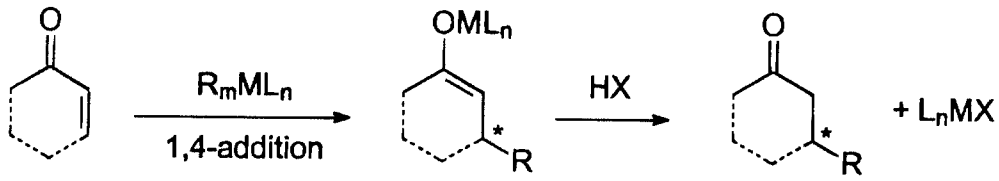
Catalytic Asymmetric Conjugate Additions using Dialkylzinc Reagents

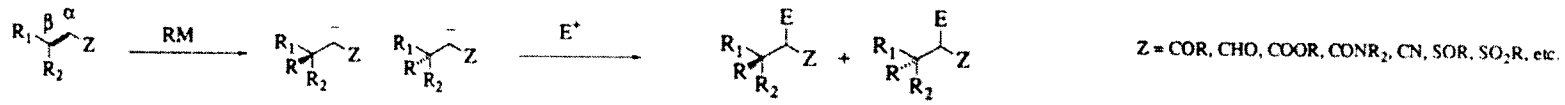


John Heemstra Jr.

May 28, 2002

Conjugation Addition using Organometallic Reagents

•Alkyl portion of the organometallic reagent adds to the β carbon of an electron deficient alkene giving a stabilized carbanion, which can further react with an electrophile to give the β-substituted product.



•These reactions allow for the direct introduction of a non-stabilized organic molecules into the β position of organic structures with high chemo- and regio-selectivity.

•The reaction can also be rendered enantioselective, and a number of stoichiometric organocopper reagents with non-transferable ligands and organocuprates with additional chiral ligands have been developed that provide e.e's of >95%.

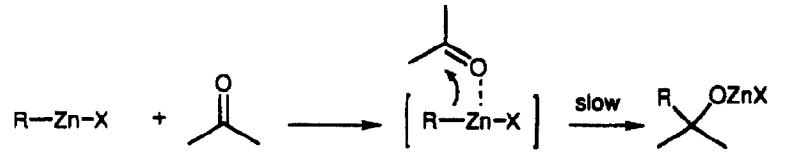
•Finding catalytic methods has proven difficult due to several factors that govern the conjugate addition step:

i) Nature of the organometallic reagent and the ligands associated with it,
ii) Aggregation of the reagents in solution, which is often solvent dependent,
iii) Activation of the enone by metal ion complexation or by additional Lewis acid,
iv) The effect additional ligands, coordinating solvents and salts have on the regio- and stereoselectivity.

Rossiter, B. E., Swingle, N. M. *Chem. Rev.* **1992**, 92 771-806

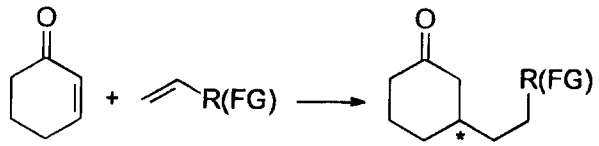
Properties of Dialkylzinc Reagents

- Dialkylzincs (R_2Zn) have a very low reactivity toward most organic electrophiles giving only moderate yields.
- The low reactivity of dialkylzincs is a result of the high covalent character of the carbon zinc bond.
- Also, the low Lewis Acidity of Zn(II) does not allow it to sufficiently activate carbonyl groups toward addition reactions.



(1)

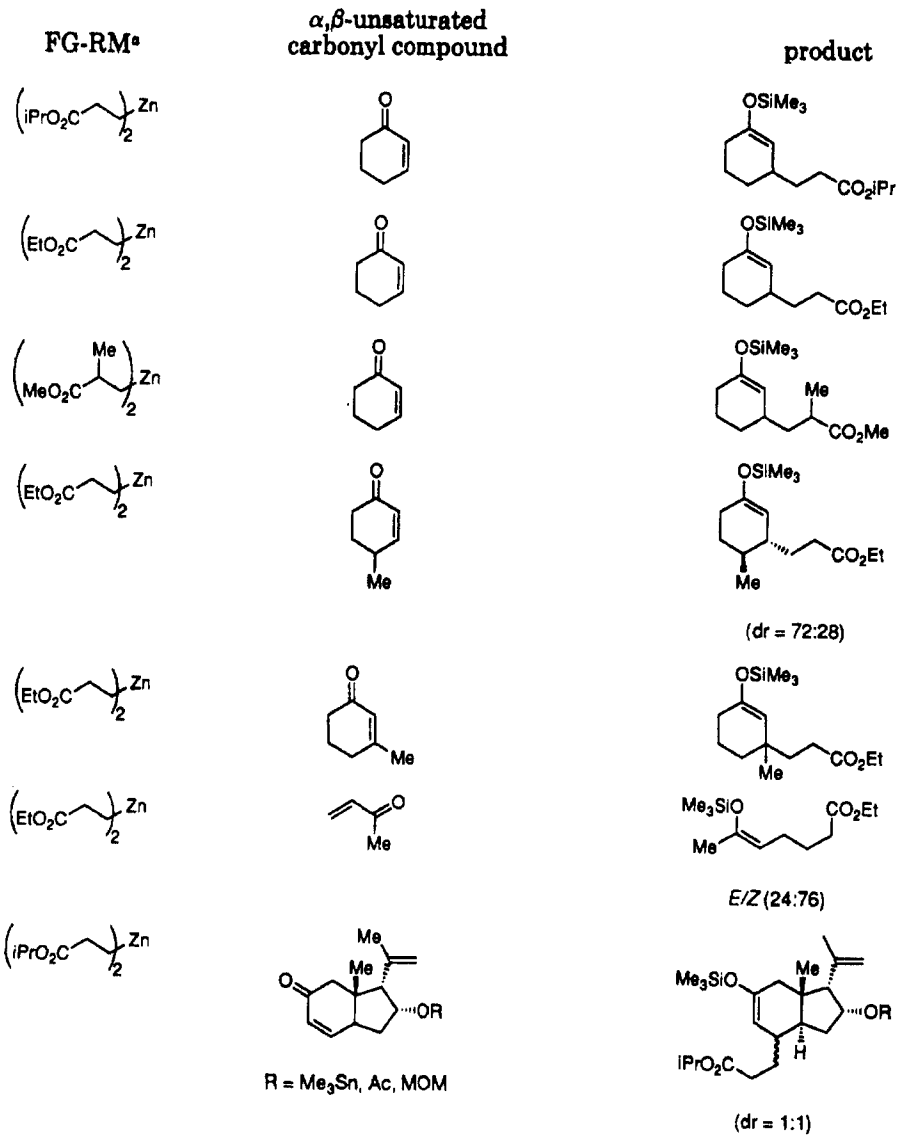
- However, the low reactivity of dialkylzincs allows for the formation of functionalized organometallic reagents that are otherwise not possible with organolithium or grinard reagents.



FG = functional group

Knochel, P., Singer, R. D., *Chem. Rev.* **1993**, 93, 2117-2188

Functionalized Dialkylzinc Reagents

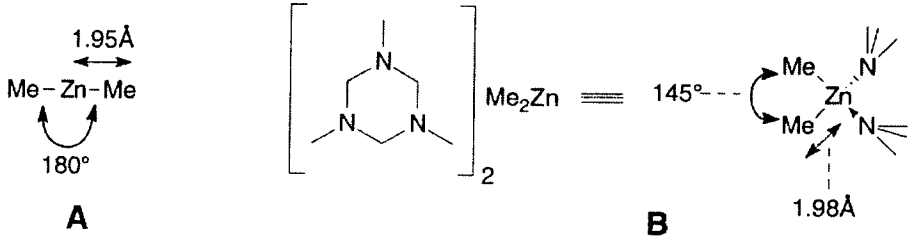


- Functionalized dialkylzincs can be activated to undergo conjugate addition reactions.
- Me_2Zn, Et_2Zn, and $(i\text{-}Pr)_2Zn$ are also used in synthesis.

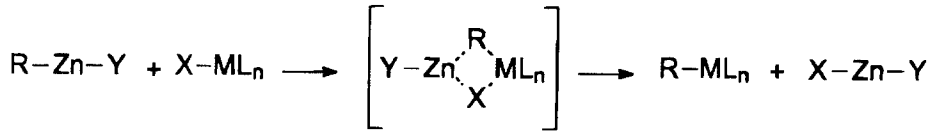
Knochel, P., Singer, R. D., *Chem. Rev.* **1993**, 93, 2117-2188

Catalytic Activation of Dialkylzinc reagents

- Dialkylzinc has a linear structure that is unreactive toward carbonyl compounds. However, upon coordination to triazine, a tetrahedral configuration at the zinc atom is found with elongated carbon-zinc bonds.



- Alkyl transfer to a second metal forming in situ a more reactive carbon-metal bond.

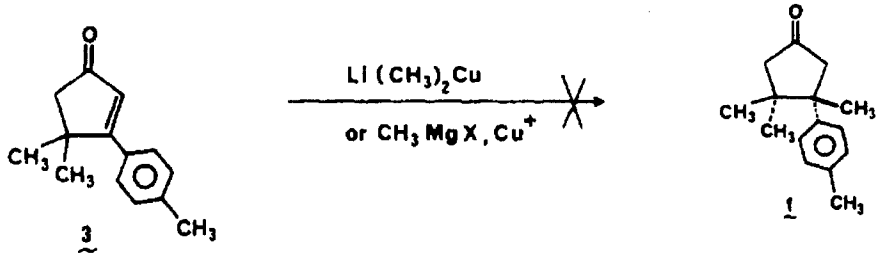


Y = R, halide
M = Ti, Pd, Ni, Cu
X = halide, OTf

- The low reactivity of dialkylzinc has made it an attractive reagent for catalytic conjugate addition reactions.

