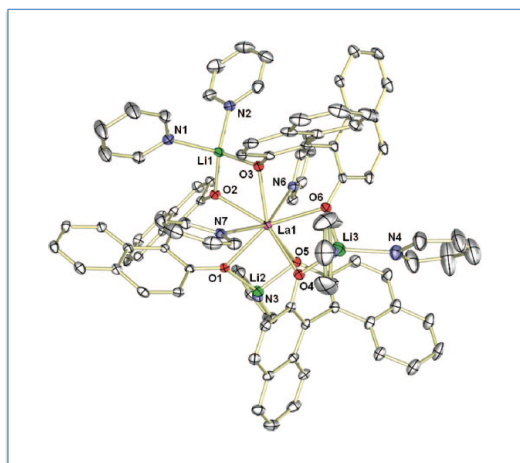


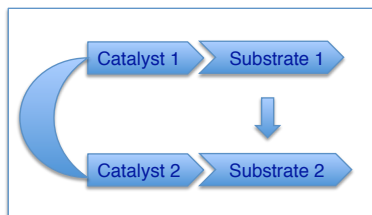
Polymetallic Asymmetric Catalysts
A review of the prominent catalytic systems



MacMillan Group Meeting, November 17, 2010
Brian Ngo Laforteza

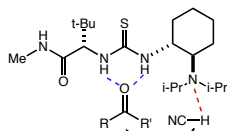
Multimetallic Bifunctional Catalysis
Defining the concept

■ What do we consider "bifunctional catalysis"?

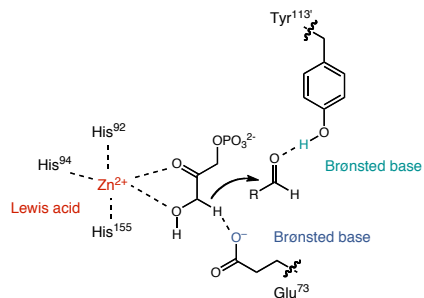


- Simultaneous activation of multiple reaction partners by different catalytically active centers
- Activation sites can either be in separate complexes or linked together

■ Familiar examples



- Organocatalysis

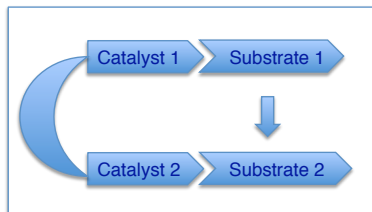


- Enzymes: Class II Aldolase

Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872.

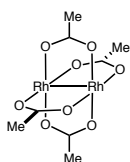
Multimetallic Bifunctional Catalysis Defining the concept

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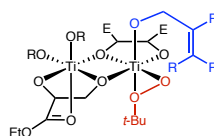
- Simultaneous activation of multiple reaction partners by different catalytically active centers
- Activation sites can either be in separate complexes or linked together

- Substrates must be activated by different catalytic centers, unlike the following examples:



- Only one Rh center acts as a carbene binding site
- Other Rh site acts as an extra "ligand" for stability

Rhodium carbene chemistry

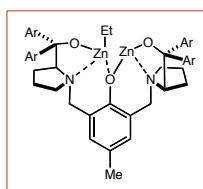
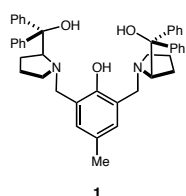


- One Ti center activates/coordinates both peroxide and allylic alcohol

Sharpless asymmetric epoxidation

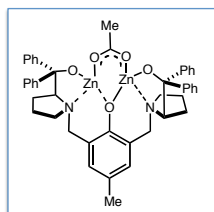
Dinuclear Zinc Proline-Derived Catalysts Barry M. Trost

- Trost pioneered the use of dinuclear zinc complexes as bifunctional catalysts



- C_2 -symmetric Bis-ProPhenol ligand
- One zinc center believed to act as Lewis acid
- Remaining zinc-alkoxide acts as Brønsted base

- Very few structural and mechanistic studies have been done
 - Addition of 2 equiv. of $ZnEt_2$ liberates 3 equiv. of ethane
 - Addition of H_2O liberates fourth equiv. of ethane from catalyst



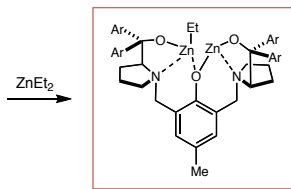
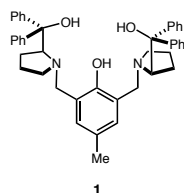
- Addition of acetic acid results in proposed structure
- Electrospray mass spectrometry provides mass peaks consistent with molecular formula

Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

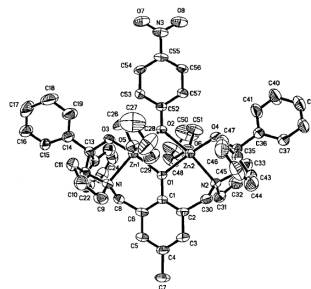
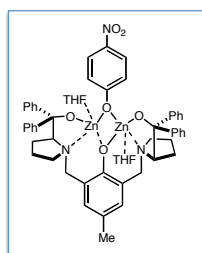
Dinuclear Zinc Proline-Derived Catalysts Barry M. Trost

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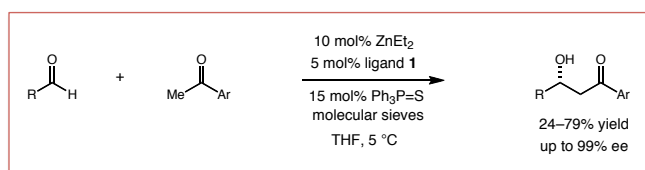
- Kuiling Ding – first crystal structure of related complex



Xiao, Y.; Wang, Z.; Ding, K. *Chem. Eur. J.* **2005**, *11*, 3668.

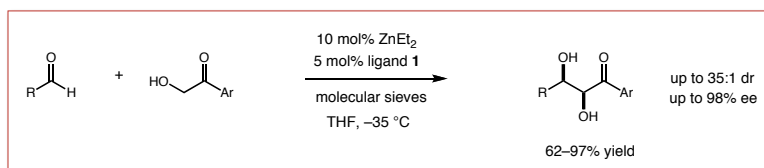
Dinuclear Zinc Proline-Derived Catalysts Enantioselective aldol reactions

- Direct catalytic enantioselective aldol



Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

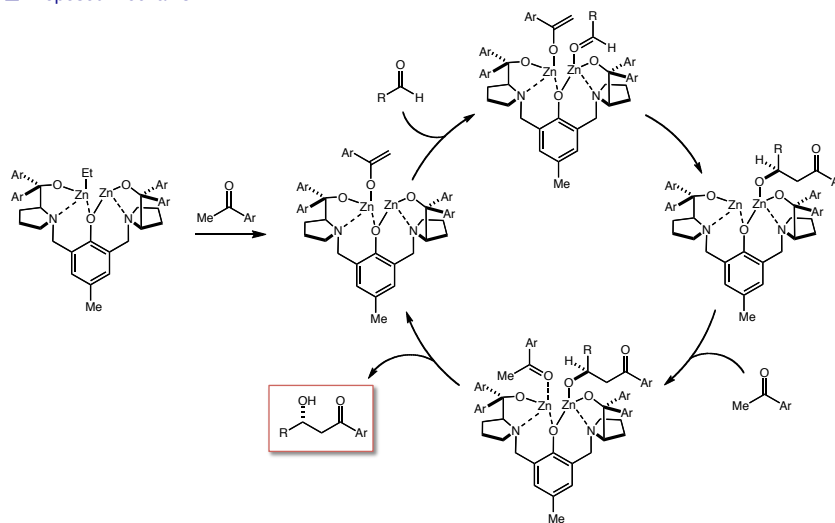
- Syn*-selective aldol using α -hydroxy ketones as donors



Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts
Proposed catalytic cycle

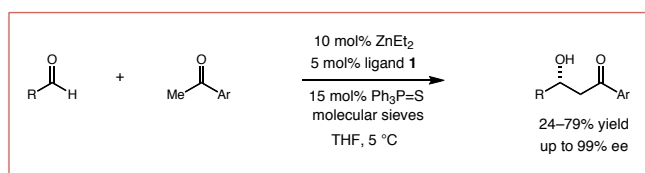
■ Proposed mechanism



Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

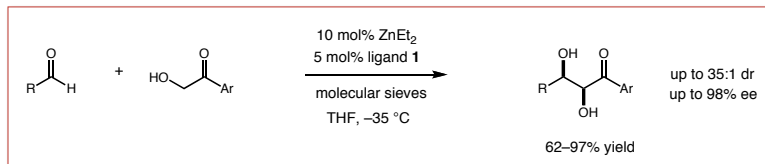
Dinuclear Zinc Proline-Derived Catalysts
Enantioselective aldol reactions

■ Direct catalytic enantioselective aldol



Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

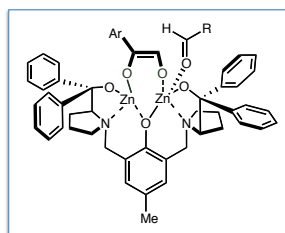
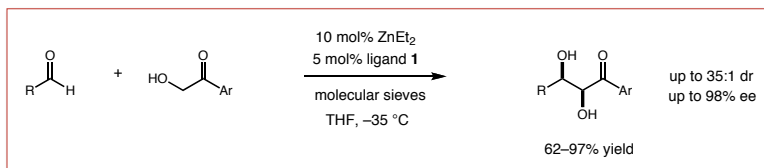
■ *Syn*-selective aldol using α -hydroxy ketones as donors



Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts
Transition state hypothesis

■ Proposed transition state

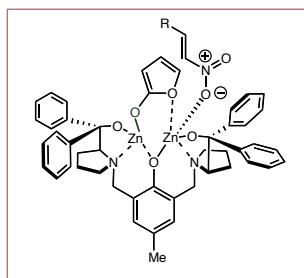
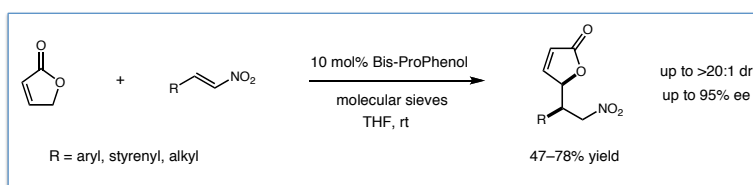


- α -hydroxy ketone bridges both zinc metal centers
- Aldehyde coordinates to most sterically accessible face of catalyst

Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts
Other nucleophiles and electrophiles

■ Vinylogous nucleophilicity of butenolide

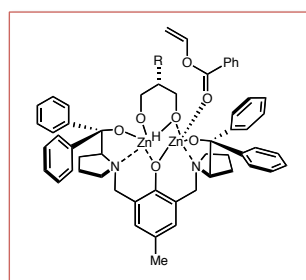
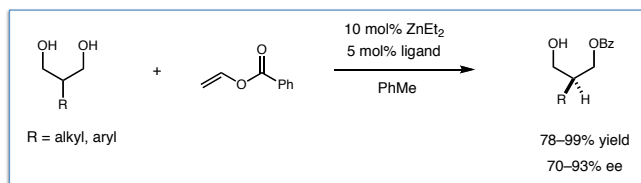


- Binds as bidentate bridging aromatic enolate

Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2001**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts
Other nucleophiles and electrophiles

■ Desymmetrization of 1,3-diols

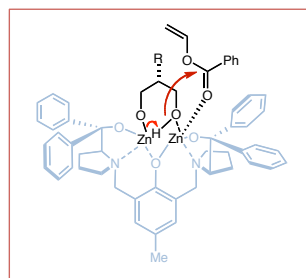
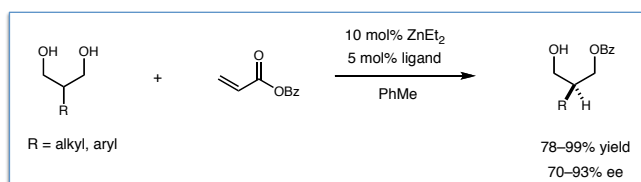


- Diol coordinates both zinc centers

Trost, B. M.; Malhotra, S.; Mino, T.; Rajapaksa, N. S. *Chem. Eur. J.* **2008**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts
Other nucleophiles and electrophiles

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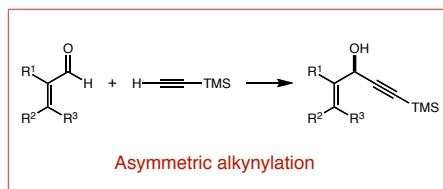


- Diol coordinates both zinc centers
- Proton transfer proposed to account for sense of induced stereochemistry

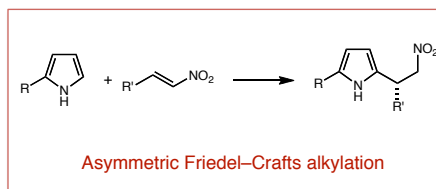
Trost, B. M.; Malhotra, S.; Mino, T.; Rajapaksa, N. S. *Chem. Eur. J.* **2008**, *123*, 3367.

Dinuclear Zinc Proline-Derived Catalysts Other nucleophiles and electrophiles

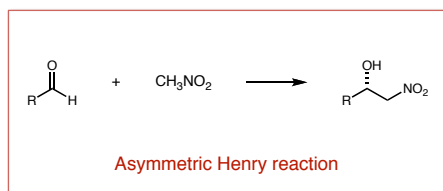
Select examples



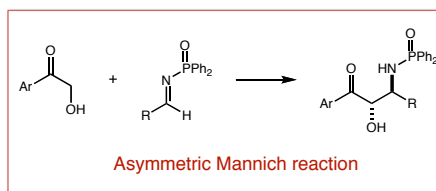
J. Am. Chem. Soc. **2006**, *128*, 8-9.



J. Am. Chem. Soc. **2008**, *130*, 2438.



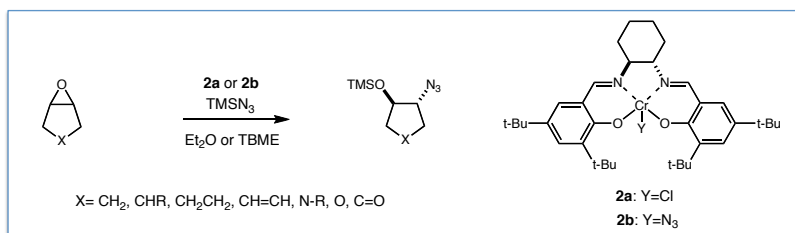
Angew. Chem. Int. Ed. **2006**, *41*, 861.



