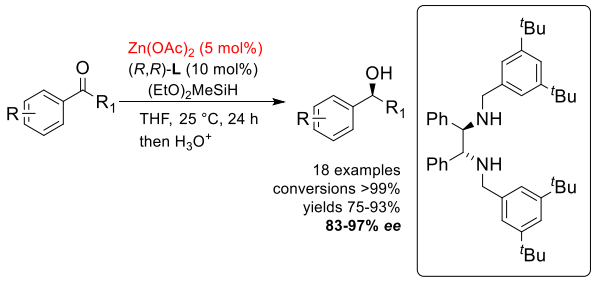
# selected recent topics of research and achievements from Mlynarski group

# more at jacekmlynarski.pl

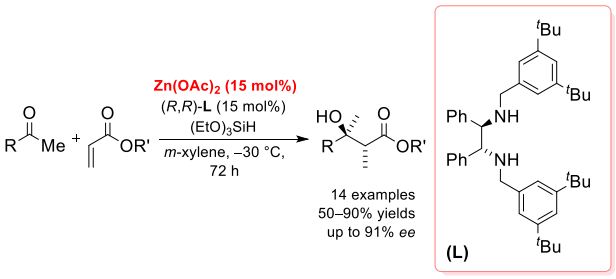
## 1/ zinc- and iron-based catalysts for asymmetric synthesis

### 1.1. asymmetric reduction of prochiral ketones and imines promoted by zinc complexes



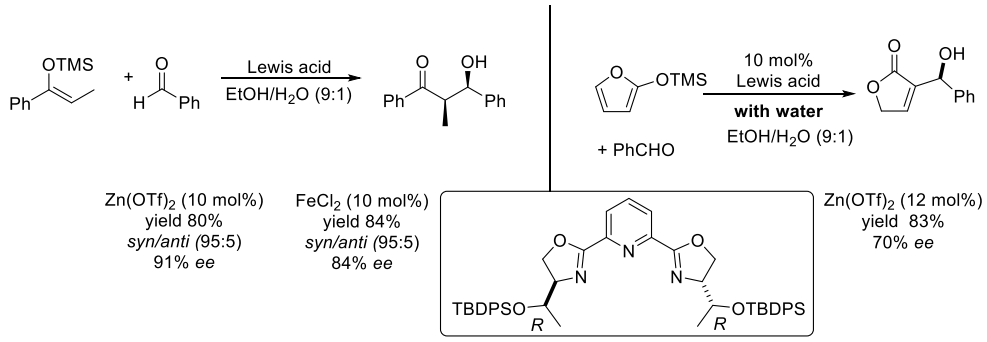

In recent years asymmetric hydrosilylation of prochiral ketones with zinc complexes was extensively investigated. However, in the vast majority of these studies hazardous dialkylzinc compounds were applied as a metal source and polymethylhydrosilane (PMHS) as a hydrogen donor. Recently, we discovered that zinc acetate complexes with chiral diphenyletylenediamine (DPEDA)-derived ligand is highly efficient catalysts for enantioselective hydrosilylation of aryl ketones and imines. Replacing pyrophoric dialkyl zinc with readily available zinc salt simplifies the procedures and provides excellent conversions (up to >99%) and enantioselectivities (ees up to 97%). Recently, we showed zinc acetate promoted asymmetric hydrosilylation under solvent-free conditions by using an unprecedented low catalyst loading. Exposure of ketones to only *0.05 mol % Zn-based chiral diamine complex* in the presence of triethoxysilane afforded enantioenriched alcohols in excellent yields (up to 98 %) and enantioselectivities (up to 97 % *ee*). This methodology also allowed for the chemoselective 1,2-reduction of α,β-unsaturated ketones and imines.