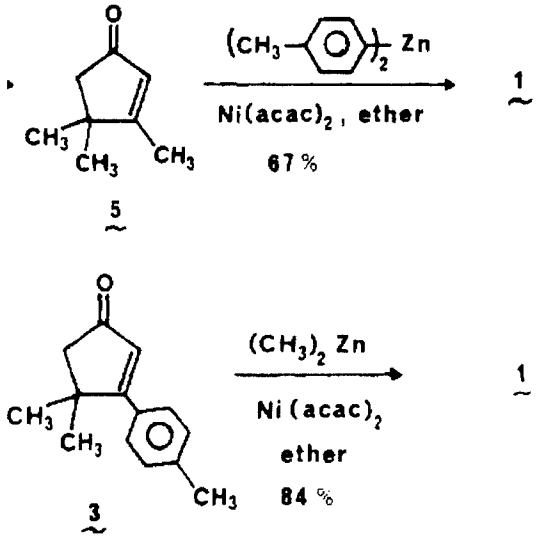
Feringa, B. L., *Tetrahedron*, **2000**, 56, 2865 - 2878

Synthesis of (+_)-β-Cuparenone



3 1

•Molecule **3** is "inert to lithium dimethylcuprate and copper catalyzed methyl grignard 1,4 additions."



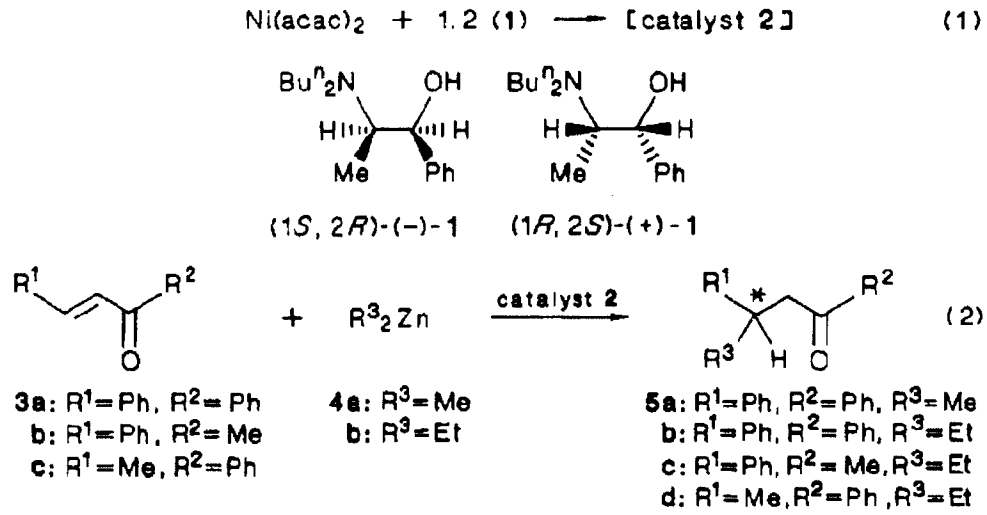
•Zinc reagents prepared from Li, RBr, $ZnBr_2$, ether, ultrasonic irradiation.

•Only trace amounts of 1,2 addition products were formed.

•Synthesis illustrated the largely unrecognized power of dialkylzinc reagents in conjugate additions.

Greene, A. E., Luche. J, et. Al. *J. Org. Chem.* **1984**, 49, 931 - 932

First Enantioselective Catalytic Conjugate Addition



The catalyst was prepared by stirring the $Ni(acac)_2$ and norephedrin in toluene for 1 hr.. The enone was then added to the solution followed by the dropwise addition of dialkylzinc at -30°C.

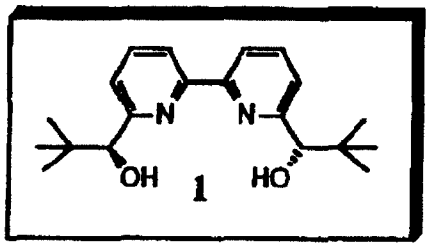
Table I. Catalytic Asymmetric Addition of Dialkylzincs to Enones 3 Using 2

entry	3	4, R^3	molar ratio 2:3	5				
					[α] (c, solvent)	yield, %	% ee[a]	config[b]
1	a	Me	0.60[c]	a	$[\alpha]^{24}_{546}$ −6.78° (1.80, CCl_4)	72	40	*R*
2	a	Et	0.50[c]	b	$[\alpha]^{22}_{365}$ −58.09° (2.50, EtOH)	75	45	*R*
3	a	Et	0.06[c]	b	$[\alpha]^{22}_{D}$ −1.92° (2.50, EtOH)	94	20	*R*
4	a	Et	0.06[d]	b	$[\alpha]^{25}_{D}$ +1.32° (2.50, EtOH)	89	22	*S*
5	b	Et	0.60[c]	c	$[\alpha]^{23}_{D}$ −3.48° (2.30, EtOH)	63	12	*R*
6	c	Et	0.50[c]	d	$[\alpha]^{22}_{D}$ −4.26° (1.01, Et_2O)	78	44	*R*

- Enantioselectivities are highly dependent on the molar ratio of **2:3** (catalyst : enone).
- Soai speculates that aggregation(s) of the complex between the catalyst and dialkylzinc may be the reactive species, or the catalyst is unstable and decomposes to another Ni species that can also catalyze the reaction. Therefore the concentration of the catalyst may effect the e.e.

Soai, K., et. Al. *J. Org. Chem.* 1988, 53, 4149 - 4150

Catalytic Nickel Complexes using Chiral Bipyridines



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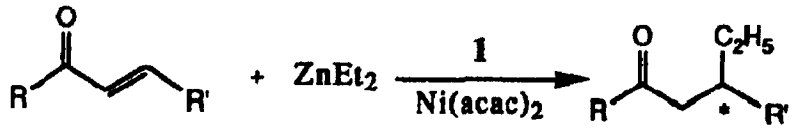


2a/3a R = C_6H_5, R' = C_6H_5
2b/3b R = *p*-$CH_3OC_6H_4$, R' = C_6H_5
2c/3c R = CH_3, R' = C_6H_5

Table. Enantioselective conjugate addition to enones catalyzed by Ni(acac)$_2$/(*S,S*)-1.

Entry	Substrate	mol% Ni(acac)$_2$	Ratio Ni : 1	Yield[b] [%]	ee[c] [%]
1	2a	1	1 : 30	55	72
2	2a	1	1 : 20	75	72
3	2a	1	1 : 10	82	54
4	2a	1	1 : 5	74	20
5	2a	2	1 : 5	66	48
6	2a	2	1 : 3	73	18
7	2a	5	1 : 3	58	58
8	2a	5	1 : 1	69	18
9	2b	5	1 : 10	68	74
10	2c	5	1 : 5	76	2[d]

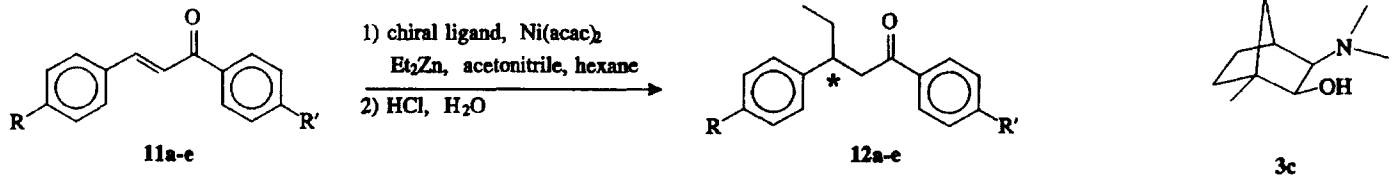
[a] The diethyl zinc was added as a 1 M solution in hexane. [b] After column chromatography. [c] Determined by HPLC analysis using a chiral column (see experimental); major for **3a** and **3c**: (*R*)-configuration; for **3b**: undetermined. [d] According to rotation value.[5]

Reactions run in acetonitrile under heterogeneous conditions at -30 C.

- Asymmetric induction is highly dependent on Ni : bipyridine ratio.
- Reactions run in Toluene, THF, or DMF give products with lower e.e.'s.
- Methyl substituted derivative **2c** gives essantially a racemic product.

Bolm, C., Ewald, M. *Tetrahedron Letters* **1990**, 31, 5011-5012

Effects of Catalyst Composition



11a-e **12a-e** **3c**

R and R' = H

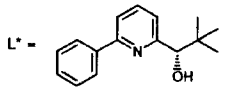
entry	ligand, mol %	nickel salt, mol %	add. ligand, mol %	yield,[b] %	ee,[b] %	abs. conf.[b]
1	**3c**, 16	$Ni(acac)_2$, 7	-	81	65	*R*
2	**3c**, 16	$Ni(acac)_2$, 7	2,2'-bipyridine, 7	82	64	*R*
3	**3c**, 16	$Ni(acac)_2$, 7	2,2'-bipyridine, 12	86	63	*R*
4	**3c**, 20	$Ni(acac)_2$, 7	2,2'-bipyridine, 7	90	69	*R*
5	**3c**, 15, **13b**, 2	$Ni(acac)_2$, 7	2,2'-bipyridine, 7	74	55	*R*
6	**3c**, 16	$Ni(acac)_2$, 8	-	82	55	*R*
7	**3c**, 16	$Ni(acac)_2$, 3	-	79	70	*R*
8	**3c**, 16	$Ni(acac)_2$, 1	-	69	72	*R*
9	**3c**, 2	$Ni(acac)_2$, 0.4	-	69	31	*R*
10	**3c**, 0.2	$Ni(acac)_2$, 0.04	-	71	6	*R*
11[c]	**3c**, 10	-	-	nd[d]	6	*S*
12[c]	**3c**, 20	-	-	nd[d]	15	*S*
13[c]	**3c**, 50	-	-	nd[d]	21	*S*
14[c]	**3c**, 20	-	-	nd[d]	16	*S*
15	**3c**, 16	$NiBr_2$, 7	-	80	39	*R*
16	**3c**, 16	$NiBr_2$, 7	2,2'-bipyridine, 7	74	54	*R*
17	**3c**, 8, **13b**, 8	$Ni(acac)_2$, 7	2,2'-bipyridine, 7	74	13	*S*

