**Topic: Catalytic Enantioselective 1,2 Additions**

1. **ENANTIOSELECTIVE KETONE REDUCTION**
   1. Catalytic asymmetric metal hydride reduction

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| Corey developed the chiral oxazaborolidine catalysts, which are impressively effective in the reduction of a wide variety of aromatic, unsaturated, and cyclic ketones with high enantioselectivities. The catalysts can be used in reduction of a variety of functionalized ketones. |
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| Corey *ACIE* **1998**, *37*, 1986 |

* 1. Catalytic asymmetric hydrogenation

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| [RuCl2{P{C6H5)3}3] is a great catalyst for hydrogenation of terminal olefin but very inactive for reaction of carbonyl compounds. In the presence of 1 equivalent of ethylenediamine and 2 equivalents of KOH with respect to ruthenium, [RuCl2{P{C6H5)3}3] selectively hydrogenates carbonyls. |
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| Noyori *ACIE* **2001**, *40*, 40 |

* + 1. Hydrogenation of functionalized ketones

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| BINAP-Ru-catalyzed hydrogenation of functionalized ketones  -Chelation of Ru atom to carbonyl and/or heteroatom to form 5- or 6-membered ring is important in stereo-differentiation. |
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| Noyori *JACS* **1988**, *110*, 629 |
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| Noyori *JACS* **2000**, *122*, 6510 |

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| Carbonyl selective hydrogenation of unsaturated aldehydes and ketones using RuCl2(phosphane)n-1,2-diamine-KOH |
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| Noyori *JACS* **1995**, *117*, 10417 |

* + 1. Hydrogenation of simple ketones

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| Zhang *ACIE* **1998**, *37*, 1100 |

* 1. Catalytic asymmetric transfer hydrogenation

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| Hydride transfer from the H-donors can occur through two mechanisms:  - Direct H-transfer (metal-templated concerted process)  Metal acts as a template for the concerted shift of hydride from H-donor to acceptor. |
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| Hydrogen donors |
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| Gladiali *Chem. Soc. Rev.* **2006**, *35*, 226 |

* + 1. Reduction of simple ketones

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| Noyori *JOC* **2001**, *66*, 7931 |

* + 1. Reduction of functionalized ketones

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| Ikariya *Tetraheron* **2004**, *60*, 7411 |

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| Noyori *JACS* **1997**, *119*, 8738 |

1. **ENANTIOSELECTIVE C=O ADDITIONS**

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| -Nucleophilic addition of organometallic reagents to aldehydes and ketones is one of the most popular methods for construction of C-C bonds.  -Development of enantioselective addition of organometallic reagents to carbonyls is attractive and immense research has been described. |

* 1. Catalytic enantioselective C=O additions of dialkylzinc
     1. Catalyzed by DIAB

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| -Dialkylzinc addition to C=O is historically well known and is one of the most successful examples in enantioselective additions.  -Noyori’s camphor-derived β-amino alcohol (−)-DIAB was the first chiral ligand that can mediate dialkylzinc addition to aldehyde in a *highly* catalytic enantioselective fashion. |
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| Noyori *JACS* **1986,** *108*, 6071 and *JACS* **1995**, *117*, 4832 |

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| -The mechanism of diethylzinc addition has been studied extensively.  -Noyori proposed that the active species is the monomeric zinc complex rather than its dimeric complex.  -Positive nonlinear effect was observed in these reactions. |
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* + 1. Catalyzed by Ti-TADDOL

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| -Ti-TADDOL is a great catalyst for dialkylzinc addition to aldehyde, and very high ees were obtained. |
| -Not many dialkylzinc reagents are commercially available. Seebach developed a method that can generate dialkylzinc (other than diethylzinc) *in situ* from the corresponding Grignard reagent. |
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| Seebach *ACIE* **1991**, *30*, 1008 |

* + 1. Catalyzed by *C2*-Symmetric disulfonamide and Ti(Oi-Pr)4

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| The combination of *C2*-Symmetric disulfonamide and Ti(O*i*-Pr)4 gives very reactive catalyst that can facilitates the addition of higher organozinc homologues to aldehydes. |
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| Ohno *Tetrahedron* **1992**, *48*, 5691 |

* 1. Enantioselective Grignard additions

-Grignard addition to carbonyls is one of the most reliable methods of forming C-C bonds. Grignard reagents are, however, so reactive that their fast background reaction via uncatalyzed pathway would greatly diminish the enantioselectivity. Grignard reagent has been considered unsuitable for asymmetric alkylation.