**selected papers:**
*ChemCatChem.* **2016** *8* 3575-3579
*J. Org. Chem.* **2016** *81* 336-342
*Adv. Synth. Catal.* **2015** *357* 3727–3731
*Eur. J. Org. Chem.* **2016** 1060-1065
*Adv. Synth. Catal.* **2014** *356* 591-595
**patent:**
**PL**231016B1



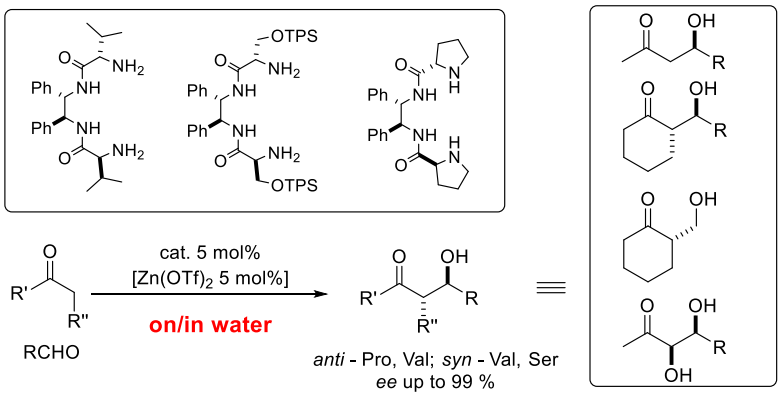
Recently, we have developed a new strategy for the asymmetric reductive aldol reaction of ketones with α,β-unsaturated esters promoted by the chiral zinc catalyst. This is also the first successful application of zinc hydride reagent in stereoselective reductive aldol reaction of ketones. The elaborated catalytic system is based on cost-effective, environmentally benign and easily accessible zinc acetate-complex with the readily available chiral diamine ligands. Furthermore, presented method provides a facile access to a broad range of highly functionalized enantioenriched β-hydroxy esters with very good yields and high enantioselectivities. Although the reaction diastereoselectivity is substrate-dependent and requires further improvement, this efficient protocol offers application of various aryl and heteroaromatic ketones without the use of high-priced catalysts previously reported.
**selected papers:**
*Adv. Synth. Catal.* **2020** doi: 10.1002/adsc.201901457

### 1.2. aldol reaction in water and in aqueous solvents – water compatible zinc Lewis acids




An important direction of research in the asymmetric aldol reaction is undoubtedly the use of cheap and environmentally friendly metals. Application of iron- and zinc-based chiral Lewis acids to asymmetric synthesis seems to be particularly exciting as iron is one of the most abundant metals on earth and consequently one of the cheapest and most environmentally acceptable. In 2007, we demonstrated first application of the iron salt with pybox ligand as water compatible chiral Lewis acid for Mukaiyama reaction of aromatic aldehydes with high diastereoselectivity and moderate enantioselectivity up to 84% *ee*. An easy to prepare from threonine hydrophobic hindered pybox showed high selectivity in the reaction catalysed by both most abundant sustainable terrestrial metals - $Fe^{2+}$ and $Zn^{2+}$.
**selected papers:**
*Adv. Synth. Catal.* **2020** doi: 10.1002/adsc.201901218
*Chem. Commun.* **2012** *48* 11029-11031

Study of reaction performed under aqueous conditions reveals also that water may offers new reactivity or stereoselectivity. For example, regioselectivity of vinylogous Mukaiyama aldol reaction (VMAR) can be controlled by simple solvent tuning and application of water medium offers entry to unexpected products.




We also deeply explored the utility of water compatible amino acid-based catalysts in the development of diastereo- and enantioselective direct aldol reactions of broad range of substrates. Chiral $C_2$-symmetrical proline-, and valine-based amides and their ZnII complexes were designed for use as efficient and flexible chiral catalysts for enantioselective aldol reactions in water, on water, and in the presence of water.

