**Topic: Kinetic Resolution and Desymmetrization**

1. **Introduction**
   1. Methods for Asymmetric Synthesis

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| |  |  |  |  | | --- | --- | --- | --- | | Table: Methods to obtain enantiomerically enriched products | | | | | **Method** | **Advantage** | **Disadvantage** | **Example** | | chiral auxiliary | often excellent *er* | additional steps to introduce/remove auxiliary | Evans-Aldol-reaction;  Oppolzer’s camphor sultam | | chiral reagent | often excellent *er* | few examples, limited substrate scope | BINAL-H-reduction, Alpine-Boran®-reduction | | chiral catalyst | economical | few examples | organocatalysis,  CBS-reduction | | **resolution** | both enantiomers available | maximum 50 % yield (usually) | Jacobsen’s hydrolytic kinetic resolution,  diastereomeric salt formation | | chiral pool | *er* ˃ 99:1 | limited substrates and stereochemistry | amino acids or sugars | |
| Clayden, Greeves, Warren, Wothers, *Organic Chemistry* |

* 1. What is a Kinetic Resolution (KR)?

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| - Resolution = separating enantiomers  - Three types of resolutions: |
| *A. classical resolution* = use of a stoichiometric amount of a chiral resolving agent to generate a pair of diastereomers which are then separated (physical separation) |
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| Jacobsen [*JOC* **1994**, *59*, 1939](http://dx.doi.org/10.1021/jo00086a062) |
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| *B. chiral chromatography* = use of a chiral stationary phase to resolve enantiomers (physical separation) |
| *Racemic HPLC/SFC trace* |
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| Enantiomers can be physically separated. |
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| *C. kinetic resolution* = use of a chiral catalyst or reagent to promote a selective reaction of one enantiomer over the other (can be dynamic, parallel); one enantiomer reacts faster. This will be the main focus of this lecture (chemical separation) |
| - Why would we need it?  Racemates are usually cheaper than the enantiomerically pure compounds. |
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| Sigma-Aldrich: <http://www.sigmaaldrich.com/> |

* 1. Selectivity factor (s-factor)

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| - In kinetic resolutions any enantiomeric ratio can be obtained by sacrificing yield (by controlling conversion)  - s-factor is a measurement for the effectiveness of a kinetic resolution  - Relative rates of the reaction of the two enantiomers with the chiral reagent  - Calculated using the conversion c and the *ee* of the recovered starting material  - *S*-factor is related to the difference in free energy between the diastereomeric transition states | |
| 1st order kinetic resolution S factor:    or    ee = substatre %ee & ee’ = product %ee |  |
| Kagan [*Top. Stereochem.* **1998**, *18*, 249](http://dx.doi.org/10.1002/9780470147276.ch4)  Gawley [*JOC* **2006**, *71*, 2411](http://dx.doi.org/10.1021/jo052554w)  Graphing tool: Goodman [*Tetrahedron Lett.* **1999**, *40*, 8715](http://dx.doi.org/10.1016/S0040-4039(99)01850-X) ([KR calculation](http://www-jmg.ch.cam.ac.uk/tools/magnus/KinRes.html)) | |

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| A point of clarification: kinetics (rate order) and kinetic resolutions  - The two equations above apply only to cases where the reaction is first order with respect to substrate and any order with respect to the co-reactants or catalysts.  - Below is an equation for KR with non-first order rate law (less common) where p = any rate order except 1. |
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| Kagan [*JACS* **1999**, *121*, 9299](http://dx.doi.org/10.1021/ja990793t) |

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| The complex rate laws based on mechanistic considerations for catalytic KR has also been discussed. |
| Blackmond [*JACS* **2001,** *123,* 545](http://dx.doi.org/10.1021/ja002562o) |

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| Example 1: (local) 1st order KR |
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| Blackmond & Lloyd-Jones [*JACS* **2006**, *128*, 7450](http://dx.doi.org/10.1021/ja062173f) |
| Example 2: (global) 0th order KR |
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| Tokunaga [*JACS* **2006**, *128*, 4481](http://dx.doi.org/10.1021/ja058112j) |

* 1. A Good Kinetic Resolution?