* + 1. Chiral ligands used in enantioselective Grignard additions

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| There are a wide variety of chiral ligands that have been used to induce enantioselectivity. Only a few papers report high enantioselectivities and also these methods require non-ideal conditions such as very low temperature (<-100 °C) and stoichiometric quantity of chiral ligands. |
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| Luderer *Tetrahedron: Asymmetry* **2009**, *20*, 981; Seebach *Tetrahedron* **1994**, *50*, 6117 |

* + 1. Catalytic enantioselective alkylation of aldehydes with Grignard reagent

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| -So far there’s no catalytic enantioselective Grignard addition.  -Harada’s organotitanate derived from Grignard reagent, DPP-binol and Ti(O*i*Pr)4 adds to aldehydes catalytically and enantioselectively (an indirect way of doing catalytic enantioselective Grignard addition).  -This system works very well with aromatic aldehydes, alkyl- and aryl- Grignards.  -The titanate is generated at -78 °C by adding Grignard reagent to Ti(O*i*Pr)4. |
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| Harada *ACIE* **2008**, 47, 1088; *CEJ* **2008**, 14, 10560; *Bull. Chem. Soc. Jpn.* **2010**, 83, 19 |
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| -Da reported a similar indirect way of doing catalytic enantioselective Grignard addition.  -Catalytic asymmetric addition was achieved by deactivating Grignard reagents through chelation with bis[2-(N,N-dimethylamino)ethyl]ether (BDMAEE).  -In this carbonyl addition reaction, MgBr2 and MgBr(O*i*Pr) are formed. These Lewis acids promote the background reaction to form the racemic product and thus lower the enantioselectivity of the process. Addition and chelation of DBMAEE to the *in situ* generated MgBr2 and MgBr(O*i*Pr) suppress their activity and so the asymmetric catalytic additions can be highly enantioselective.  -The catalytically active specie is also a titanate.  -Reaction can be run at room temperature. |
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| Da *OL* **2009**, *11*, 5578 |
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* 1. Catalytic enantioselective alkyne addition
     1. Boron alkynilide addition to aldehydes

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| -Corey’s boryl acetylides gives good yields and enantioselectivities. |
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| Corey *JACS* **1994**, *116*, 3151 |

* + 1. Alkylzinc-mediated enantioselective alkynylation of aldehyde

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| -Many amino alcohol-zinc complexes have shown the activity for catalyzed alkynylation of aldehydes.  -Trost’s ProPhenol catalyst is commercially available, which works well with aromatic and α,β-unsaturated aldehydes with high yields and ees. |
| Trost *JACS* **2006**, *128*, 8 |

* + 1. Titanium-catalyzed zinc acetylide addition to aldehydes

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| -Pu found that BINOL and Ti(O-*i*Pr)4 catalyzed alkynylzinc addition to aldehydes.  -High temperature was required in the first step and caused decomposition of some functional alkynes.  -Subsequent reports showed that addition of HMPA allows the reaction to run at r.t. and tolerates more functional groups.  -High yields and ees were obtained with aromatic, aliphatic and α,β-unsaturated aldehydes. |
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| Pu *Adv. Synth. Catal.* **2009**, *351*, 963; *PNAS* **2004**, *101*, 5417; *OL* **2002**, *4*, 4143 |

* + 1. Metal-catalyzed addition of terminal acetylenes to aldehydes

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| -Additions of *in situ* generated metal alkynilide to aldehyde were achieved with catalytic amount of metal salt. |
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| Carreira *JACS* **2001**, *123*, 9687 |



Shibasaki *JACS* **2005**, *127*, 13760

* 1. Catalytic enantioselective allylations
     1. Diasteroselectivity of allylating reagents



Carreira C5.3, 5.6, 5.8

* + 1. Catalytic enantioselective addition of allylic silanes and stannanes

These allylations are most efficiently achieved by the combination of Lewis acid and allyl trialkylsilanes and trialkylstannanes (type II allylating agents).

