*n*Pent	3 [{$Me_2CH(CH_2)_3$}$_2$Zn]	[Zr(O*t*Bu)$_4$]	16	6	60	98
3		11 [Me_2Zn]	[Zr(O*t*Bu)$_4$]	17	6	75	92
4	TBSO	11 [Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	16	6	70	>98
5	TMSO, Me, Me 	12 [Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	19	20	86	84
6		13 [Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	21	22	89	86
7	Ph	2 [Me_2Zn]	[Zr(O*t*Bu)$_4$]	23	6	84	80
8	Ph	2 [Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	24	6	85	>98
9	Ph	2 [{$Me_2CH(CH_2)_3$}$_2$Zn]	[Zr(O*t*Bu)$_4$]	25	6	81	91
10		14 [Me_2Zn]	[Zr(O*t*Bu)$_4$]	26	6	75	93

[a] Conditions: alkyl zinc reagent (6 equiv), 4 h for reactions with [Et_2Zn], 24 h for other alkyl zinc reagents. [b] Yields of product isolated after silica-gel chromatography; >98% conversion in all cases. [c] Enantioselectivities determined by HPLC (chiralcel OD).

Dipeptide Ligand 6, 20, 22



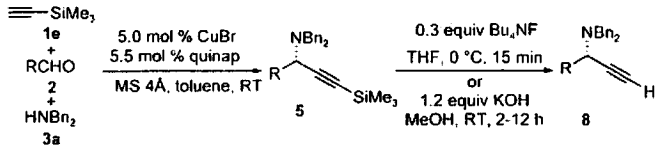


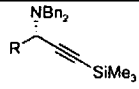
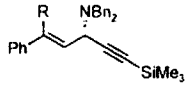
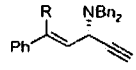
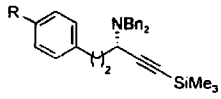
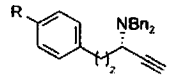
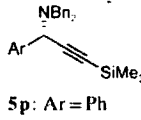


b. Knochel Group: Copper(I)-Quinap complex

Angew. Chem. Int. Ed. **2002**, *41*, 2535
Angew. Chem. Int. Ed. **2003**, *42*, 5763
Chem. Eur. J. **2006**, *12*, 4380

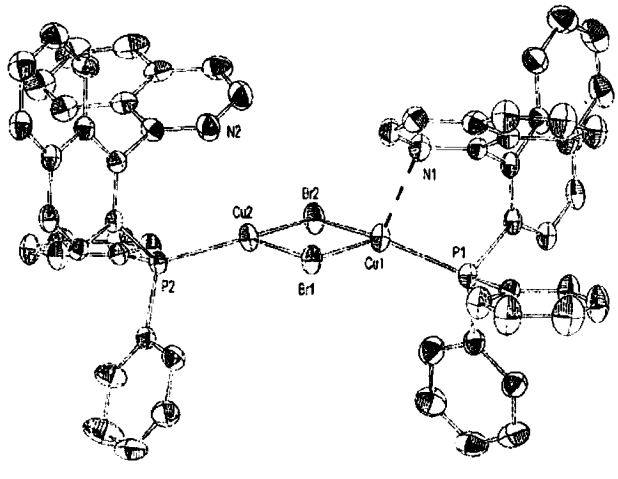
Table 11 Enantioselective three-component one-pot synthesis of silylated propargylamine 5 and disilyation to terminal propargylamines 8



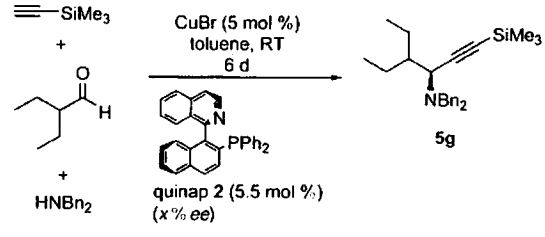
Entry	Aldehyde 2	Propargylamine 5	Yield [%][a]	*ee* [%][b]	Propargylamine 8	Yield [%][a]
						
1	**2m**: *n*PrCHO	**5c**: R = *n*Pr	90	90[c]	**8a**: R = *n*Pr	98[c]
2	**2a**: *n*BuCHO	**5d**: R = *n*Bu	82	90[c]	**8b**: R = *n*Bu	92[c]
3	**2n**: *n*PentCHO	**5e**: R = *n*Pent	99	88[d]	**8c**: R = *n*Pent	96[c]
4	**2b**: *i*BuCHO	**5f**: R = *i*Bu	85	94[d]	**8d**: R = *i*Bu	99[c]
5	**2o**: *neo*-PentCHO	**5g**: R = *neo*-Pent	94	94[d]	**8e**: R = *neo*-Pent	99[c]
6	**2c**: *i*PrCHO	**5h**: R = *i*Pr	87	96[c]	**8f**: R = *i*Pr	96[c]
7	**2p**: *s*-PentCHO	**5a**: R = *s*-Pent	95	98[c]	**8g**: R = *s*-Pent	98[c]
8	**2q**: *c*-PrCHO	**5i**: R = *c*-Pr	98	92[c]	**8h**: R = *c*-Pr	99[c]
9	**2r**: *c*-PentCHO	**5j**: R = *c*-Pent	98	96	**8i**: R = *c*-Pent	99[c]
10	**2s**: *c*-HexCHO	**5b**: R = *c*-Hex	86	97[c]	**8j**: R = *c*-Hex	93[c]
						