J. Am. Chem. Soc. **2006**, *128*, 2778.

Metal Salen Complexes as Bifunctional Catalysts Eric N. Jacobsen

Ring-opening of meso epoxides with TMSN₃



Preliminary investigations support activation of TMS-N₃ by Cr(salen) complex

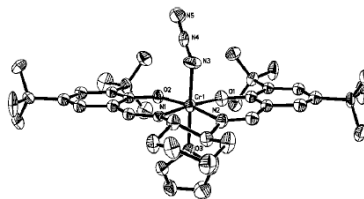
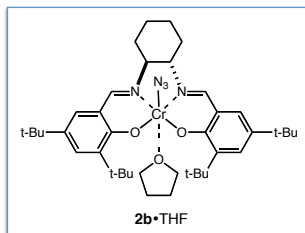
- Catalyst **2a** is precatalyst, while **2b** is active catalyst in reaction mixture
 - IR studies: observance of Cr-N₃ stretch
 - use of catalyst **2b** directly affords product

Can Cr(salen) complex also act as a Lewis acid?

Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.

Metal Salen Complexes as Bifunctional Catalysts Support for cooperative catalysis

Crystal structure of **2b**·THF



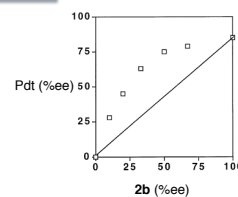
Supports possibility of Lewis acid activation of epoxides

Kinetic studies

- Second-order rate dependence on catalyst

Investigation of enantiomeric purity of **2b** vs. enantioselectivity of reaction

- Significant non-linear effects* observed (supports interaction between two chiral entities)

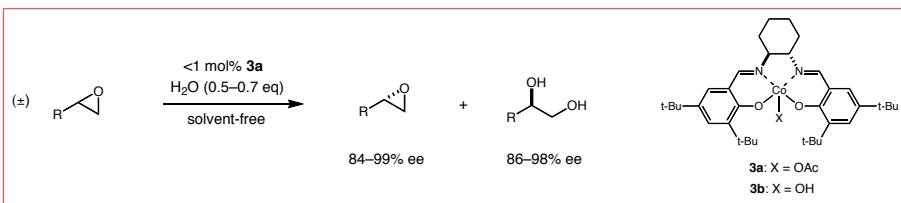


Hansen, K. B.; Leighton, J. L.; Jacobsn, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.

*Nonlinear effects: Guillauneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

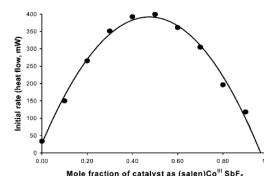
Metal Salen Complexes as Bifunctional Catalysts Hydrolytic Kinetic Resolution of Terminal Epoxides

Hydrolytic kinetic resolution (HKR) of terminal epoxides, and 1,2-diol synthesis



Mechanistic investigations

- Both enantiomers bind to catalyst with similar affinity
 - selectivity arises from only one of the epoxide complexes
- Ratio of **3a** to **3b** throughout reaction plays crucial role in reaction rate
 - Rate = $k_{\text{cat}} [\text{Co-OH}]_{\text{tot}} [\text{Co-X}]_{\text{tot}}$
 - 1:1 ratio optimal
 - ratio is affected by reactivity of counterion (X = OAc vs. Cl vs. OTs, etc.)

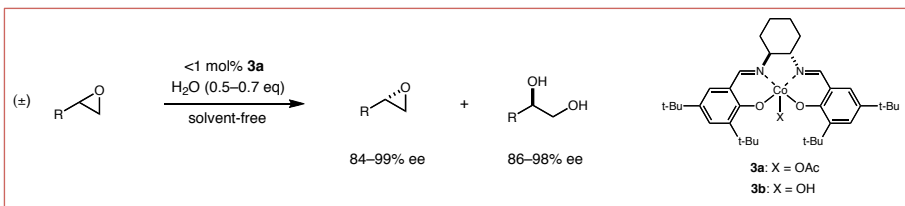


Tokunaga, M.; Larow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

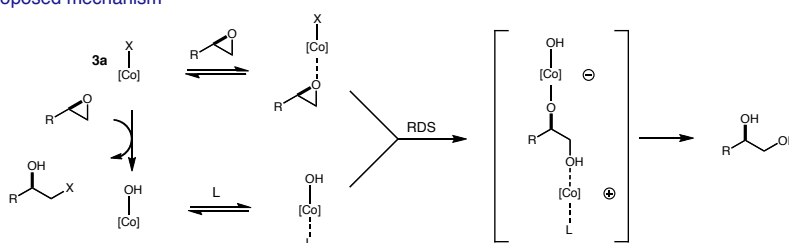
Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360.

Metal Salen Complexes as Bifunctional Catalysts Hydrolytic Kinetic Resolution of Terminal Epoxides

- Hydrolytic kinetic resolution (HKR) of terminal epoxides, and 1,2-diol synthesis

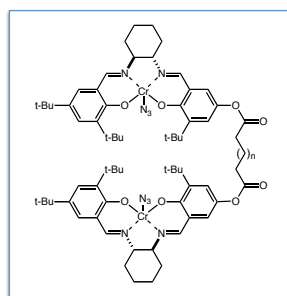


- Proposed mechanism

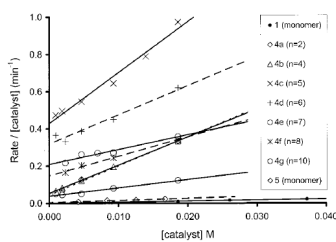


Metal Salen Complexes as Bifunctional Catalysts Enforcing cooperative catalysis through covalent linkage

- Covalently linked dimers could effect cooperative catalysis more efficiently



- Rate greatly accelerated compared to monomeric catalyst
- rate highly dependent on tether length
- No loss in enantioselectivity



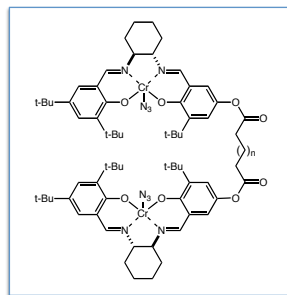
- Mechanistic considerations

- Kinetic studies indicate involvement of both inter- and intramolecular pathways
 - considering two-term rate equation: $k_{\text{intra}}[\text{cat}] + k_{\text{inter}}[\text{cat}]^2$, and plotting $\text{rate}/[\text{cat}]$ vs. $[\text{cat}]$
 - y-intercept = k_{intra} , slope = k_{inter}

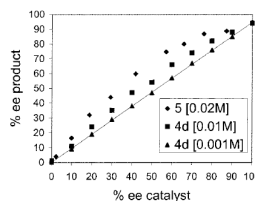
Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.

*Metal Salen Complexes as Bifunctional Catalysts
Enforcing cooperative catalysis through covalent linkage*

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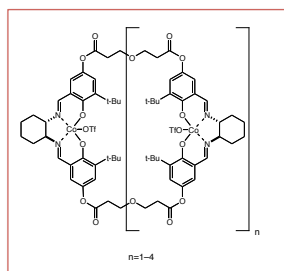
- Mechanistic considerations

- Comparing nonlinear effects in plot of catalyst ee vs. reaction ee with monomeric catalyst
 - high concentrations, attenuated nonlinear effect – participation of both 1st and 2nd-order pathways
 - low concentrations, strictly linear effect – expected for purely intramolecular pathway

Konsler, R. G.; Karl, J.; Jacobsn, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.