2.4.2.1 Chiral acyloxy borane (CAB)-catalyzed

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| Yamamoto achieved the first example of chiral Lewis acid-catalyzed enantioselective allylation of aldehydes in 1991 using CAB catalysts. |
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| Yamamoto *Synlett* **1991**, 561; *JACS* **1993**, *115* 11490 |

2.4.2.2 Titanium/BINOL-catalyzed

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| -Titanium/BINOL-catalyzed allylation is one of the most extensively studied chiral Lewis acid-catalyzed allylations. |
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| Tagliavini/Umani-Ranchi *JACS* **1993**, *34*, 7001; Keck *JACS* **1993**, *34*, 8467 |
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| BINOL/Ti(IV) catalysts are relatively weak Lewis acids, and not very effective to promote reaction with allylic silanes, which are less nucleophilic and toxic. Carreira found that reactivity is enhanced when using TiF4 in place of Ti(O-*i*Pr)4. |
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| Carreira *ACIE* **1996**, *35*, 2363; *JOC* **2001**, *66*, 6410 |

* + 1. Catalytic enantioselective allylboration

-Allylboration has the advantages that the reaction is stereospecific and highly diasterospecific.

-If Lewis acid can catalyze allylboration without interfering the chair-like 6-membered cyclic transition state, the reaction would allow a catalytic, enantioselective, regiospecific and diastereospecific approach to chiral homoallylic alcohol.

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| Chiral diol- SnCl4 Catalyzed |
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| Hall *JACS* **2008**, *130*, 8481 |
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| Chiral Bronsted acid-catalyzed |
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| Antilla *JACS* **2010**, *132*, 11884 |
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| First catalytic enantioselective allylboration and crotylation of ketones |
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| Shibasaki *JACS* **2004**, *126*, 8911 |

* + 1. Catalytic enantioselective allylation with allylic halides

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| -*In situ* generation of allylic organometallic reagents from allylhalides and metals is synthetically advantageous because it does not require the preparation, isolation and handling of toxic or sensitive reagents.  -Chromium catalyzed enantioselective addition of allylic halide to aldehydes using chiral salen ligand gives high ees for aromatic and aliphatic aldehydes. |
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| Umani-Ronchi *ACIE* **1999**, *38*, 3357; *Pure App. Chem.* **2001**, *73*, 325 |

* + 1. Catalytic enantioselective transfer hydrogenative allylation and crotylation

-Krische reported allylation and crotylation under hydrogenative condition, where non-activated substrates such as allylic acetate and butadiene were utilized as nucleophiles.

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**** Krische *JACS* **2008**, *130*, 14891; *Org. Process Res. Dev.* **2011**, *15*, 1236



Krische *Science* **2012**, *336*, 324

1. **ENantioselective Aldol Reactions**
   1. Types of aldol reactions

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* 1. Mukaiyama aldol reaction
     1. Background and mechanism

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| The crossed aldol reaction between a silyl enolate and a carbonyl compound in the presence of Lewis acid is referred to as a *Mukaiyama aldol reaction*. |
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| Mukaiyama *Chem. Lett.*  **1973**, 1011 |

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| Mechanism:  - Diastereoselection.  - Stereochemical outcome is explained by open-transition model, based on steric- and dipolar effects. |
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| Mahrwald *Chem. Rev.* **1999**, *99*, 1095-1120 |

