**Topic: Enantioselective aldol reactions**

1. **Introduction**

Formation of a new C-C bond with the possibility of forming two new stereocenters🡪 4 diastereomers. First described in 1848 by Kane and in 1872 Charles-Adolphe Wurtz would go on to describe such products as maintaining the properties of alcohol and aldehyde.

* 1. **Types of Enolates Aldols**

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* 1. **Acid and Base Catalysis**

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* 1. **Stereocontrol Elements**

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| - Relative configuration: Configuration of the product is determined by enolate configuration. High diastereoselectivity has been achieved through ordered 6-membered transition states. |
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| - Absolute configuration – is controlled by chirality within molecule from:  (a) Removable chiral auxiliaries  (b) Chiral enolates  (c) Chiral catalysts (chiral ligand + metal)  (d) Chiral amine catalysis |
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1. **Chiral Auxiliaries**
   1. **Diastereoselective Control *Syn***

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| Evans’ Oxazolidinones: Highly selective towards *Z* enolates. High diastereoselectivity to yield a single *Syn* product. Sterics often dominate the most preferred transition state. |
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| Evans, *JACS* **1981**, *103*, 2127 |
| Effective only for chelating aldehydes. The second equivalent of titanium is necessary for the diastereoselective control. Chelation overrides steric control, but less as chelating group is further away from carbonyl. |
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| Ghosh, *TL* ,**1997**, *38*, 7171 |
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* 1. **Diastereoselective Control *Anti***

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| *Anti* diastereoselectivity is achieved for the aryl sulfonamide indanyls when using one equivalent of titatanium. |
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| Ghosh, *TL* ,**1997**, *38*, 7171 |
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| Evans found that the generation of magnesium enolates with the oxazolidinone auxiliaries would give anti adducts. A closed TS that does not follow the Zimmerman Traxler model is thought to be prevalent. TMSCl does not catalyze the reaction but quenches the aldol adduct. |
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| Evans, *JACS* , **2002**, *124*, 394 |

* 1. **Asymmetric Propionate Aldols *Syn***

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| With the use of 2 equivalents of titanium, a non-Evans is achieved. The second equivalent of titanium is thought to abstract a chloride that allows chelation to the thiazolidinethione. |
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| Crimmins *JACS*, **1997**, *119*, 7883 |

* 1. **Asymmetric Propionate Aldols *Anti***

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| Norephedrines as auxiliaries- *E*-enolates are selectively formed and yield the *anti* products via six-membered TS. |
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| Abiko *JOC*, **2002**, 67, 5250 |
| A chelating substituent on the enolate provides a different mechanistic pathway for the thiazolidinethiones. *Z* enolate is formed but the anti product is obtained with the use of two equivalents of titanium. |
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| Crimmins *OL*, **2003**, *5*, 591 |
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* 1. **Asymmetric Acetate Aldols**

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| Asymmetric control with acetates is more challenging than with propionates. Increased bulk of thiazolidinethione auxiliary allows for moderate to high diastereoselectivity. This is not possible with Evans’ oxazoldinone auxiliaries. |
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| Phillips *OL*, **2002**, *4*, 2253 |

1. **Chiral Boron Enolates**

**Enol Boronates**

*Z*🡪*syn* aldol and *E*🡪 *anti* aldol. With the use of chiral alkyl boronates, moderate enantioselectivity can be afforded.

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| Paterson *Tetrahedron*, **1990**, *46*, 4663 |

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 Catalytic Enantioselective Mukaiyama Aldol Addition**

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| - Background silyl-catalyzed achiral aldol addition |
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| Carreira *Tetrahedron Letters* **1994**, 35, 4323-4326  Bosnich *JACS* **1995**, 117, 4570-4581 |
| *- 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 |

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| Synthetic route to monosaccharides from achiral compounds |
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| Kobayashi *Synlett* **1993**, 911 |
| *Guidelines for designing more recent catalysts:*  (1) Ligands with electron donors.  (2) Stabilizing aromatic stacking interactions.  (3) Reaction conditions minimize the silyl-catalyzed achiral aldol addition. |

* 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 |
| *α,β*-Unsaturated aldehydes reveal excellent diastereo- and enantioselective due to the π interaction. Reaction with aliphatic aldehyde resulted in slight reduction of optical and chemical yields. |

* + 1. *Anti*

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

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| Synthesis of Khafrefungin |
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| Kobayashi *JOC* **2001**, *66*, 5580 |

* + 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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| Synthesis of Phorboxazole A |
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| Smith *JACS* **2001**, *123*, 10942 |

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| - Complex of chiral Bis(oxazolidine) (BOX) or bis(oxazoline) (PYBOX) and metals by Evans |
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| Evans *JACS* **2000**, *122*, 10033  Evans *ACIE* **1997**, *36*, 2744 |

2.4.4 *Ketones as electrophiles*

- Evans developed a family of chiral bis(oxazolidine) (BOX) and bis(oxazoline) (PYBOX) complexing with different metals as catalysts for enantioselective Mukaiyama aldol addition. Diverse stereo outcomes can be obtained based on the metal and ligand used in the complex.

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).

Broad range of nucleophiles: thioester-derived ketene acetals, ketene acetals, ketone-derived enolates.