*Metal Salen Complexes as Bifunctional Catalysts
Enforcing cooperative catalysis through covalent linkage*

- One step further: oligomeric catalysts



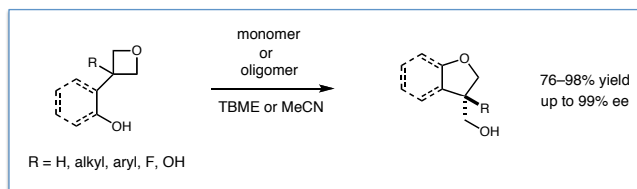
- Oligomeric catalysts can provide a dramatic increase in both rate and selectivity
- Polymer-supported and dendrimeric catalysts also provide similar significant rate enhancements

Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.

Breinbauer, R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 3604.

Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687.

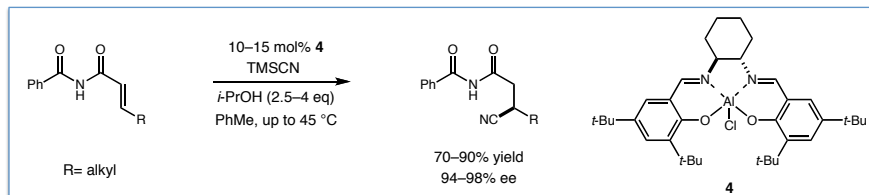
- Intramolecular ring-opening of oxetanes



Loy, R. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 2786.

Metal Salen Complexes as Bifunctional Catalysts
Enantioselective Conjugate Addition of Cyanide

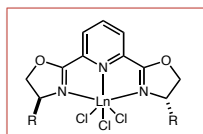
■ Asymmetric conjugate addition of cyanide to α,β -unsaturated imides



Sammis, G. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442.

■ High catalyst loadings and temperatures required

- Al(salen) complexes promote conjugate additions of other nucleophiles to unsaturated imides efficiently
- Insufficient activation of cyanide nucleophile?



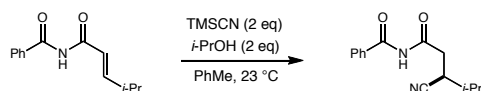
- Ln(pybox) complexes efficiently promote addition of TMSCN to epoxides
- Displays little to no reactivity for the above conjugate addition reaction

Can one utilize each catalyst's independent activation in a cooperative manner?

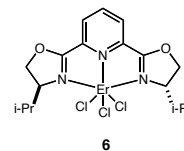
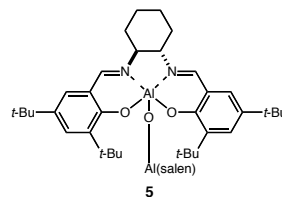
Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.

Metal Salen Complexes as Bifunctional Catalysts
Mixed catalytic systems

■ Conjugate addition with individual catalysts vs. dual-catalyst system



entry	catalyst system	conversion (%)	ee (%)
1	(<i>S,S</i>)-5	<3	-
2	(<i>S,S</i>)-6	<3	-
3	(<i>S,S</i>)-5 + (<i>S,S</i>)-6	99	96



■ Diastereomeric ligand combination

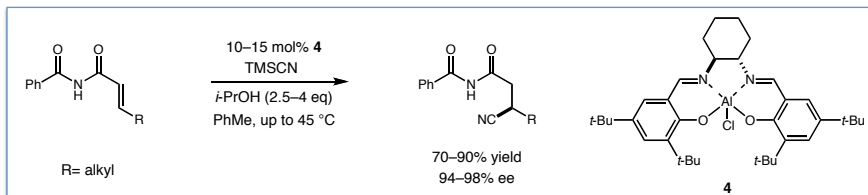
- Use of (*R,R*)-6 led to substantially decreased selectivities and rate
- When achiral Ln(pybox) was used, intermediate levels of selectivities were produced
- Achiral Al(salen) + 6 resulted in selectivity greater than with 6 alone (16% after 17 d)

Both complexes engage in rate-determining step and function cooperatively in asymmetric induction

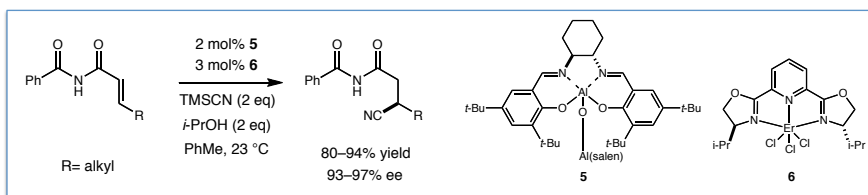
Sammis, G. N.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928.

Metal Salen Complexes as Bifunctional Catalysts Improved reaction conditions

Asymmetric conjugate addition of cyanide to α,β -unsaturated imides



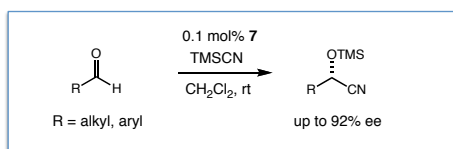
Sammis, G. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442.



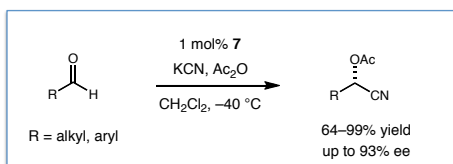
Sammis, G. N.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928.

Dinuclear Ti(Salen) Complexes Michael North

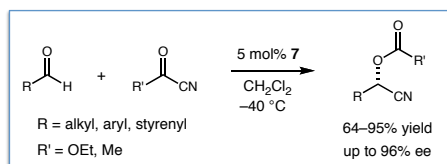
Cyanation of aldehydes



Belokon', North, *et al. J. Am. Chem. Soc.* **1999**, *121*, 3968.



Belokon', North, *et al. Helv. Chim. Acta* **2002**, *85*, 3301.

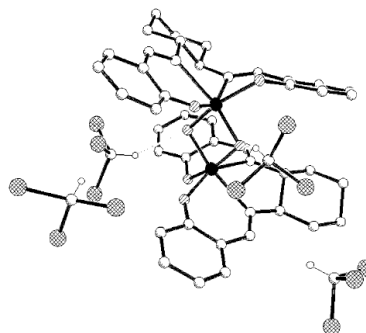
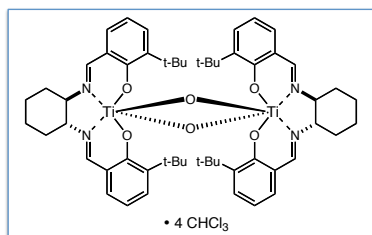


Belokon', North, *et al. Org. Lett.* **2003**, *5*, 4505.

Moberg *et al. J. Am. Chem. Soc.* **2005**, *127*, 11592.