* + 1. Challenges to metal-catalyzed enantioselective Mukaiyama aldol Reaction

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| - Background achiral silicon-catalyzed aldol addition |
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| Carreira *TL* **1994**, 35, 4323; Bosnich *JACS* **1995**, 117, 4570 |
| *- Anti* *vs* *Syn* (in aldol reaction with substituted silyl enolates) |

* + 1. Historic enantioselective Mukaiyama aldol addition

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| The first enantioselective catalytic Mukaiyama aldol addition |
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| Mukaiyama, Kobayashi *Chem. Lett.* **1990**, 129, 1455 |

* + 1. Silyl ketene acetals, thioester-derived silyl ketene acetals as nucleophiles
       1. *Syn*

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| - Chiral (acyloxy)borane (CAB) complexes of tartrate-derived ligands by Yamamoto |
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| Yamamoto *Synlett* **1991**, 439 |

* + - 1. *Anti*

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| - Chiral BINOL and Zr(IV) complexes by Kobayashi |
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| Kobayashi *JACS* **2000**, *122*, 5403; *JACS* **2002**, *124*, 3292 |

* + - 1. *Acetate Mukaiyama aldol addition*

Like chiral auxiliaries, metal catalysts have also had difficulties in obtaining high enantioselectivity in acetate aldol additions (acetate derived nucleophiles).

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| - Chiral oxazaborolidine complex generated from C*α*-alkylated *α*-amino acids by Masamune |
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| Masamune *JACS* **1991**, 113, 9365 |

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| - BINOL and Ti(IV) complexes by Keck and Mikami  BINOL/TiClx(OTf)y  catalyzes acetate aldol addition with excellent yields and enantioselectivity.  Broad scope of aldehydes including simple aldehydes and functionalized aldehydes such as trifluoroacetadehyde, chloroacetaldehyde, benzyloxyacetaldehyde, ethyl glycolate… |
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| Mikami *JACS* **1993**, *115*, 7039, *JACS* **1994**, *116*, 4077; *Synlett* **1995**, 1057 |

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| - Complex of Ti(IV), tridentate Schiff base and di *tert*-butylsalicylic acid by Carreira |
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| Carreira *JACS* **1994**, *116*, 8837  Carreira, Kvaerno *Classics in stereoselective synthesis* p.133-134 |

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| - Complex of chiral Cu(II)-Pyridine Bis(Oxazoline) (PyBOX) complex by Evans |
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| Evans *JACS* **2000**, *122*, 10033; *ACIE* **1997**, *36*, 2744 |

* + - 1. *Ketones as electrophiles*

- Evans developed a family of chiral BOX complexs with different metals as catalysts for enantioselective Mukaiyama aldol reactions.

Bidentate chelation leads to the formation of a square pyramidal complex and the *re* aldehyde enantioface is shielded -> High level of diastereoselectivity and enantioselectivity.

The requirement of chelation limits the scope of electrophiles (α-alkoxyacetaldehydes, pyruvates, glycolates, α-diketones, 5-formyloxazoles).

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| Chiral Cu(II)/*tert*-Bu-BOX complex |
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| Evans *JACS* **1997**, *119*, 7893 |

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| Chiral Sn(II)/Ph-PyBOX complex |
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| Evans *JACS* **1997**, *119*, 10859 |

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| - Complex of Cu(I)fluoride and chiral Taniaphos ligand by Shibasaki  Examples of effective catalyzed enantioselective aldol reactions with simple ketone acceptors are scarce due to the attenuated reactivity of ketones and reversibity of their aldol addition. Stereocontrol is also challenging. |
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| Shibasaki *JACS* **2006**, *128*, 7164 |

* + 1. Silyl enol ethers as nucleophiles
       1. *Syn*

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| - Chiral (acyloxy)borane (CAB) complex of tartrate-derived ligands by Yamamoto. |
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| Yamamoto *JACS* **1991**, 113, 1041 |