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| Chiral Bis(oxazolidine) (BOX) or bis(oxazoline) (PYBOX) and Cu(II) complexes |
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| Evans *JACS* **1997**, *119*, 7893 |

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| Chiral Bis(oxazolidine) (BOX) or bis(oxazoline) (PYBOX) and tin(II) |
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| Evans *JACS* **1997**, *119*, 10859 |

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| Chiral Bis(oxazolidine) (BOX) or bis(oxazoline) (PYBOX) and scandium(III) |
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| Evans *OL* **2002,** *4.* 3379 |

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| - Complex of Cu(I)fluoride and chiral Taniaphos ligand by Shibasaki  Examples of effective catalyzed enantioselective aldol addition involving 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. **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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| Synthesis of cheimonophyllal |
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| Tadano *JOC* **2002**, *67*, 6690 |

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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. *Acetate 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 *Tetrahedron Lett*ers **1992**, *33*, 6907 |

* 1. **Dienolates as nucleophiles**

Addition reactions of dienolates and aldehydes lead to four-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  Carreira *ACIE* **1998**, *37*, 3124  *Synthesis of Leucascandrolide* Carreira *JOC* **2003**, *68*, 9274 |

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| Evans *JACS* **2008**, *130*, 16295 |

1. **Lewis bases on trichlorosilyl enols**

A metalloenolate 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. **Achiral Methyl Ketone derived Trichlorosilyl Enols**

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

* 1. **Achiral Ethyl Ketone trichlorosilyl enols**

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

* 1. **Chiral Methyl Ketone derived trichlorosilyl enols**

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| Double diastereoselection with the use of chiral catalyst and chiral enolate. Matched case here involves the use of the (*R,R*) phosphoramide catalyst, whereas the (*S,S*) gives very low *syn* selectivity. TBS protection of alcohol is necessary to prevent chelation and lower diastereoselection. |
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| Denmark, JACS, 2000, 122, 8837 |

* 1. **Ethyl Ketone trichlorosilyl enols**

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| Diastereoselectivity for these mostly dependent dependent on enolate configuration. The (*R,R*) and (*S,S*) phosphoramide catalysts give similar diastereoselectivities. |
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| Denmark *OL*, **2001**, *3*, 2202 |

1. **Direct catalytic enantioselective aldols**

These involve the in situ generation of enolates (donor) in the presence of an aldehyde (acceptor), circumventing the use of preformed enolates and decreasing waste. Often substoichiometric catalysts amounts of catalyst can be used.

* 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 (Donor and Acceptor Activation)

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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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6.2.1 Shibasaki’s first catalysts were barium and Lanthanum based and could provide moderate to high ee for methyl ketones. Reaction times were long and large excess of ketone was necessary -

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| Shibasaki *TL*, **1998**, *39*, 5561 and Shibasaki *ACIE*, **2003**, *36*, 1871 |
| 6.2.2 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

6.3.1 Direct aldols with acetone(enantioselectivity lower for alpha unbranched aldehydes)

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| Trost *OL*, **2001**, *3*, 2497 |

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| 6.3.2 Chelation of alpha hydroxyl ketone increases reactivity of donor and allows close to equimolar equivalents with respect to aldehyde(highly *syn* selective). |
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| Trost *JACS*, **2001**, *123*, 3367 |

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| 6.3.3 Mild conditions allow for use of ynones as substrates for aldol, used in the total synthesis of dephosphofostriecin. |
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| Trost, *JACS*, **2004**, *126*, 2660 |

1. **CHIRAL AMINE catalysis**

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| In Nature: |
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| Trost *Chem. Soc. Rev.* **2010**, *39*, 1600 |

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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 |

**Mechanism of Proline-catalyzed aldol addition**

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| Different proposed mechanisms and models for transition state | |
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| Hajos *JOC* **1974**, *39*, 1615  Agami *JACS* **1986**, *108*, 2353  Swaminathan *Tetrahedron Asymmetry* **1999**, *10*, 1631  Houk *JACS* **2003**, *125*, 2475  List *Acc. Chem. Res.* **2004**, *37*, 548  Seebach&Eschenmoser *Helv. Chim. Acta* **2007**, *90*, 425 | |
| Discussion on mechanism:  Houk *ACIE* **2004,** *43*, 5766  List *PNAS* **2004**, *101*, 5839  Blackmond *Bioorg. Med. Chem. Lett.* **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 |

**7.1** **Progress**

* + 1. *Aldehyde electrophiles*

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| Cross-aldol of aldehydes |
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| MacMillan *ACIE* **2008**, *47*, 3568  Cross-trimerizations |
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| Cordova *ACIE* **2005**, *44*, 1343 & MacMillan *Science* **2004**, 1752 |

* + 1. *Activated Ketone electrophiles*

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| Zhao *Tetrahedron Letters*  **2006**, *47*, 3383 & Jorgensen *Chem. Comm.* **2002**, 620 |

1. **Other Classes of Aldols**

8.1 Reformatsky Reaction

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| Reformatsky *Berichte der Deutschen Chemischen Gesellschaft*, **1887**, *20*, 1210 |

8.1.1

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| Enolates with a CF3 α to an ester or amide are often unstable, but they work well in Reformatsky reactions. |
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| Ishihara *TL*, **2006**, *8*, 1129 |

8.1.2

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| The Indium tends to yield *E* enolates and can provide high diastereoselectivity in the formation of β-lactones. |
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| Baba *OL*, **2006**, *8*, 3029 |

8.2 Ketene Aldehyde Cycloadditions

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| Acyl halides can be transformed to the corresponding ketenes in the presence of base. With a chiral lewis base and a lewis acid, asymmetric aldols can be mediated to give β-lactones. |
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| Nelson *JACS*, **2004**, *126*, 5352 |