11	**2t**: PhCH=CH-CHO	**5k**: R = H	96	82[c]	**8k**: R = H	97[f]
12	**2u**: Ph_2C=CH-CHO	**5l**: R = Ph	82	84[c]	**8l**: R = Ph	97[f]
						
13	**2v**: $Ph(CH_2)_2CHO$	**5m**: R = H	78	88[c]	**8m**: R = H	98[c]
14	**2w**: 4-Br-C_6H_4-$(CH_2)_2CHO$	**5n**: R = Br	73	88[c]	**8n**: R = Br	98[c]
15	**2x**: 4-CO_2Et-$C_6H_4(CH_2)_2CHO$	**5o**: R = CO_2Et	96	87	**8o**: R = CO_2Et	90[c]
						
16	**2d**: PhCHO	**5p**: Ar = Ph	98	68		
17	**2y**: 2-naphthyl-CHO	**5q**: Ar = 2-naphthyl	69	54		
18	**2z**: 2-thiophen-CHO	**5r**: Ar = 2-thienyl	81	80[c]	**8p**: Ar = 2-thienyl	99[f]
19	**2aa**: 3-thiophen-CHO	**5s**: Ar = 3-thienyl	85	74[c]	**8q**: Ar = 3-thienyl	99[f]
20	**2ab**: 2-benzothiophenyl-CHO	**5t**: Ar = 2-benzothienyl	42	89		
21	**2i**: 3-benzothiophenyl-CHO	**5u**: Ar = 3-benzothienyl	92	82	**8r**: Ar = 3-benzothienyl	93[f]

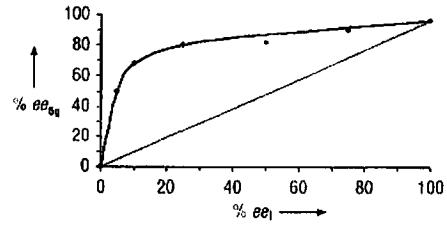
[a] Isolated yield of analytically pure product. [b] Enantiomeric excess determined by HPLC analysis using Chiracel OD-H column (*n*-heptane/*i*PrOH). [c] The *ee* was determined after desilylation. [d] The *ee* was determined after acylation with PhCOCl. [e] Desilylation was carried out with Bu_4NF. [f] Desilylation was carried out with KOH.

Scheme 30 Structure of the complex $[BrCu(Quinap)]_2$

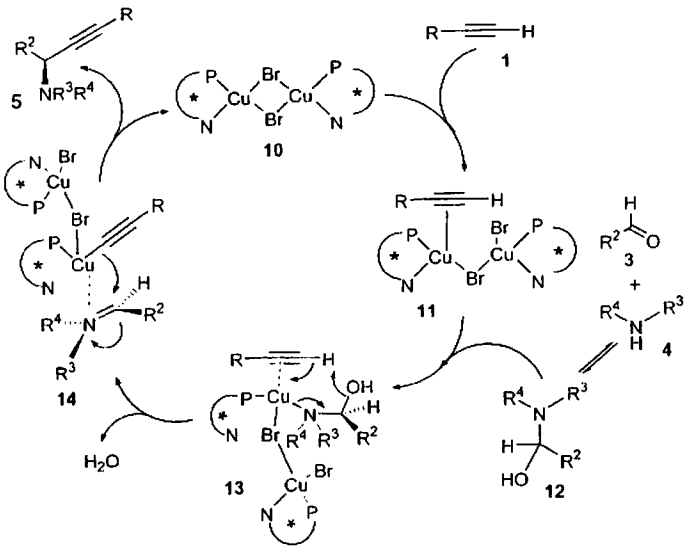


Scheme 31 Nonlinear effects





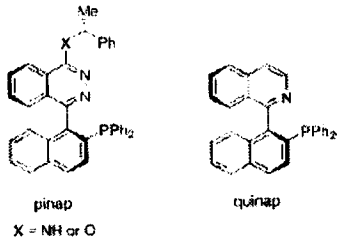
Scheme 32 Tentative mechanism of the three-component reaction



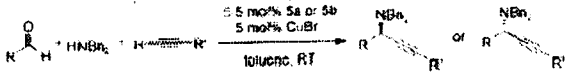
c. Carreira Group:Copper(I)-Pinap complex

Angew. Chem. Int. Ed. **2004**, *43*, 5971

Scheme 33 Structure of Pinap



Scheme 34 Cu-catalyzed addition of alkynes to imines



R	R'	Ligand	Yield [%]	*ee* [%]	Quinap [% *ee*][a]
*i*Pr	Me_3Si	5a	84	98 (*R*)	92
		5b	82	99 (*S*)	
*i*Pr	Ph	5a	88	90 (*R*)	84
		5b	82	95 (*S*)	
*i*Bu	*n*Bu	5a	74	91 (*R*)	82
		5b	72	94 (*S*)	

Advantage of Pinap:
1. Convenient preparation
2. Easily modify

Other Application of Pinap ligand:
Catalytic, Enantioselective, Conjugate Alkyne Addition *J. Am. Chem. Soc.* **2005**, *127*, 9682.