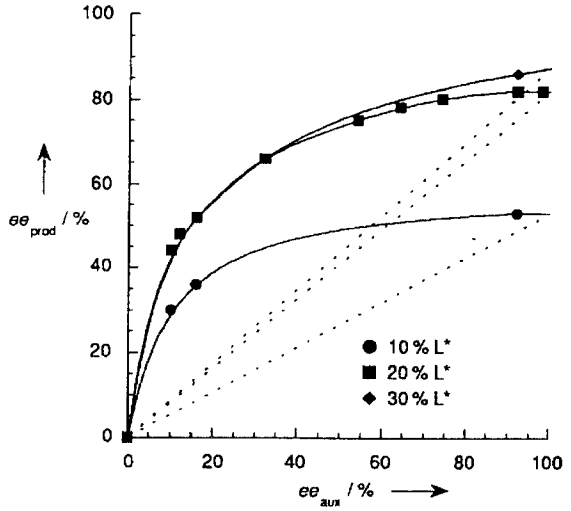
- An appropriate ligand-to-nickel ratio and chiral ligand concentration is required.
- The enantioselective catalyst is a diastearomeric mononuclear complex.

$$Ni(acac)_2 + 2\,L^* \rightleftarrows Ni(acac)L^* + L^* \rightleftarrows NiL_2^*$$

Feringa, B. L. *Tetrahedron* **1994**, 50, 4479 - 4491

Asymmetric Amplification using Nickel Catalysts





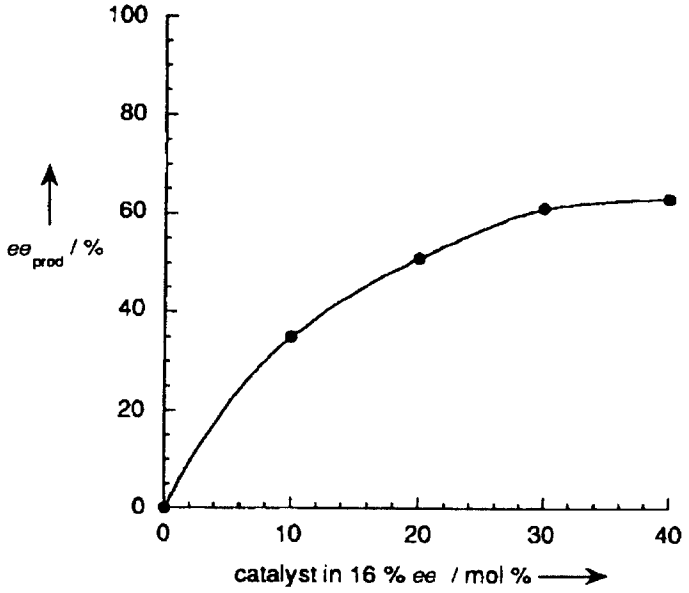


Figure 24. (+)-NLEs encountered in the pyridine alcohol (20 mol %) catalyzed asymmetric 1,4-addition of diethylzinc to chalcone (**12**) (1 mol % [$Ni(acac)_2$], acetonitrile, −30 °C).

- Catalyst concentration has a large effect on the (+)-NLE, a smaller amount of catalyst lowers the enantioselectivity.
- Results suggest there is a reservoir effect present.

Kagen, H. B., Girard, C. *Angew. Chem. Int. Ed.* **1998**, 37, 2922-2959

More Stable *Meso* Complex Hypothesis

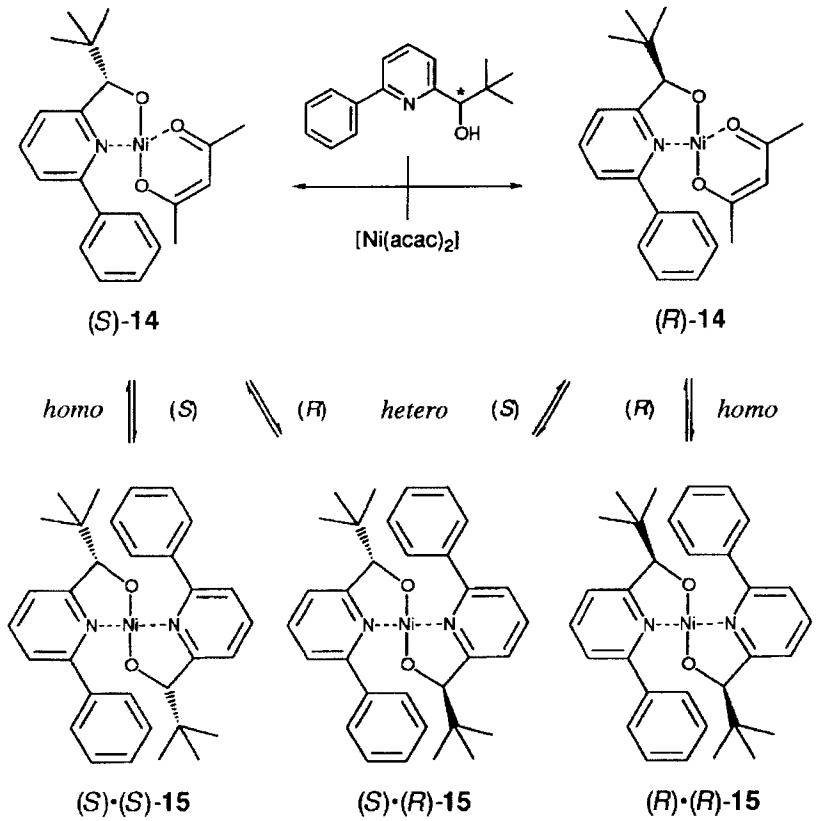
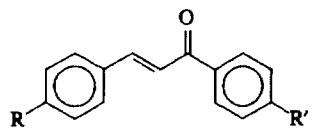


Figure 26. Proposed equilibrium between the monomers and dimers in the catalyzed addition of dialkylzinc compounds in the presence of nickel(II).

- Dialkylzinc reacts with the less stable nickel complex, and from the (+)-NLE, it has to be the homochiral complex.
- The hetrochiral species diverts the minor enantiomer ligand from the catalytic pathway and generates the (+)-NLE.

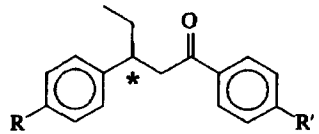
Kagen, H. B., Girard, C. *Angew. Chem. Int. Ed.* **1998**, 37, 2922-2959

Variations of Substrate, Solvent, and Temperature



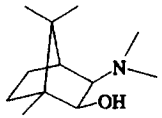
11a-e

1) chiral ligand, Ni(acac)$_2$
Et_2Zn, acetonitrile, hexane
2) HCl, H_2O



12a-e

11/12	a	b	c	d	e
R	H	OMe	H	Cl	H
R'	H	H	OMe	H	Cl



3c

entry	substrate	solvent	temp. °C	yield,[b] %	ee,[b] %	abs. conf.[b]
1	4-methoxychalcone (**11b**)	acetonitrile	-30	nd[c]	57	*R*
2	4'-methoxychalcone (**11c**)	acetonitrile	-30	nd[c]	51	*R*
3	4-chlorochalcone (**11d**)	acetonitrile	-30	nd[c]	61[d]	*R*
4	4'-chlorochalcone (**11e**)	acetonitrile	-30	nd[c]	59	*R*
5	3-nitrochalcone (**11f**)	acetonitrile	-30	< 10	-	-
6	**11a**	butyronitrile	-30	nd[c]	69	*R*
7	**11a**	butyronitrile	-50	84	81	*R*
8	**11a**	propionitrile	-50	77	72	*R*
9	**11a**	isobutyronitrile	-50	79	72	*R*
10[e]	**11a**	propionitrile	-50	82	84	*S*

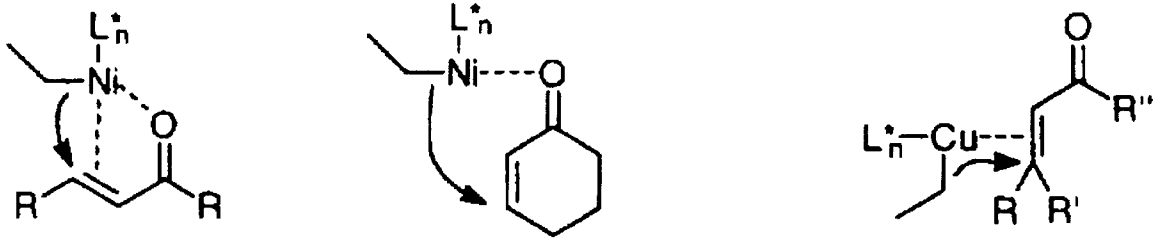
a. Reactions at -30°C in 2 ml acetonitrile and 1.5 ml hexane using an *in situ* prepared catalyst from 7 mol % $Ni(acac)_2$ and 16 mol % chiral ligand (see text and experimental). Reaction time 16 hours. b. Isolated yield of crude product. Conversion > 95 % (based on GC analysis). c.

- Methoxy and chloro substituants on the aryl ring cause a decrease in enantioselectivities (chalcone gave 65% e.e. in identical conditions).
- Acetonitrile or propionitrile as solvents are essential for high enantioselectivities.
- Decreasing the reaction temperature will increase the enantioselectivity, especially with butyronitrile

Feringa, B. L. *Tetrahedron* **1994**, 50, 4479 - 4491

Limitations of the Nickel based Catalysts

- High concentrations of catalyst and ligands were needed for both high yields and enantioselectivities.
- No clear picture of catalytic mechanism.
- Lack of one highly enantioselective and reactive catalyst for acyclic enones.
- No significant enantioselectivities toward cyclic enones.