Dinuclear Ti(Salen) Complexes Structure of dinuclear Ti-catalysts

■ Bridged dinuclear Ti(salen) catalyst

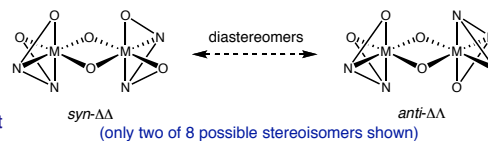


■ Central metalocycle consists of two long Ti–O bonds, and two short Ti–O bonds

■ Two bridging oxygens must be *cis* to one another

- Forces salen ligands out of planarity

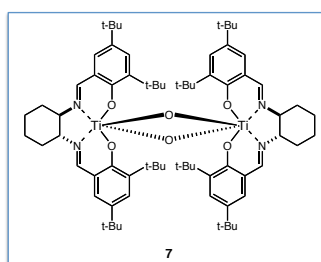
■ *syn-ΔΔ* diastereomer believed to be active catalyst



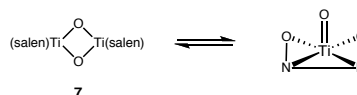
Belokon', North, *et al. Tetrahedron* **2007**, *63*, 5287.

Dinuclear Ti(Salen) Complexes Mechanistic Analysis

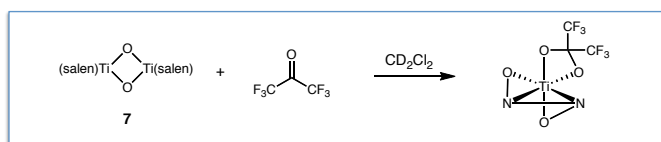
■ Preliminary investigations



- Ti already 6-coordinate
- existing bond must break to accommodate additional ligand
- ¹⁷O and ¹H NMR suggests equilibrium of dimeric and monomeric species



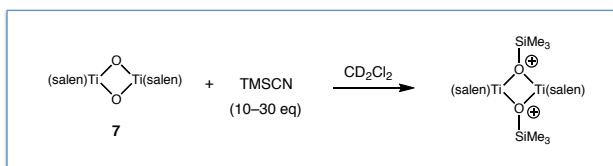
■ Addition of electrophilic carbonyl compound results in metalla-acetal



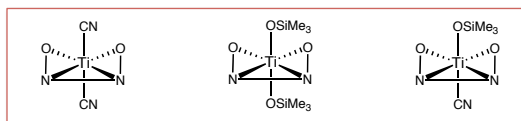
Belokon', North, *et al. Eur. J. Org. Chem.* **2000**, 2655.

Dinuclear Ti(Salen) Complexes Mechanistic Analysis

- Addition of TMSCN results in disilated catalyst



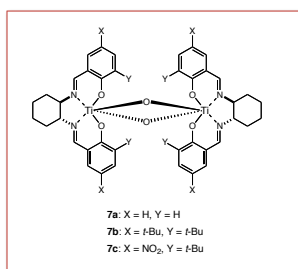
- Proposed structure difficult to isolate
 - new signals in ^1H NMR corresponding to incorporation of TMS groups
 - FAB mass spectrometry suggests dimeric structure
- Readily decomposes into proposed monomeric species:



Belokon', North, *et al. Eur. J. Org. Chem.* **2000**, 2655.

Dinuclear Ti(Salen) Complexes Mechanistic Analysis

- Kinetic studies suggest active catalyst is dimeric in nature



- First order in TMSCN
- Zero order in aldehyde
- Order with respect to catalysts **7a–7c**:
 - **7a**: 1.6
 - **7b**: 1.3
 - **7c**: 1.8

What do these orders tell us?

- Assume rapid equilibrium between mono- and dinuclear complexes of *precatalyst* **7**
 - initial concentration of $[\text{C}]_0$
- Two situations can arise for presumed mononuclear catalyst (Cat_{mono}) and dinuclear catalyst (Cat_{di}):

Assume mononuclear species Cat_{mono} is catalyst

- if Cat_{mono} is predominant species, rate = $k[\text{C}]_0$
- if Cat_{di} is predominant species, rate = $k[\text{C}]_0^{1/2}$

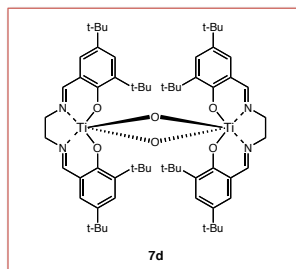
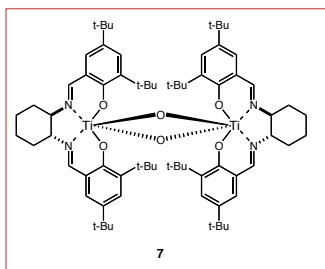
Assume dinuclear species Cat_{di} is catalyst

- if Cat_{mono} is predominant species, rate = $k[\text{C}]_0^2$
- if Cat_{di} is predominant species, rate = $k[\text{C}]_0^1$

For full derivation of rate laws, see: Belokon', North, *et al. Eur. J. Org. Chem.* **2000**, 2655.

Dinuclear Ti(Salen) Complexes Mechanistic Analysis

- Kinetic studies suggest active catalyst is dimeric in nature



- Catalyst **7d** catalyzes reaction, but at rate much slower than **7** (by 1000 at 0 °C)

entry*	catalyst system	conversion (%)	ee (%)
1	7	100	82
2	7d	34	0
3	7 + 7d	20	34

- Normally would expect **7** to dominate catalysis, leading to high yield and ee

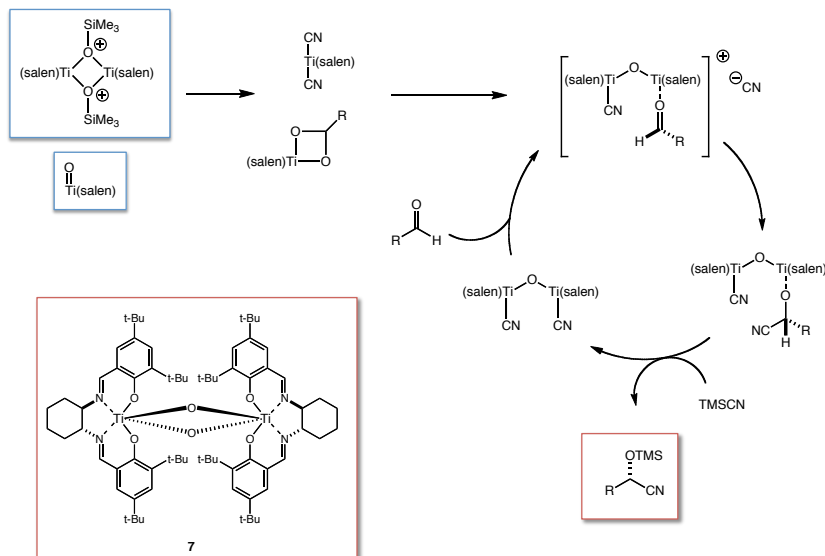
*Runs were conducted at room temperature

7 + 7d forms new, bimetallic species in situ

Belokon', North, *et al. Tetrahedron* **2007**, *63*, 5287.