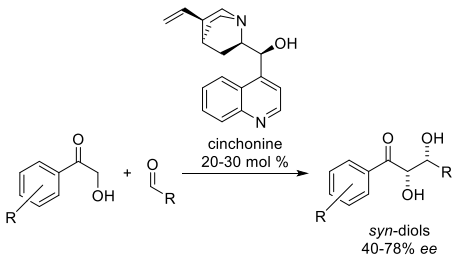
**selected papers:**

*J. Org. Chem.* **2012** *77* 173-187
*Tetrahedron Lett.* **2010** *51* 4088-4090
*Adv. Synth. Catal.* **2007** *239* 1041-1046
*J. Org. Chem.* **2007** *72* 2228-2231
*Green Chem.* **2011** *13* 1155-1157

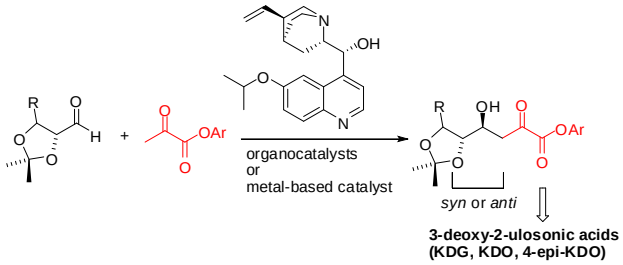
**reviews from our group on the subject:**

*Chem. Soc. Rev.* **2008** *37* 1502-1511
*Angew. Chem. Int. Ed.* **2009** *48*, 4288-4297
*Chem. Soc. Rev.* **2014** *43* 577-587

**2/ direct asymmetric aldol reaction promoted by tertiary amines – synthesis of aldols, ulosonic acids and aldoses**




We have found a class of tertiary amine catalysts that work effectively with aromatic hydroxyketones as highly *syn*-selective aldol catalysts. Simple commercial and unmodified cinchona alkaloids were found to efficiently promot the direct aldol reaction of hydroxyketones with various aldehydes with good yields and good enantioselectivities up to 60-70%. This is a valuable observation not only because of the direct availability of catalysts but also because of the lack of other organocatalysts activating 2-hydroxyacetophenone derivatives.

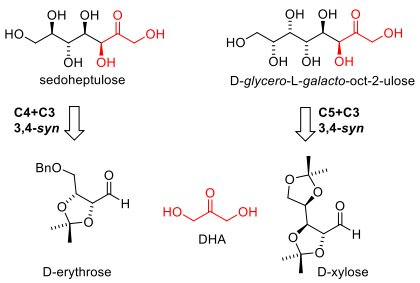



The reaction developed by us may be useful for the synthesis of aldoses by cross-aldol reaction of aldehydes. Moreover, we presented new concept of direct aldol reaction of ketoesters promoted by chiral tertiary amines. Described methodology delivers flexible entry to both *syn*- and *anti*-configured aldols while *syn*-selectivity was not achievable previously by using stechiometricaly generated lithium enolates. This may be seen as the best methodology for the synthesis of ulosonic acids, so far.

**selected papers:**

*Eur. J. Org. Chem.* **2015** 5075-5078
*Adv. Synth. Catal.* **2015** *357* 2098–2104
*Eur. J. Org. Chem.* **2013** 6917-6923
*Adv. Synth. Catal.* **2013** *355* 281-286
*Eur. J. Org. Chem.* **2012** *14* 2724-2727
*Tetrahedron Lett.* **2009** *50* 1639-1641