I II III

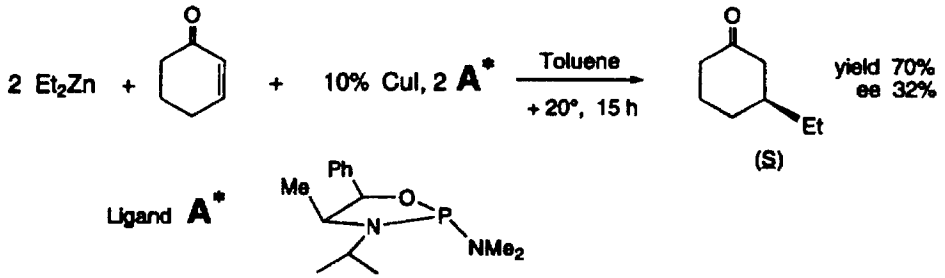
- Feringa speculated that the coordination of the Nickel catalyst to the carbonyl placed the chiral species too far away from the B-position to induce any asymmetry in the conjugate addition.

- However, copper offers the possibility of enantioselective alkyl transfers to both cyclic and acyclic enones due to its coordination to the carbon-carbon double bond.

Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, 8, 1467 - 1473

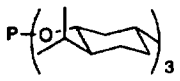
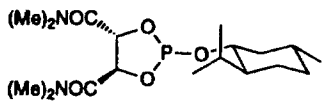
Catalytic Conjugate Additions Using Copper

- Alexakis reported the first example of a copper catalyzed conjugate addition of dialkylzinc to a cyclic enone.



Catalyst showed no reactivity with chalcone.

- He then moved on to use cyclic phosphites due to their ability to enhance reaction rates and their stability toward moisture.

Ligand	Enone	Conditions	Yield[a] %	ee[b]	Abs. Conf.
	cyclohexen-2-one	-20°, 15 min	98	36	R
	chalcone	-20°, 50 min	98	23	S
	benzalacetone	-20°, 3 h	57	4	R
	cyclohexen-2-one	-5°, 1 h	99	40	R
	chalcone	-20° to 0°, 5 h	60	20	S
	benzalacetone	-20° to 0°, 5 h	98	28	S

Reactions run with 0.5% $Cu(OTf)_2$ and 1% ligand in CH_2Cl_2

•High yields can be obtained with the phosphites, but with only moderate to low enantiomeric excess.

Alexakis, A., et. al. *Tetrahedron Asymmetry* **1993**, Vol: 4, No. 12, 2427-2430
Alexakis, A., et. al. *Tetrahedron Asymmetry* **1997**, Vol. 8, No.19, 3193-3196

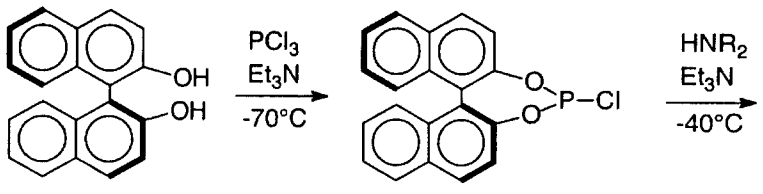
Designing a Novel Catalyst for Conjugate Addition

Feringa's objectives:

- First, find a catalyst that will achieve efficient ligand accelerated catalysis with both cyclic and acyclic enones.
- Secondly, make the metal-ligand complex highly enantioselective.
- Finally, determine if the catalyst will tolerate functional groups.

Phosphoramidities

- Phosphoramidities had not been used previously as ligands for asymmetric catalysis.
- They have electron donor- acceptor properties typically between those of arylphosphines and arylphosphites.
- The phosphoramidite based on 2,2'-binapthol are remarkable stable toward hydrolysis.



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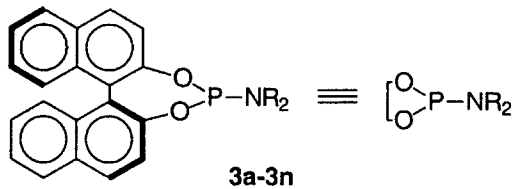
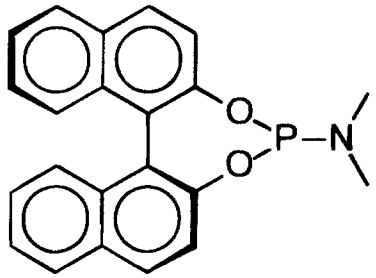
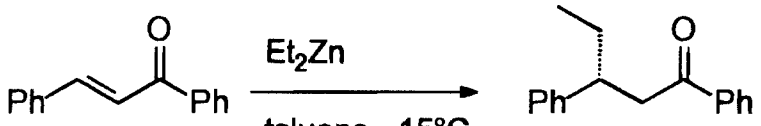


3a-3n

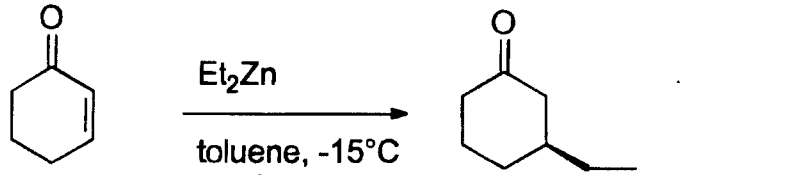
Feringa, Ben L. et al. Tetrahedron **2000**, 56, 2865-2878

Phosphoramidite catalyzed conjugate addition





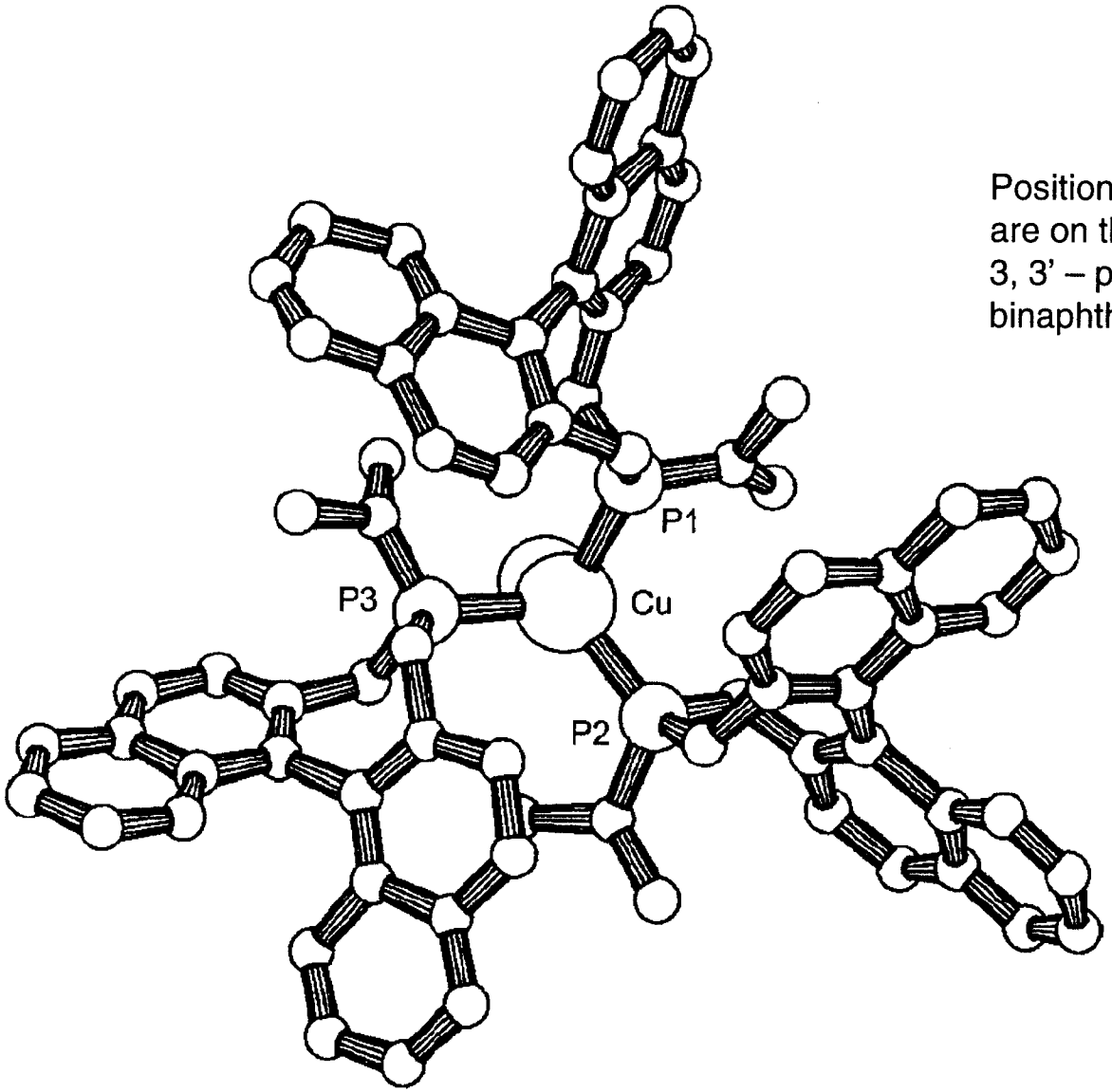
- Reactions were complete within 3 hours.



- Phosphoramidities achieve efficient ligand-accelerated catalysis, and reacted with both cyclic and acyclic enones.