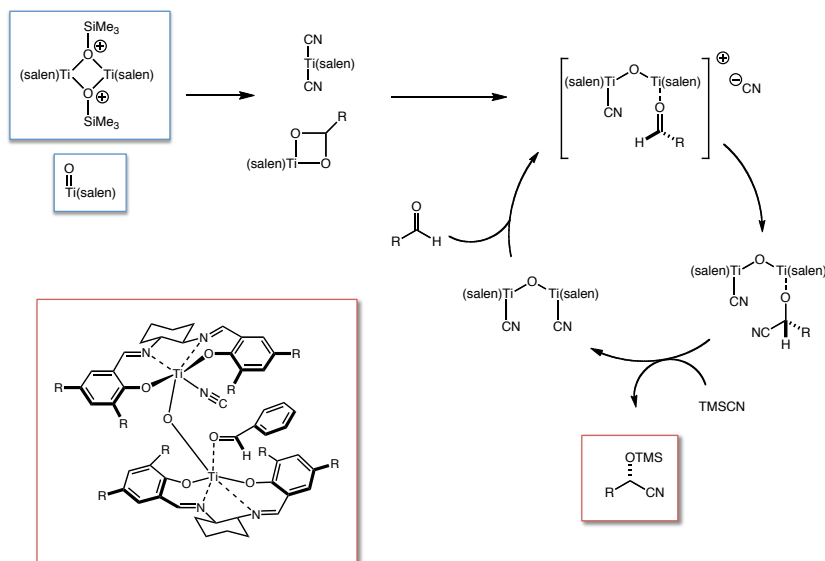
Dinuclear Ti(Salen) Complexes Proposed Mechanism

- Proposed mechanism



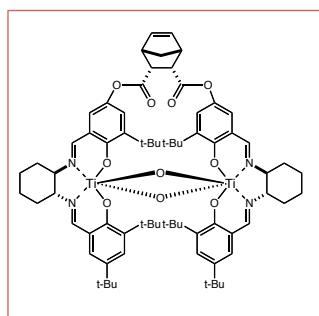
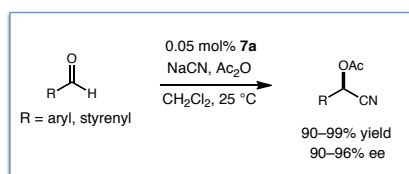
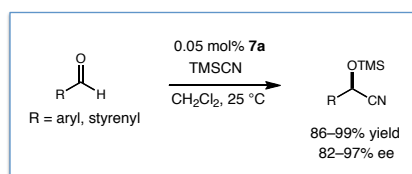
Dinuclear Ti(Salen) Complexes Proposed Mechanism

Proposed mechanism



Dinuclear Ti(Salen) Complexes Enforcing cooperative catalysis

Ding – tethering the (salen) ligand

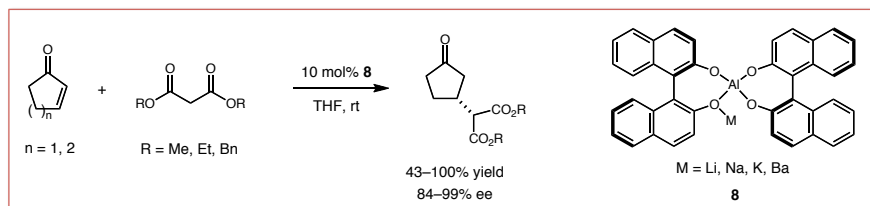


- Significant improvement over parent catalyst
- Activity/selectivity highly dependent on tether choice
- Catalyst enantiopurity vs. reaction enantioselectivity
 - strict linear relationship: intramolecular pathway

Zhang, Z.; Wang, Z.; Zhang, R.; Ding, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 6746.

BINOL-Derived Bimetallic Catalysts
Masakatsu Shibasaki

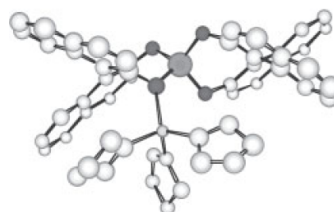
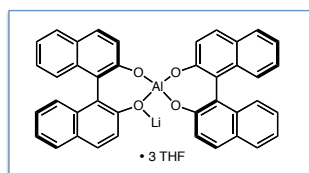
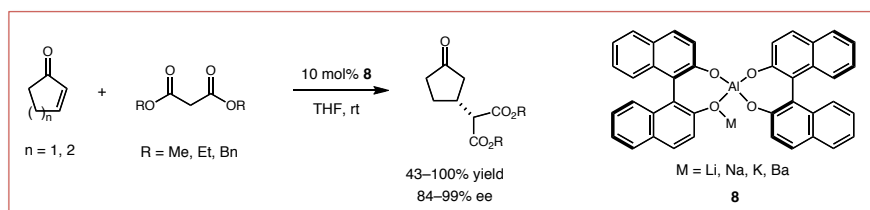
■ Alkali metal heterobimetallic asymmetric catalysis



Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 104.

BINOL-Derived Bimetallic Catalysts
Masakatsu Shibasaki

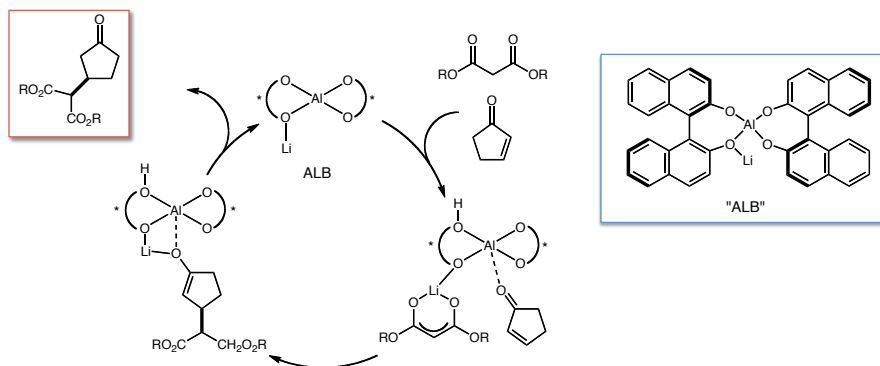
■ Alkali metal heterobimetallic asymmetric catalysis



Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 104.

BINOL-Derived Bimetallic Catalysts Mechanism

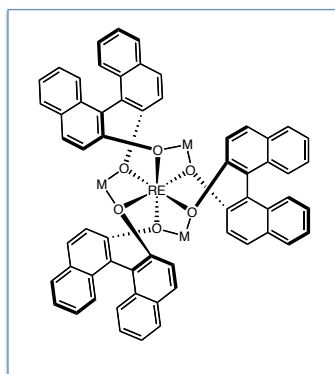
Proposed mechanism



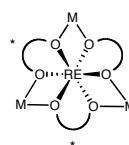
- Aluminum center acts as Lewis acid
- Lithium-alkoxide behaves as Brønsted base

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts Masakatsu Shibasaki

- REMB catalysts are among the most prominent multifunctional catalysts in organic synthesis



≡

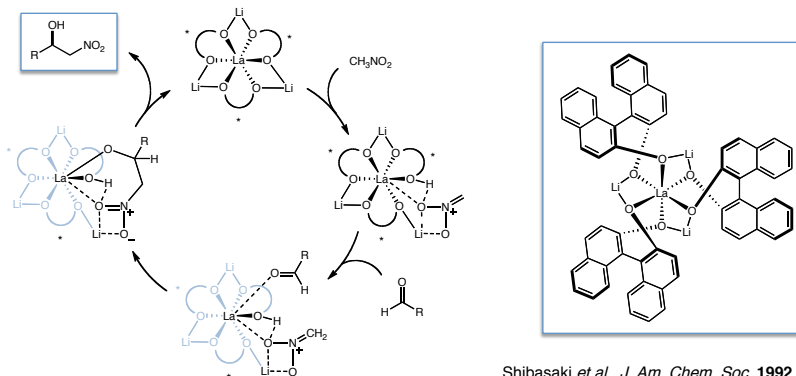
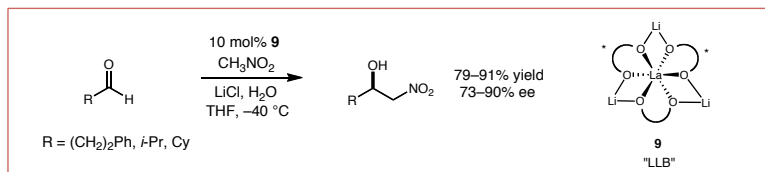