**3/ direct aldol reaction of hydroxyacetone and dihydroxyacetone: organocatalytic synthesis of carbohydrates**

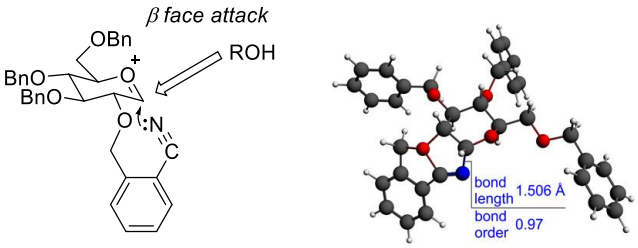



We demonstrated biomimetic attempt to *de novo* synthesis of carbohydrates by using organocatalysts based on proline and valine molecules. By reacting protected DHA as the C3 unit with dimethoxyacetaldehyde or glyceraldehyde in the presence of substoichiometric amounts of proline- or valine-based catalysts protected derivatives of carbohydrates can be easily reached. Configuration of resulting ketohexoses depends on configuration of starting aldehydes as well as configuration of catalysts. Using our catalysts (both metal complexes and organocatalysts, I and II asymmetric carbon-carbon formation reaction have been realized by using enzyme-like activation pathway. More recently, we used this methodology as an efficient protocol for the synthesis of naturally occurring higher-carbon seduheptulose (D-*altro*-hept-2-ulose) and D-*glycero*-L-*galacto*-oct-2-ulose, from the readily available sugar aldehydes and dihydroxyacetone (DHA). The key step includes diastereoselective organocatalytic *syn*-selective aldol reaction of DHA with D-erythrose and D-xylose, respectively.

**selected papers:**

*ChemistryOpen* **2015** *4 717-721*
*J. Org. Chem.* **2014** *79* 5728-5739
*Eur. J. Org. Chem.* **2013** 7484-7487
*Eur. J. Org. Chem.* **2013** 1296-1305
*Chem. Soc. Rev.* **2012** *41* 587-596

**4/ application of 2-substituted benzyl groups in stereoselective glycosylation**



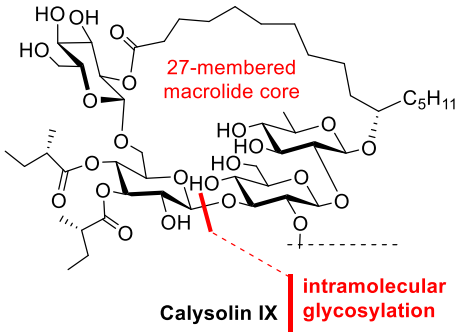

The use of 2-*O*-(2-nitrobenzyl) and 2-*O*-(2-cyanobenzyl) groups control stereoselective formation of 1,2-*trans*-glycosidic linkage *via* arming participation effect. Observed stereoselectivity arise likely from the intramolecular formation of cyclic intermediate between electron rich substituent and donor oxacarbenium ion providing expected facial selectivity for the attack of the glycoside acceptor. The stereodirecting effect of the 2-nitro- and 2-cyanobenzyl groups attached at remote position (C-3, C-4, and C-6) of donor molecule have also been investigated. To prove postulated mechanism based on participation effect of 2-substituted benzyl groups in the glycosylation stereoselectivity we used DFT theoretical calculation methodology.

**selected papers:**

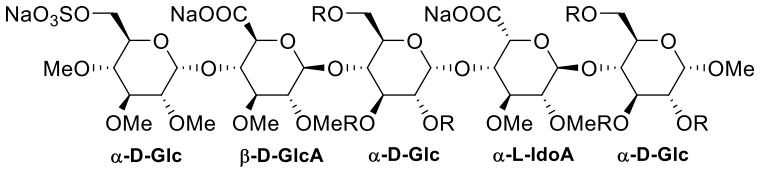
*Eur. J. Org. Chem.* **2013** 3988-3991

*J. Org. Chem.* **2015** *80* 770-780

**5/ synthesis of complex natural products and bioactive targets – new methods in total synthesis**

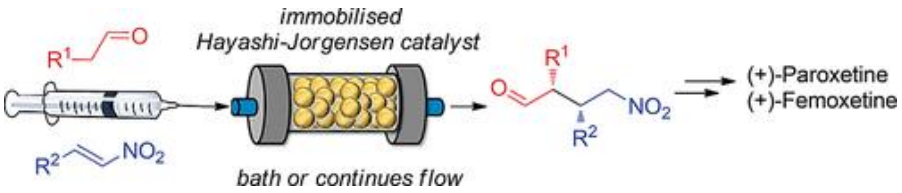



Achieving high efficiency and stereocontrol in glycosylation reactions is arguably still the major effort in the synthesis of widely distributed carbohydrate containing oligomers. The utility of intramolecular glycosylation for the synthesis of 27-membered macrocyclic ring is highlighted in this first total synthesis of the most complex resin glycoside isolated to date - Calysolin IX. As the glycosidic bond must be created en route to target structure, we show that this unusual yet efficient approach can effectively reduce the number of steps in total synthesis of complex natural macrolides. This attempt is documented as an efficient tool in the synthesis of gigantic macrolide rings thus proving their practical utility in the total synthesis of sugar-containing targets.