Feringa, B. L., et. Al. *Angew. Chem. Ed. Engl.* **1996**, 35, 2374-2376

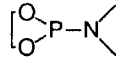
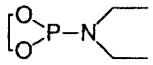
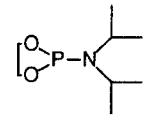
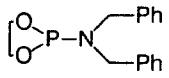
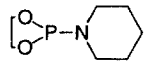
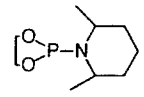
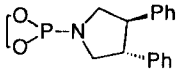
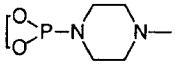
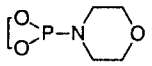
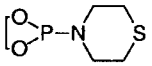
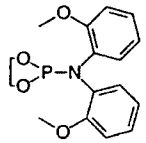
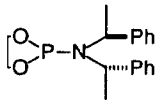
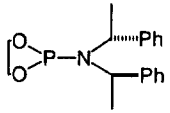
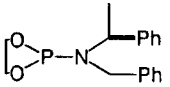
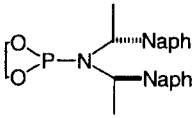
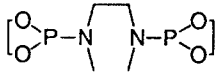
X-Ray structure of the CuI complex of ligand 2

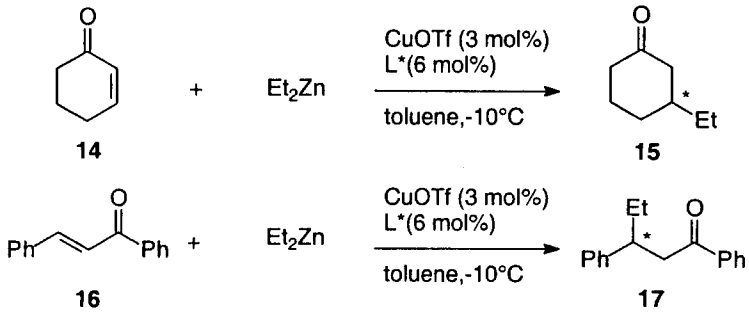


Positions for ligand modification are on the amine and at the 3, 3' – positions of the binaphthyl.

Feringa, Ben L. *Acc. Chem.* Res. **2000**, 33, 346-353

Structural Modifications on the Amine

Entry	Phosphoramidite	
1		**3a**
2		**3b**
3		**3c**
4		**3d**
5		**3e**
6		**3f**
7		**3g**
8		**3h**
9		**3i**
10		**3j**
11		**3k**
12		**3l**
13		**3m**
14		**3n**
15		**3o**
16		**3p**

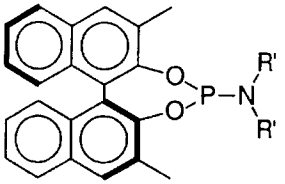


Entry	Chiral ligand	e.e. of **15** (%) (*S*)	e.e. of **17** (%) (*S*)
1	**3a**	39	65
2	**3b**	27	–
3	**3c**	60	83
4	**3d**	53	53
5	**3f**	43	79
6	**3g**	47	50
7	**3h**	0	–
8	**3I**	50	71
9	**3j**	55	70
10	**3k**	48	13
11	**3l**	75[a]	40[a]
12	**3m**	>98[a]	75[a]
13	**3n**	72[a]	72[a]
14	**3o**	94[a]	42[a]
15	**3p**	37	–
16	**11a**	56	52

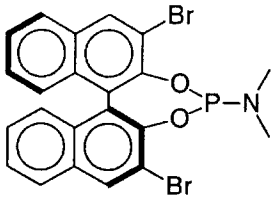
•Steric bulk on the amine has large effect on the enantioselectivities

Feringa, Ben L. et al. *Tetrahedron* **2000**, 56, 2865-2878

Structural Modifications on the Binaphthol Moiety



11a R' = Me
11b R' = *i*-Pr
11c R' = -$(CH_2CH_2)_2O$



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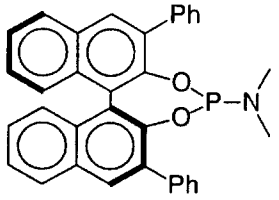

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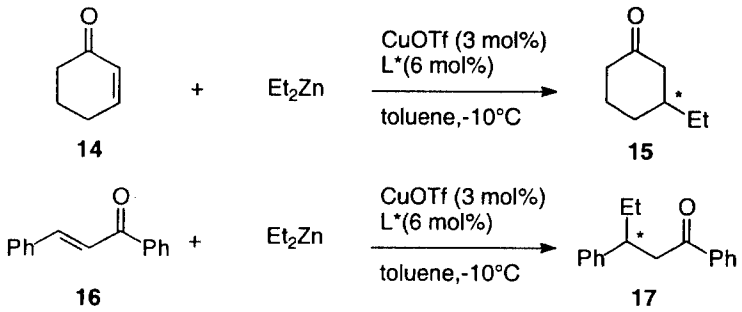


14 **15** **16** **17**

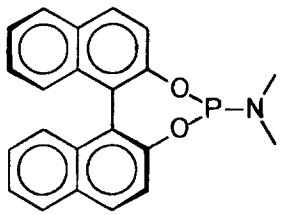
Entry	Chiral ligand	e.e. of **15** (%) (*S*)	e.e. of **17** (%) (*S*)
16	**11a**	56	52
17	**11b**	59	81
18	**11c**	51	76
19	**12**	51	23
20	**13**	35	<20[b]

- The large bromide and phenyl groups at the 3 and 3'-positions results in decreased enantioselectivities.

- A methyl group at 3 and 3'- postitions slightly increases the e.e. for conjugate addition to cyclohexanone but decrease the e.e. for chalcone.

Feringa, Ben L. et al. *Tetrahedron* **2000**, 56, 2865-2878

Structural Modifications on the Amine



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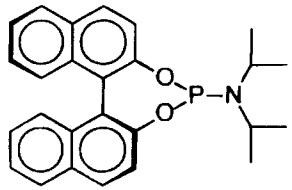
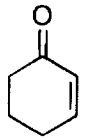


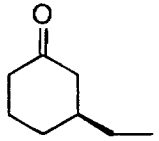
3

Catalyst 3 gives the highest Enantioselectivities for acyclic enones.

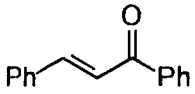


Et_2Zn

toluene, -15°C
catalyst:
CuI/**2** (3 mol%): 75% yield, 35% e.e.
$Cu(OTf)_2$/**3** (3 mol%): 78% yield, 60% e.e.

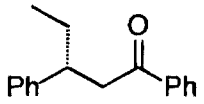


- Enantioselectivities are enhanced by bulkier alkyl groups around the amine



Et_2Zn

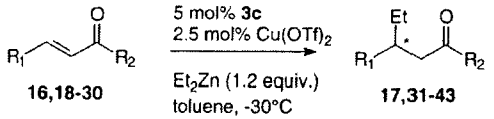
toluene, -15°C
catalyst:
CuOTf/**2** (3 mol%): 83% yield, 49% e.e.
$Cu(OTf)_2$/**3** (3 mol%): 88% yield, 90% e.e.



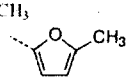
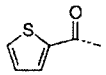
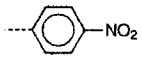
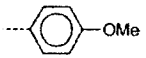
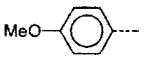
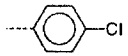
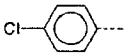
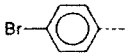
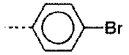
- Cu(OTf)2 was used to increase the solubility of the catalyst, which also lead to higher enantioselectivities

Feringa, Ben L. *Acc. Chem.* Res. **2000**, 33, 346-353

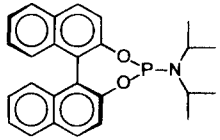
Conjugate Addition to Acyclic Enones



16,18-30 → 17,31-43

Entry	Enone	R_1	R_2	Product	Yield (%)	e.e.[a] (%)
1	16	Ph	Ph	17	85	89
2	18	CH_3	CH_3	31	0	–
3	19	Ph	CH_3	32	75	60
4	20			33	40	15
5	21			34	48	40
6	22			35	30	60
7	23	Ph		36	69	29
8	24	Ph		37	64	15
9	25	Ph		38	85	80
10	26		Ph	39	86	70
11	27	Ph		40	94	75
12	28		Ph	41	65	88
13	29			42	80	75
14	30			43	85	89

[a] Configurations or optical rotations of the prevailing enantiomers were not determined.

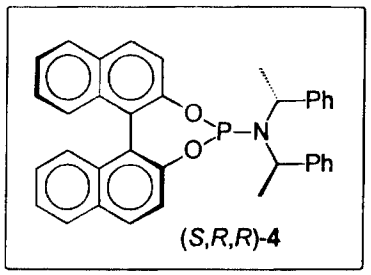


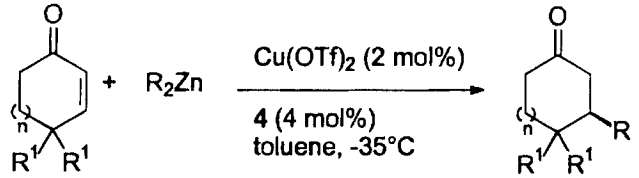
3

- High regio-, chemo, and enantioselectivities are limited to aryl substituted acyclic ketones.
- Competitive binding to the copper catalyst by heteroaromatic enones leads to lower yields and enantioselectivities.
- If it is assumed that the nitro group interferes with coordination of the catalyst, then electron donating or withdrawing properties of the substituents have little effect on the stereoselection.

Feringa, Ben L. et al. Tetrahedron **2000**, 56, 2865-2878

A Matched Combination of Chiral Structural Units



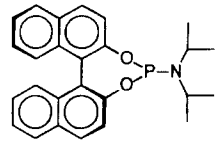


R	R^1	*n*	yield (%)	ee (%)
C_2H_5	H	1	94	>98
C_2H_5	H	0	75	10
C_2H_5	H	2	95	>98
C_2H_5	H	3	95	97
C_2H_5	CH_3	1	74	>98
C_2H_5	C_6H_5	1	93	>98
CH_3	H	1	72	>98
CH_3	CH_3	1	68	>98
C_7H_{15}	H	1	95	95
i-C_3H_7	H	1	95	94
$(CH_2)C_6H_5$	H	1	53	95
$(CH_2)_5OAc$	H	1	77	95
$(CH_2)_3CH(OC_2H_5)_2$	H	1	91	97

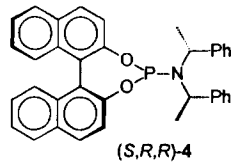
- High enantioselectivities is found in conjugate additions to cyclohexanones, cycloheptanones, and cyclooctanones, but not cyclopentanones.
- Functionalized dialkylzinc reagents are tolerated.
- When only 0.5% catalyst is used, the e.e.'s are still >98%.