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| - BINOL and Ti(IV) complexes by Keck and Mikami |
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| Mikami *JACS* **1993**, *115*, 7039 |
| Broad scope of enolates (esters, thio-esters, ketone-derived enolates) |

* + - 1. *Anti*

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| Enantioselective aldol addition of enolates to aldehyde catalyzed by BINAP/Silver(I) complex by Yamamoto |
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| Yamamoto *JOC* **2003,** *68*, 5593 |

* + - 1. *Methyl ketone Mukaiyama aldol aditions*

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| - Another class of amino acid derived *N*-sulfonamide oxazaborolidines by Corey.  Effective catalyst with a variety of aldehydes.  The existence of hydrogen bonding between the catalyst and aldehyde contributes much to the significant facial differentiation. |
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| Corey *TL* **1992**, *33*, 6907 |

* + 1. Dienolates as nucleophiles

Additions of dienolates to aldehydes lead to 4-carbon subunits in one step, which facilitates the synthesis of polyketides.

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| - Complex of Ti(IV), tridentate Schiff base and di *tert*-butylsalicylic acid as catalyst |
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| Carreira *JACS* ***1995*,** *117*, 12360  *Synthesis of Macrolactin A* Carreira *ACIE* **1998**, *37*, 1261 |

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| - Bisphosphine Cu(I) complex |
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| Carreira *JACS* **1998**, *120*, 837; *ACIE* **1998**, *37*, 3124  *Synthesis of Leucascandrolide* Carreira *JOC* **2003**, *68*, 9274 |

* 1. Lewis bases on trichlorosilyl enol ethers

A metal-enolate is activated by a chiral Lewis base. This activated complex is much more reactive than the free enolate species. Association and activation of the aldehyde allows for a closed transition state. Enolate geometry is transferred directly to the diastereoselectivity of the products.

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* + 1. Methyl ketone derived trichlorosilyl enol ethers

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| Denmark *JACS*, **2000**, *122*, 8837 |

* + 1. Ethyl ketone derived trichlorosilyl enol ethers

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| Denmark *JOC*, **2003**, *68*, 5045 |

* 1. Direct catalytic enantioselective aldol reactions

These involve the *in situ* generation of enolates (donor) in the presence of an aldehyde (acceptor), circumventing the use of preformed enolates and decreasing wastes.

* + 1. Ito’s Au(I) catalyst

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| First example of a direct asymmetric catalysis by Ito and coworkers. Gold(I) catalyzed the reaction between α-cyanoacetate and an aldehyde to yield trans oxazolines. These lead trans products and do not have great scope beyond the use of α-cyanoacetate. |
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| Ito *JACS*, **1986**, *108*, 6405 |

* + 1. Lanthanum and barium binols as bifunctional catalysts (dual activation of donor and acceptor)

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| These catalysts serve as both lewis (lanthanum or barium) acid and bronsted base catalysts (lithium binaphthoxides or binols). Proceed with exogenous base. |
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Shibasaki’s first catalysts were barium- and lanthanide-based and could provide moderate to high ees for methyl ketones. Reaction times were long and large excess of ketone was necessary.

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| Shibasaki *TL*, **1998**, *39*, 5561; *ACIE*, **2003**, *36*, 1871 |
| Lanthanum provides moderate *anti* and *syn* selectivity complimentary to enamine catalysis (favors anti adducts) |
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| Shibasaki *JACS*, **2001**, *123*, 2466 |

* + 1. Dinuclear zinc prophenols as bifunctional catalyst

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| Trost *JACS*, **2001**, *123*, 3367 |

* 1. Chiral amine-based catalyst

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| Early 1970s, Hajos-Parrish-Eder-Sauer-Wiechert reaction |
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| Eder *ACIE* **1971**, *83*, 496; Hajos *JOC* **1974**, *39*, 1615 |

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| Pioneering findings by List, Barbas III: Proline-catalyzed enantioselective intermolecular aldol addition |
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| Barbas III *JACS* **2000**, *122*, 2395 |