- Center of asymmetry at central rare earth metal
- configuration at central metal defined by BINOL ligand

- Lewis acidic lanthanide rare earth metal center
- Lewis and Brønsted basic BINOLate oxygens

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
The asymmetric nitroaldol reaction

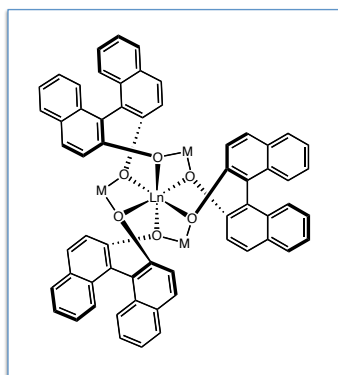
■ Seminal work – asymmetric Henry reaction



Shibasaki *et al.*, *J. Am. Chem. Soc.* **1992**, *114*, 4418.

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
Structural analysis of catalysts

■ Role of rare earth metal center in REMB



■ Early solid-state and solution phase analysis indicated solvation of only alkali metals by lewis basic ligands (THF, Et₂O, etc.)

■ Only occasionally do Ln centers bind a single H₂O molecule

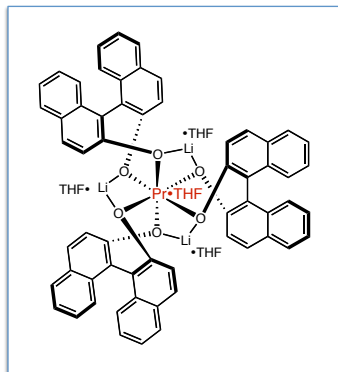
Do lanthanide centers bind substrate, or are they only a structural element?

Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807.

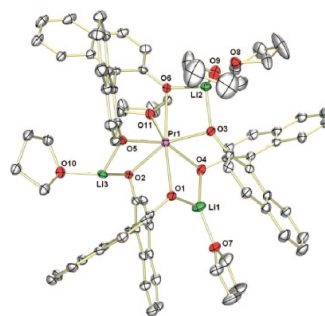
Bari, L. D.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549.

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
Structural analysis of catalysts

- Patrick Walsh – first successful crystal structures organic base-coordinated REMB catalysts



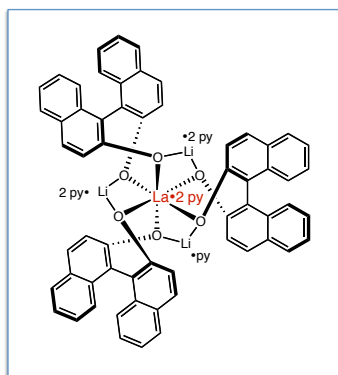
- 7-coordinate $\text{Li}_3(\text{THF})_4(\text{BINOL})_3\text{Pr}(\text{THF})$



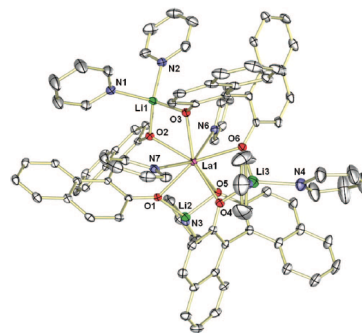
Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 7407.

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
Structural analysis of catalysts

- Patrick Walsh – first successful crystal structures organic base-coordinated REMB catalysts



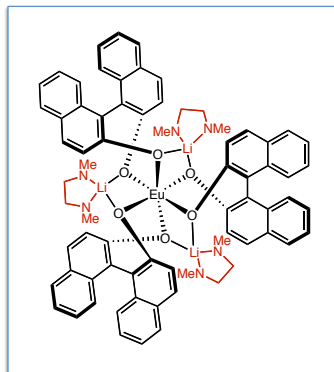
- 8-coordinate $\text{Li}_3(\text{py})_5(\text{BINOL})_3\text{Pr}(\text{py})_2$



Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 7407.

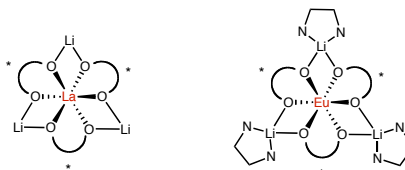
Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
Structural analysis of catalysts

■ Patrick Walsh – solution-phase structural analysis



■ 6-coordinate $\text{Li}_3(\text{DMEDA})_3(\text{BINOL})_3\text{Eu}$

- DMEDA shown not to be displaced by Lewis basic ligands
- If substrate binds, it must be to lanthanide center



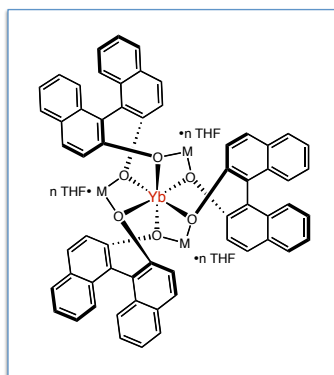
- ^1H NMR of cyclohexenone-bound complexes both display similar lanthanide-induced shifts (LIS)
- can only be attributed to carbonyl binding to lanthanide center

First definitive evidence for solution binding of Lewis bases to REMB complexes

Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 7407.

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts
Structural analysis of catalysts

■ Patrick Walsh – effect of alkali metal size



■ $\text{M}_3(\text{THF})_n(\text{BINOL})_3\text{Yb}$

- Small Yb center compared to other lanthanide complexes
- for $\text{M} = \text{Na}, \text{K}$, lanthanide center does not bind even H_2O
- Solution-phase NMR studies reveal that both cyclohexenone and DMF experience significant LIS when $\text{M} = \text{Li}$

Overriding factor in controlling binding ability is radius of main group metal, not lanthanide center

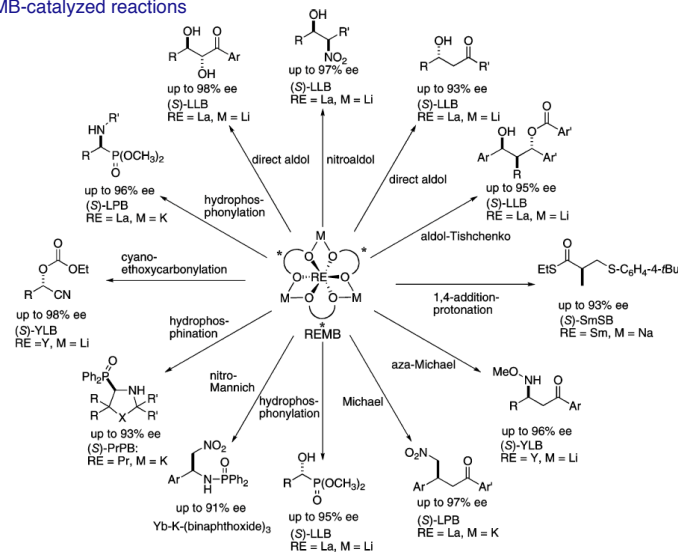
Takaoka, E.; Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Heterocycles* **1997**, *46*, 157.