Feringa, B. L. *Angew. Chem. Int. Engl.* **1997**, 36, 2620 - 2624
Feringa, B. L. *Acc. Chem.* Res. **2000**, 33, 346-353

Negative Nonlinear Effects are Observed with the Phosphoramidite Catalyst



3



(*S,R,R*)-4

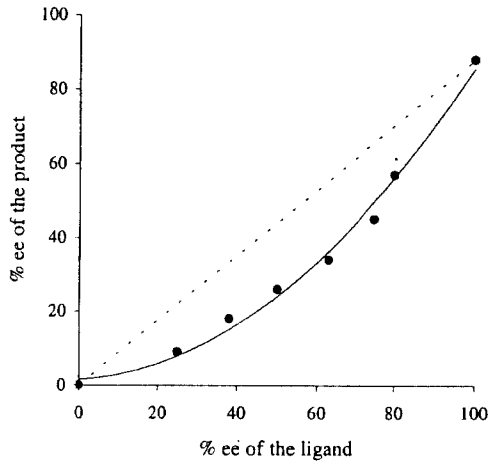


Figure 1. Correlation between the enantiomeric excess of the ligand **3c** and the e.e. of **17**.

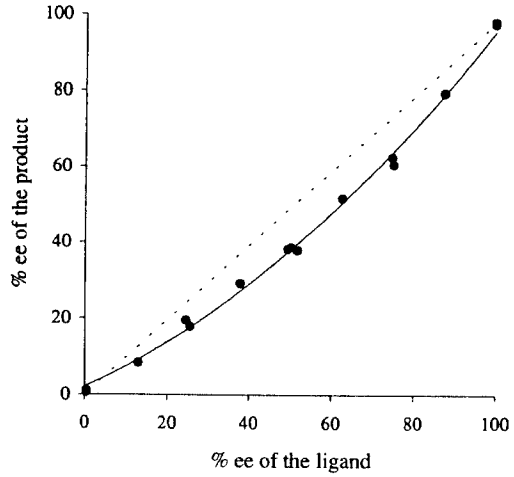
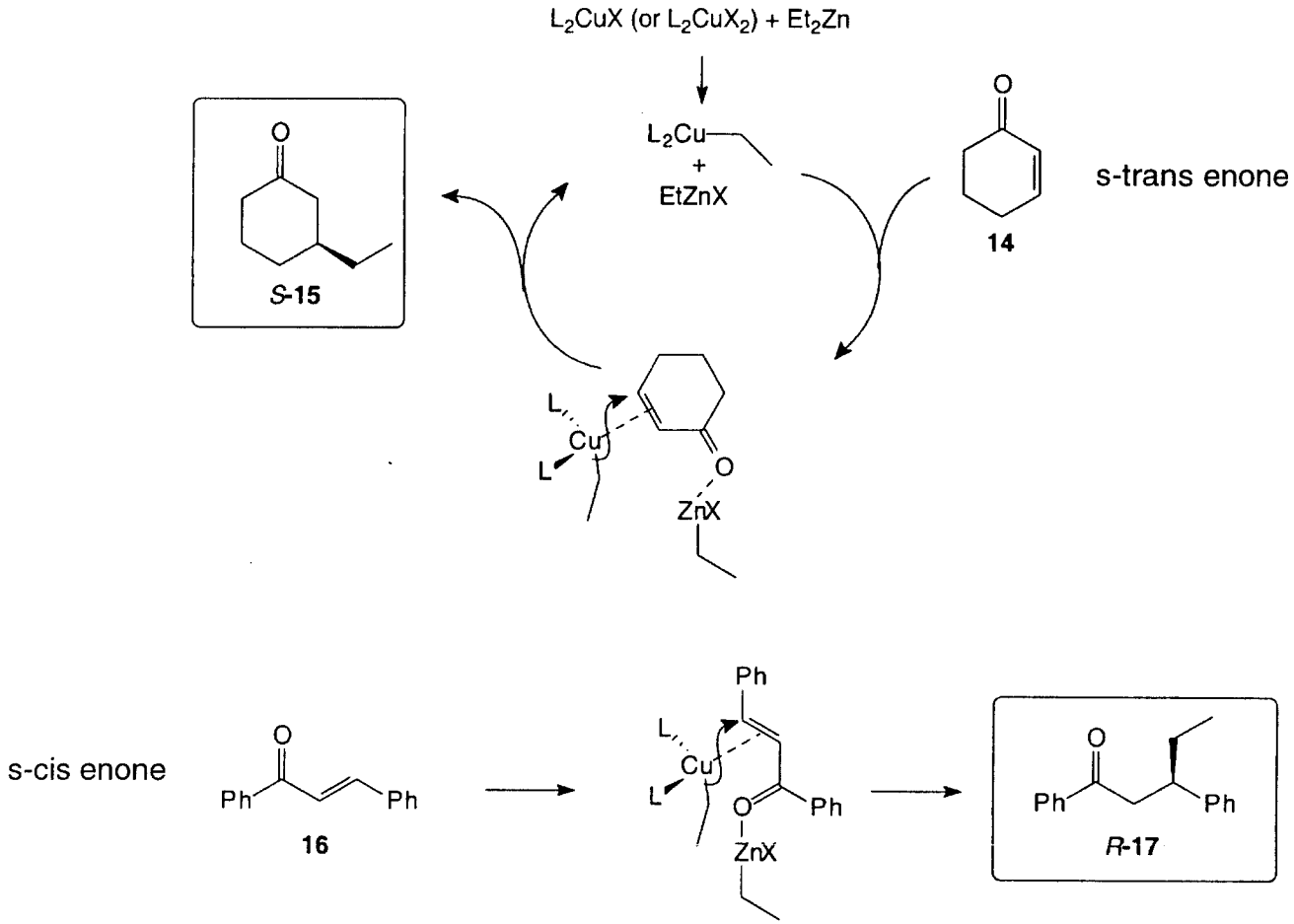


Figure 2. Correlation between the enantiomeric excess of the ligand **3m** and the e.e. of 3-ethyl-cyclohexanone **15** following standard reaction procedures.

- The most effective catalyst was made with a ligand to copper ratio of two pointing to ML_2 system.
- It is proposed that the negative non-linear effect is due to the higher reactivity of the heterochiral (meso) catalyst then the homochiral catalyst.

Feringa, Ben L. et al. Tetrahedron **2000**, 56, 2865-2878

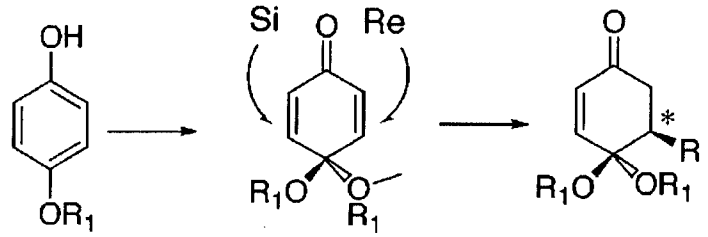
Proposed Pathway for the Copper Phosphoramidite Catalyzed Conjugate Additions



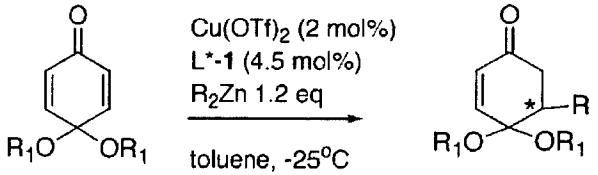
Conjugate Additions to both s-cis and s-trans enones are possible with the phosphoramidite catalyst

Feringa, B. L. *Angew. Chem. Int. Engl.* **1997**, 36, 2620 - 2624
Feringa, Ben L. et al. Tetrahedron **2000**, 56, 2865-2878

Conjugate Addition to Symmetrical Cyclic Dienones



Can the catalyst distinguish between the Re and Si faces?



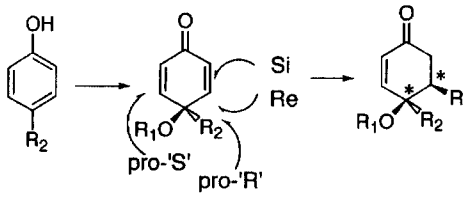
entry	dienone	R_1	R_1	R	1,4-adduct	yield[a] (%)	ee[b] (%)
1	**2**	Me	Me	Et	**7**	65	97
2	**3**	Et	Et	Et	**8**	59	92
3	**4**	$-CH_2CH_2-$		Et	**9**	68	92
4	**5**	$-CH_2CH_2CH_2-$		Et	**10**	62	89
5	**6**	$-CH_2C(Me)_2CH_2-$		Et	**11**	75	85
6	**2**	Me	Me	Me	**12**	76	99

[a] Isolated yield. [b] Ee values of **7**−**12** were determined by GC (see Supporting Information); no 1,2-adducts were observed.

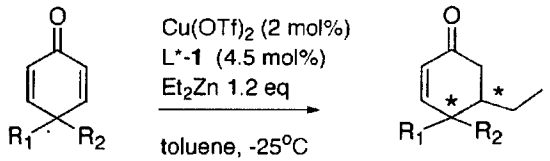
- An increase in the size of the R group causes a decrease in e.e.
- With cyclic acetals, an increase in ring size and bulk causes a decrease in e.e.

Feringa, Ben L. *Org. Lett.* **1999**, Vol. 1, No. 4, 623-625

Conjugate Addition to Asymmetrical Cyclic Dienones



Can the catalyst distinguish between the Re and Si faces And the Pro-S and Pro-R faces?