A novel total synthesis of fully protected idraparinux has been achieved. A short and efficient protocol for the synthesis of the EF fragment of idraparinux and its C5'-epi analogue (GH unit) has been developed. The same cellobiose unit was transformed in 14 steps into the fully protected EF and GH

disaccharide fragments. The key step of this approach is an epimerization of C5 by an elimination−addition sequence leading to L-ido disaccharide (GH unit) with a total yield of 24% (36% for the EF fragment). 1,6-Anhydro ring opening gave suitable substrates for efficient synthesis of fully protected idraparinux. The fully protected antithrombotic pentasaccharide idraparinux was synthesized in 23 steps for the longest linear route, with a 1.7% overall yield from D-cellobiose and D-glucose.

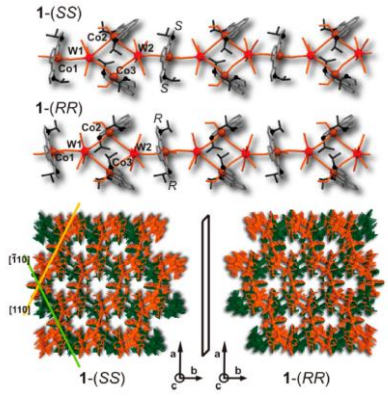



Total, asymmetric synthesis of (+)-Paroxetine and (+)-Femoxetine, selective serotonin reuptake inhibitors, used for the treatment of depression, anxiety, and panic disorders war reported in 2019. The key step was organocatalytic Michael addition of aldehydes to *trans*-nitroalkenes realized in bath or continues flow. High efficiency and selectivity in the Michael addition was achieved by application of Wang resin-supported Hayashi–Jørgensen catalyst.

**selected papers:**

*Eur. J. Org. Chem.* **2020** 45-71
*Eur. J. Org. Chem.* **2019** 6973-6982
*Angew. Chem. Int. Ed.* **2019** *58* 8383-8388
*J. Org. Chem.* **2017** *82* 12701-12714
*J. Org. Chem.* **2016** *81* 7545-7556
*Org. Biomol. Chem.* **2018** *16* 1118-1125
*Carbohydr. Res.* **2018** *258-259* 35-43
*Org. Biomol. Chem. 2019 17* 3225-3231

**8/ modern chiral magnetic materials – collaborative research with Inorganic Molecular Material Group (prof. B. Sieklucka)**




Chiral organic molecules synthesized by our research group have been also applied as new ligands in multifunctional molecular materials. The most recent research conducted by the Inorganic Molecular Materials Group run by Professor Barbara Sieklucka has been described in JACS. Recently, we have prepared two 1D cyano-bridged CoII−WV chains combining chirality and magnetic anisotropy, leading to slow magnetic relaxation. This multifunctionality is directed by an organic pybox ligand that (1) generates the 1D topology; (2) introduces optical chirality; (3) controls the magnetic anisotropy, as the decisive elongation of the octahedral CoII moieties is connected with the alignment of the pybox rings; and (4) contributes to the slow magnetic relaxation, ensuring good magnetic isolation. Magnetic molecular materials exhibit sensitivity and selectivity unattainable to conventional magnetic materials; whereas multifunctional materials by combining a wide range of physical and chemical properties enable alternative methods of recording and storing information.

**selected papers:**

*J. Am. Chem. Soc.* **2012** *134* 16151-16154
*RSC Adv.* **2013** *3* 1065-1068
*Inorg. Chem.* **2017** *56* 2777–2783.