Bari, L. D.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549.

Wooten, A. J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 7407.

Rare Earth–Alkali Metal–BINOL (REMB) Catalysts Structural analysis of catalysts

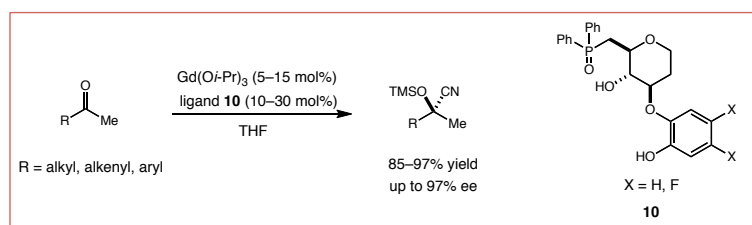
Select REMB-catalyzed reactions



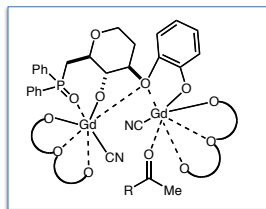
Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

Higher-Order Polymetallic Asymmetric Catalysts Masakatsu Shibasaki

Select REMB-catalyzed reactions



Self assembly of active catalyst



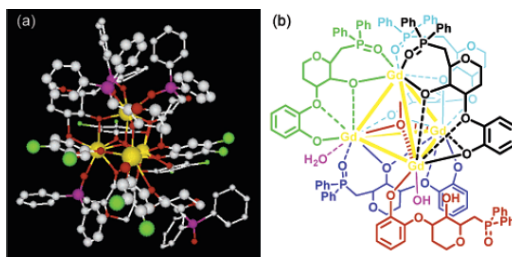
- ESI-MS studies suggest 2:3 Gd : ligand ratio
- Also observed a 4:5+oxo complex
- Changing preparation method results in formation of only one complex - with Gd(HMDS)₃, only 2:3 complex observed

Shibasaki, Curran, *et al. J. Am. Chem. Soc.* **2001**, *123*, 9908.

Kanai, Shibasaki, *et al. J. Am. Chem. Soc.* **2006**, *128*, 6768.

Higher-Order Polymetallic Asymmetric Catalysts Identity of active catalysts

- Attempts to obtain crystal structure of 2:3 complex resulted in isolation of only 4:5+oxo framework



11

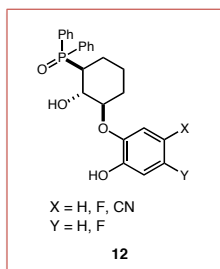
- Assembly state change during crystallization process
- Use of 11 as catalyst resulted in reaction rate 5–50 times slower than with 2:3 in situ complex
- Use of 11 as catalyst switch in enantioselectivity compared to 2:3 in situ complex

Higher-order structure, not structure of individual module, is the determining factor of catalyst function

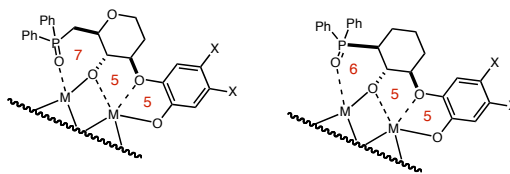
Kanai, Shibasaki, *et al. J. Am. Chem. Soc.* **2006**, *128*, 6768.

Higher-Order Polymetallic Asymmetric Catalysts Design of new higher-order catalytic structures

- *De novo* design of higher-order structures nearly impossible
- Designing more stable module might help unify higher-order structure



12



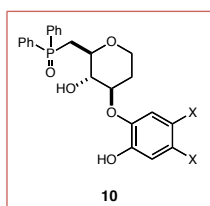
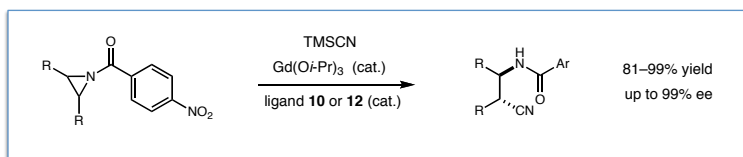
- Presumably more stable 6,5,5 ring system in individual module

- Higher-order structure observations
 - 5:6+oxo+OH complex sole species observed by ESI-QFT-MS studies
 - Attempts at crystallization resulted in 3:2+2OH complex

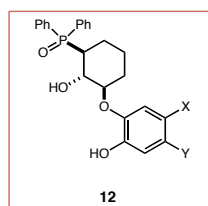
Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438.

Higher-Order Polymetallic Asymmetric Catalysts Identity of active catalysts

■ Comparison of ligands 11 and 12



10 mol% Gd required
up to 95 h reaction time



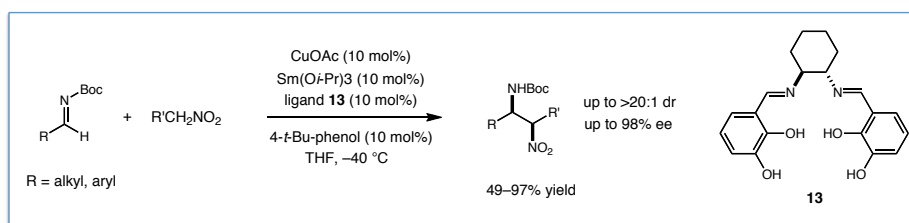
2 mol% Gd required
complete within 24 h

Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.

Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438.

Chiral Schiff Base Catalysts Structural studies

■ Nitro-Mannich reaction



■ Plot of enantiopurity of 13 vs. reaction enantioselectivity revealed weak nonlinear effect

■ In presence of phenol additive, ESI-MS revealed presence of μ -oxo trimeric species

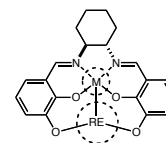
- Also see monomeric fragment

■ In absence of phenol, ESI-MS revealed presence of additional oligomeric species

- Enantioselectivity decreases in absence of phenol additive

■ Use of "well-ordered" $\text{Sm}_5\text{O}(\text{O}i\text{-Pr})_{13}$ leads to improved results

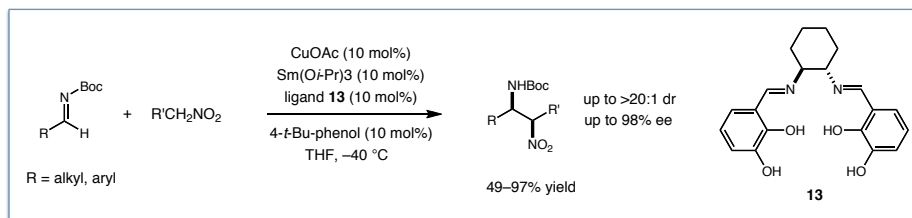
- Most likely prevents formation of detrimental oligomeric species



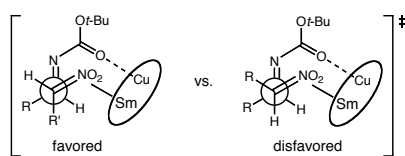
Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.

Chiral Schiff Base Catalysts Mechanism

■ Nitro-Mannich reaction



■ Proposed transition state



Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.