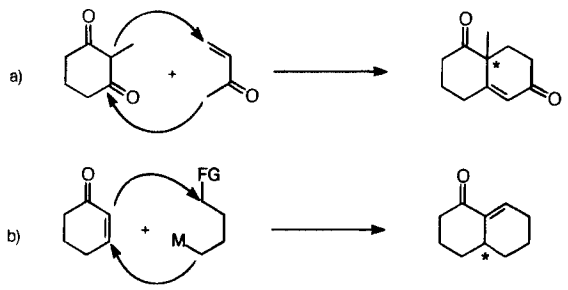
entry	dienone	R_1	R_2	1,4-adduct	yield (%)[a]	dr[b]	ee major (%)[b]	ee minor (%)[b]
1	**13**	OMe	Me	**17**	60	90/10	97	85
2	**14**	OMe	CH_2Ph	**18**	53	97/3	93	nd[c]
3	**15**	$CH_2CH_2CH_2O$		**19**	66	99/1	65	nd[c]
4	**16**	OMe	OCH_2Ph	**20**	58	1/1	98	98

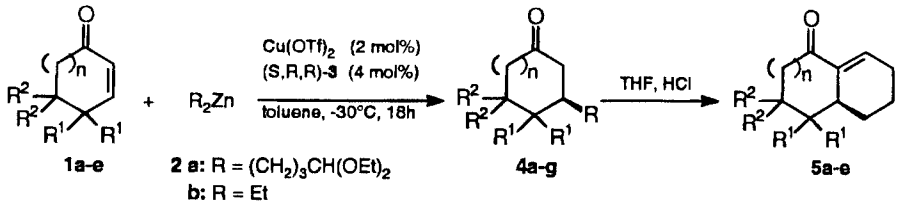
[a] Isolated yield; no 1,2 adducts were detected. [b] Dr and ee determination for **17** and **18** could not be directly performed by either GC or HPLC. Hydrogenation of the double bonds afforded products which could be separated by HPLC, Daicel AS column. Dr and ee determination of **19** and **20** was performed by HPLC, Daicel AS column. (see Supporting Information for details). [c] Not determined.

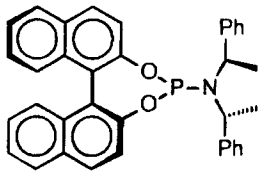
- The activated copper catalyst is directed cis to the alkoxy or acetal moiety.
- The alkoxy or acetal group has a directing effect by interacting with the metal catalyst.

Feringa, Ben L. *Org. Lett.* **1999**, Vol. 1, No. 4, 623-625

Catalytic Enantioselective Annulations







(S,R,R)-3

Stereocontrol is exerted in the aldol cyclization in a.
Stereocontrol is exerted in the conjugate addition in b.

entry	enone	R^1	R^2	*n*	R_2Zn	product	yield (%)	ee (%)	product	yield[a] (%)	ee[b] (%)
1	**1a**	H	H	1	**2a**	**4a**	91[a]	98[c]	**5a**	62	97
2	**1b**	Me	H	1	**2a**	**4b**	49[a]	n.d.	**5b**	55	>98
3	**1c**	H	Me	1	**2a**	**4c**	57[a]	n.d.	**5c**	56	84
4	**1d**	H	H	2	**2a**	**4d**	61[a]	n.d.	**5d**	50	96
5	**1e**	H	H	3	**2a**	**4e**	61[a,d]	n.d.	**5e**	42	>98
6	**1d**	H	H	2	**2b**	**4f**	>95	>98[b]			
7	**1e**	H	H	3	**2b**	**4g**	>95	97[b]			

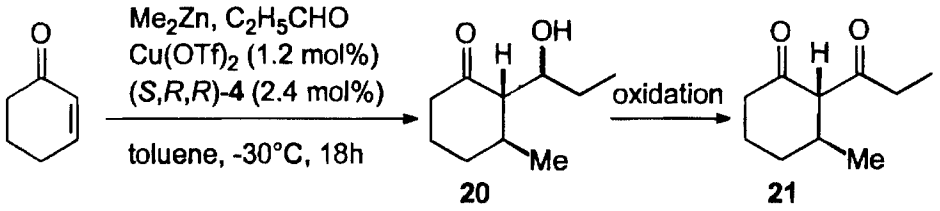
[a] Isolated yield. [b] ee's determined by chiral GC (see Supporting Information). [c] Determined by ^{13}C NMR after derivatization with (*1R,2R*)−(+)-1,2-diphenylethylenediamine. See: Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* 1993, *4*, 2431. [d] Isolated as a mixture of aldehyde and acetal due to partial hydrolysis during column chromatography.

- Catalytic enantioselective annulations reactions for cyclohexanones, cycloheptenones, and cyclooctenones.

- Catalyst shows very little stereocontrol for cyclopentanones annulations, e.e. = 10%

Feringa, Ben L. *J. Am. Chem. Soc.*, **1999**, 121, 1104-1105

Tandem Conjugate Addition-Aldol Reactions

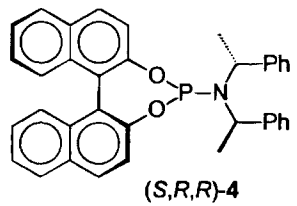


20

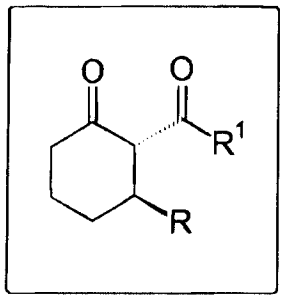
trans-erythro
trans-threo

21

81% yield, 97% e.e



(*S,R,R*)-**4**



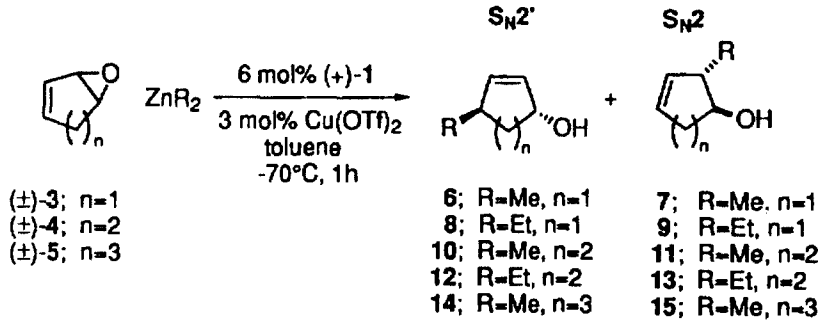
R	R^1	yield (%)	e.e. (%)
C_2H_5	C_6H_5	88	95
CH_3	C_2H_5	81	97
CH_3	m-BrC_6H_4	81	97
CH_3	C_6H_5	67	91
C_2H_5	$CHCH_2$	92	95
CH_3	$CHCH_2$	75	97

- First catalytic one pot organozinc conjugate addition-enolate trapping that proceeds with high enantioselectivities

Feringa, Ben L. *Acc. Chem.* Res. **2000**, 33, 346-353

Feringa, Ben L. et al. *Angew. Chem. Int. Ed. Eng.* **1997**, 36, No. 23 2620-2623

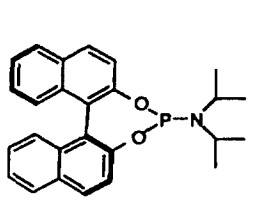
Kinetic Resolution of Diene epoxides



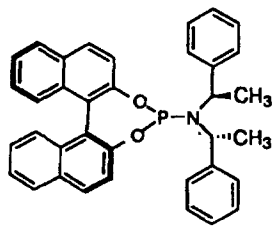
(±)-3; n=1
(±)-4; n=2
(±)-5; n=3

6; R=Me, n=1
8; R=Et, n=1
10; R=Me, n=2
12; R=Et, n=2
14; R=Me, n=3

7; R=Me, n=1
9; R=Et, n=1
11; R=Me, n=2
13; R=Et, n=2
15; R=Me, n=3



(+)-1



(+)-2

Entry	substrate	ligand	R_2Zn	yield (%)[b]	ee (%)[c]	S_N2'/S_N2[d]
1	3	1	R=Me	10[e]	46	4
2	4	1	R=Me	30	62 (-)	13
3	4	1	R=Et	18	86 (-)	>20
4	5	1	R=Me	32	60 (-)	10
5	3	2	R=Me	12[e]	50	3
6	3	2	R=Et	8[e]	54	12
7	4	2	R=Me	33	92(-)	13
8	4	2	R=Et	32	91(-)	59
9	5	2	R=Me	38	96(-)	16

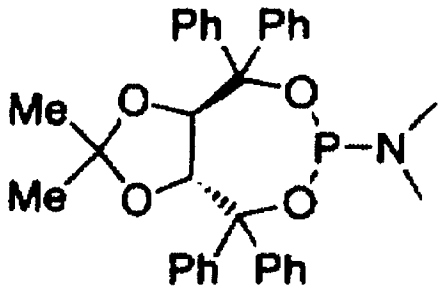
Under kinetic resolution conditions (0.5 eq of R_2Zn) maximum yield is 50%.

- 1,3-cyclopentadiene monoepoxide has low reactivity and enantioselectivities.
- 1,3-cyclohexadiene and 1,3-cycloheptadiene monoepoxides can be opened with high enantioselectivities using catalyst (+)-2.
- Et_2Zn has a higher regioselectivity for 1,4-additions than Me_2Zn

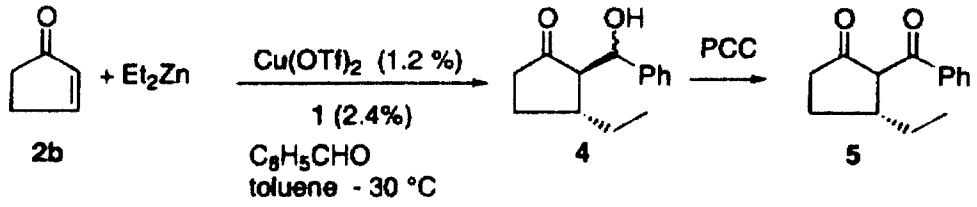
Conjugate Additions to Cyclopentenone

Problems:

- Isolated yields are low due to the reactivity of the intermediate that will oligomerize even at -30 C.
- Binaphthly based phosphoramidites show little stereocontrol in the conjugate additions give essentially racemic products.