* + 1. Mechanism of proline-catalyzed aldol addition

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| Different proposed mechanisms and models for transition state | |
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| Discussion on mechanism:  Houk *ACIE* **2004,** *43*, 5766  List *PNAS* **2004**, *101*, 5839  Blackmond *BMCL* **2009**, *19*, 3934  Trost *Chem. Soc. Rev.* **2010**, *39*, 1600 | Limitations of Proline-catalyzed aldol addition  - Relatively large amount of proline (20-30mol%)  - Large amount of ketones  - Low enantioselectivity with aromatic aldehydes |

* 1. Progress
     1. Aldehyde as electrophiles

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* + 1. Cross-aldol reactions of aldehyde

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| MacMillan *ACIE* **2008**, *47*, 3568 |

* + 1. Activated ketone electrophiles

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| Zhao *TL* **2006**, *47*, 3383; Jorgensen *Chem. Comm.* **2002**, 620 |

1. **ENANTIOSELECTIVE C=N ADDITIONS**
   1. Comparision of C=O and C=N bonds

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* 1. Enantioselective Mannich reactions
     1. Silyl ketene acetals and thio-derived silyl ketene acetals

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| - The first catalytic enantioselective Mannich reations was reported by Kobayashi in 1997  - This system is restricted to imines with *N*-aryl and a chelating group for two-point binding to the catalyst. |
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| Kobayashi *JACS* **1997,***119*, 2060 |

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| - Jacobsen developed chiral ureas and thioureas functioning as chiral hydrogen-bond donors. |
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| Jacobsen *JACS* **2002**, *124*, 12964 |
| The catalysts can tolerate the Lewis basic substrates like heteroaromatic aldimines. |

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| - Chiral Bronsted acid: BINOL-derived phosphoric acids as catalysts |
| Akiyama *ACIE* **2004**, *43*, 1566 |
| Terada *JACS* **2004**, *43*, 1566; *TL* **2007**, *48*, 497 |

* + 1. Silyl enol ethers

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| - BINAP derived metal complex of transition metals – Ag(I), Cu(I), Pd(II), Ni(II) |
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| Lecka *JACS* **1998**, *120*, 4548; *JOC* **1998**, **63**, 6090 |

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| - Chiral binuclear cationic Pd(II) complex |
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| Sodeoka *JACS* **1998**, *120*, 2474 |

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| - Chiral phosphine Ag(I) complex |
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| Snapper&Hoveyda *JACS* **2004**, *126*, 3734 |

* + 1. Direct catalytic enantioselective Mannich reactions

- Direct Mannich reactions have been explored with both metal catalysts and organocatalysts more intensively than aldol variants possibly due to the lack of retro reactions, which are normally problematic in aldol reaction.

- List succeeded in using acetaldehyde as nucleophiles in direct Mannich reactions.



List *Nature* **2008**, *452*, 453

* 1. Enantioselective Strecker reactions

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| - Jacobsen reported one of the first catalytic, asymmetric variants of Strecker reaction, using chiral urea as a catalyst. The hydrogen bonding between imine and catalyst is responsible for the induction of chirality. |
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| Jacobsen *OL* **2000**, *6I,* 867; *JACS* **2002**, *124*, 10012; *Nature* **2009**, *461*, 968 |

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| - Peptidic Schiff base ligand and Ti(IV) complexes |
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| Hoveyda *JACS* **2001**, *123*, 11594 |

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| - Lanthanide based catalysts |
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| Shibasaki *TL* **2004,** *45,* 3147 |

* 1. Catalytic enantioselective additions of other nucleophiles

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| - The first catalytic enantioselective alkyl zinc addition to C=N using chiral amidophosphine Cu(II) complex |
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| Tomioka *JACS* **2000**, *122*, 12055 |
| A range of aromatic *N*-sulfonylaldimines participated in the addition and products were obtained in high ees. |

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| - Chiral Rh(II) diene complexes for arylation of *N*-sulfonylimines |
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| Hayashi *JACS* **2004**, *135*, 13584 |