TADDOL based
chiral phosphoramidite



- Tandem conjugate addition-aldol reaction
- Overall yield = 65%, e.e. = 37%
- Addition of mol. sieves increases the e.e. to 62%

- Authors are unsure of the effect mol. sieves have on the reaction.
- TADDOL based catalyst improves stereocontrol, but the e.e. is still modest.

Feringa, Ben L., et. al. *Tetrahedron: Asymmetry* **1998**, 9, 2409-2413

Summary of Phosphoramidite Catalyst

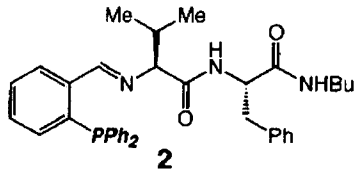
- Catalyst gives high enantioselectivities for both cyclic and acyclic enones. Maximum e.e for cyclic is >98% and for acyclic is 90%.
- Acetal and acetate funtional groups are tolerated, which allows for annulation reactions.
- High enantioselectivities can be achieved in tandem conjugate addition-aldol reactions with aldehydes.

Limitations:

- Reactions with cyclopentenone gives essentially racemic products.
- High enatioselectives are only seen with aryl substituted acyclic enones.

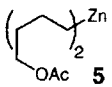
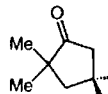
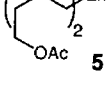
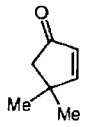
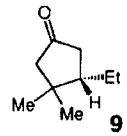
Peptide Based Chiral Phosphine Ligands: Cyclic Enones

*chiral ligand for **late** transition metals*

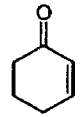
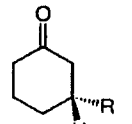
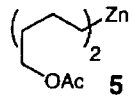
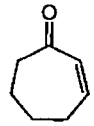
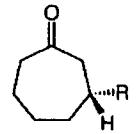


2

If OH is used instead of PPh3, the products are racemic.

entry	substrate	alkylzinc	product		2, $(CuOTf)_2$ (mol %)	conv (%), time (h) [b]	yield [c] (%)	ee [d] (%)
1		Et_2Zn		**4a**	2.4, 1.0	90, 12	78 [e]	97
2		Bu_2Zn		**4b**	2.4, 1.0	>98, 12	92 [e]	98
3		$(i\text{-}Pr)_2Zn$		**4c**	2.4, 1.0	>98, 12	90	79
4	**3**	 **5**	**4**	**4d**	2.4, 1.0	>98, 12	56	>98 [f]
5		Et_2Zn		**7a**	2.4, 1.0	>98, 6	72 [e]	>98
6		Bu_2Zn		**7b**	2.4, 1.0	95, 12	64 [e]	>98
7	**6**	 **5**	**7**	**7c**	6.0, 2.5	>98, 12	55	>98
8	 **8**	Et_2Zn	 **9**		17.5, 7.5	70, 24	56	97

[a] Conditions: indicated mol % **2** and $(CuOTf)_2 \cdot C_6H_6$, 3 equiv of dialkylzinc, toluene, −30 °C (−20 °C for entries 4 and 7). [b] Conversion determined by GLC. [c] Isolated yields after silica gel chromatography.

entry	substrate	alkylzinc	product		conv [b] (%)	yield [c] (%)	ee [d] (%)
1		Me_2Zn		**11a**	>98	71	>98
2		Et_2Zn		**11b**	>98	98	98
3		Bu_2Zn		**11c**	>98	93	95
4		$(i\text{-}Pr)_2Zn$		**11d**	>98	98	72
5	**10**	 **5**	**11**	**11e**	>98	76	95
6		Me_2Zn		**13a**	>98	80	>98
7		Et_2Zn		**13b**	>98	98	98
8		Bu_2Zn		**13c**	>98	81	95
9		$(i\text{-}Pr)_2Zn$		**13d**	88	78	62
	12		**13**				

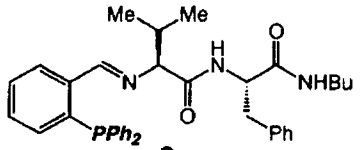
[a] Conditions: 1.0 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % **2**, 3 equiv of alkylzinc, toluene, −30 °C (−20 °C for entry 5). All reactions required 12 h, except for entries 2 and 7. [b] Conversion determined by GLC.

- Peptide based catalyst provides excellent stereocontrol for 5, 6, and 7-membered ring enones.
- Catalyst is made of commercially available components and can be easily modified.

Hoveyda, A. H., *J. Am. Chem. Soc.* **2001**, 123, 755 - 756

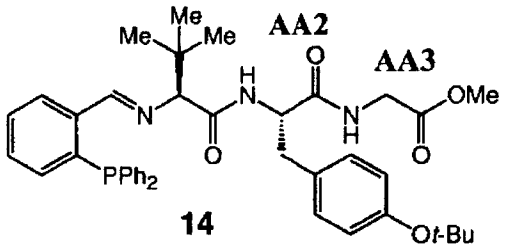
Improved Enantioselectivities for $(i\text{-Pr})_2Zn$

*chiral ligand for **late** transition metals*

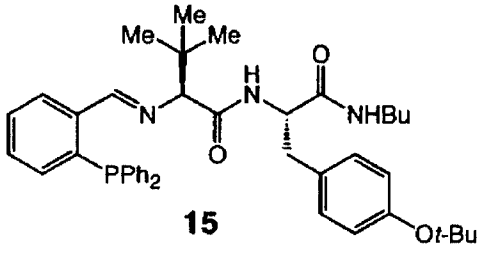


2

AA1 **AA2** **AA3**

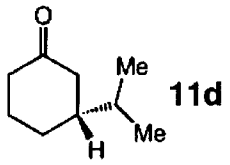


14

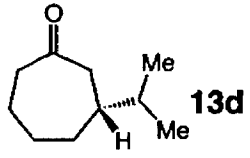


15

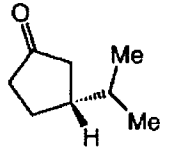
Conditions:
1.0 mol% $(CuOTf)_2$, C_6H_6
2.4 mol% chiral ligand, 3 eq. of $(i\text{-Pr})_2Zn$, -30 C



11d



13d



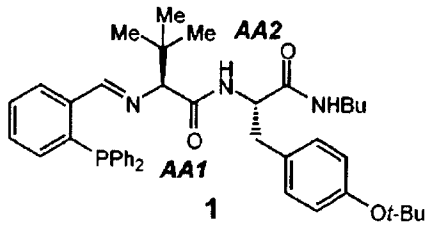
4c

	98%, 91% ee	***92%, 81% ee***	***94%, 85% ee***
Cat. 2	**98%, 72% ee**	**78%, 62% ee**	**90%, 79% ee**

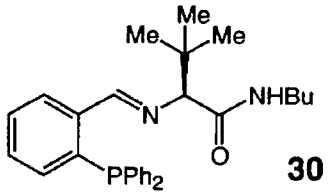
- These results imply it may be possible to find the ideal ligand for each substrate if ligand screening is carried out for that particular enone.

Hoveyda, A. H., *J. Am. Chem. Soc.* **2001**, 123, 755 - 756

Key Points using Peptide Ligands



1



30

- The identity of the peptides are critical to enantioselectivities. The use of AA1 = L-Val and AA2 = L-Phe gives lowered enantioselectivities.

- The AA2 moiety is essential for high asymmetric induction. When **30** is used instead of **1**, the enantioselectivities drop to around 50%.

- Hoveyda suggests this catalyst is acting as a bifunctional catalyst, similar to other peptidic Schiff base-metal complexes.

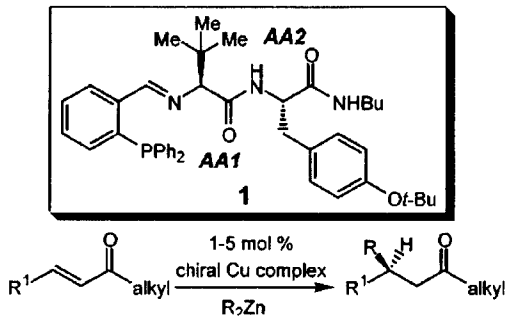
- Most substrates give optimal enantioselectivities around room temperature.

Hoveyda, A. H. *J. Am . Chem. Soc.* **2002**, 124, 779 -781

Peptide Based Chiral Phosphine Ligands: Acyclic Enones

entry	substrate	product	time (h); temp (°C)	yield (%)[b]	ee (%);[c] config[d]
1	R = Ph **2**	**3**	3; –20	90	93; *S* (+)
2	R = *p*-OMePh **4**	**5**	3; –20	93	94; (+)
3	R = *p*-NO_2Ph **6**	**7**	3; –20	72	92; (+)
4	R = *p*-CF_3Ph **8**	**9**	3; –20	87	90; (+)
5	*n*-pent, Me **10**	*n*-pent, Me **11**	1; +22	85	95; *R* (+)
6	Me, *n*-hex **12**	Me, *n*-hex **13**	1; +22	87	90; (+)
7	*n*-pent, *i*-Pr **14**	*n*-pent, *i*-Pr **15**	1; +22	75	90; (+)
8	*n*-pent, *t*-Bu **16**	*n*-pent, *t*-Bu **17**	24; +22	42	58; (+)
9	*i*-Pr, Me **18**	*i*-Pr, Me **19**	1; +22	69	91; (+)
10	OAc, Me **20**	OAc, Me **21**	1; +22	88	89; (+)

[a] Conditions: 1 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % **1**, 3 equiv of Et_2Zn, toluene; 5 mol % **1** for entries 6 and 10. [b] Isolated yields after chromatography; all conversion >98% except for entry 8 (GLC). [c] Selectivities



- Me_2Zn and $(i\text{-}Pr)_2Zn$ can also be used, with slightly lower e.e.'s.
- Catalyst offers high enantioselectivities for aliphatic enones.
- Functional groups on the substrate decrease the enantioselectivities.

Hoveyda, A. H. *J. Am . Chem. Soc.* **2002**, 124, 779 - 781