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| A) **Ideal** enantioselective transformation | |
| - quantitative yield  - *er* ˃ 99:1  - cheap and readily available starting material/  catalyst/reagent  - short reaction times | - easy isolation and purification  - reliable and reproducible  - broad substrate scope and functional group compatibility  - no better way to make product |
| B) **Practical** kinetic resolution | |
| - highly selective  - effective at low catalyst loadings  - recyclable catalyst | - safe, easy to run and economical reaction  - product and starting material easily separable |
| Jacobsen [*Adv. Synth. Catal.* **2001**, *343*, 5](http://dx.doi.org/10.1002/1615-4169(20010129)343:1%3C5::AID-ADSC5%3E3.0.CO;2-I) | |

1. **Enzymatic Kinetic Resolutions**
   1. History

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| - 1858: Louis Pasteur treats racemic ammonium tartrate with *Penicillium glaucum*, which consumes one enantiomer faster than its antipode. |
| Pasteur *C. R. Hebd. Seances Acad. Sci.* **1858**, *46*, 615; Kauffman & Myers [*The Chemical Educator* **1998**, *3* (6), 1](http://dx.doi.org/10.1333/s00897980257a) |
| - 1890: Emil Fischer treats racemic hexoses with yeast which destroys the D-hexoses |
| Fischer[*Ber. Dtsch. Chem. Ges.***1890**, *23*, 370](http://dx.doi/org/10.1002/cber.18900230162) |

* 1. Examples

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| - An industrial application |
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| Bayer AG, [EP 0812363 B1, **1995**](https://data.epo.org/publication-server/document?iDocId=4630225)  A review for industrial methods to produce optically active intermediates: Hauer [*ACIE* **2004**, *43*, 788](http://dx.doi.org/10.1002/anie.200300599) |

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| - After acylation, vinylalcohol formed tautomerizes to acetaldehyde and is removed from the equilibrium. |
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| Panek [*Org. Synth.* **1997**, *75*, 78](http://dx.doi.org/10.15227/orgsyn.075.0078) |

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| - Enzymes: highly selective but limited substrate scope  - A new approach to asymmetric catalysis is the directed evolution of enzymes |
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| Reetz [*PNAS* **2004**, *101*, 5716](http://dx.doi.org/10.1073/pnas.0306866101) |

1. **Non-Enzymatic Kinetic Resolutions**
   1. Hydrolytic Kinetic Resolution (HKR)

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| - Enantioselective hydrolysis of racemic epoxides |
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| Jacobsen [*Science* **1997**, *277*, 936](http://dx.doi.org/10.1126/science.277.5328.936); [*JACS* **2002**, *124*, 1307](http://dx.doi.org/10.1021/ja016737l) |
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| - Second-order dependence on Cobalt-catalyst; co-operative bimetallic mechanism  - Both enantiomers bind equally well but only one is hydrolysed |
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| Blackmond & Jacobsen [*JACS* **2004**, *126*, 1360](http://dx.doi.org/10.1021/ja038590z); [*JOC* **2012**, *77*, 2486](http://dx.doi.org/10.1021/jo300181f) |

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| Positive non-linear effect in Jacobsen HKR  - A small positive non-linear effect is observed with hydrolytic kinetic resolution of epoxides catalyzed by Co |
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| Singleton [*JACS* **1999**, *121*, 9307](http://dx.doi.org/10.1021/ja991921g) |

* 1. Sharpless Resolution

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| - racemic allylic alcohols as substrates in an asymmetric epoxidation; creates an additional stereocenter!  - one enantiomer is epoxidized faster than the other one |
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| Sharpless [*JACS* **1981**, *103*, 6237](http://dx.doi.org/10.1021/ja00410a053) |

* 1. Oxidative KR of secondary alcohols

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| - Pd-catalyzed aerobic oxidative kinetic resolution |
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| Sigman [*JACS* **2002** *124*, 8202](http://dx.doi.org/10.1021/ja026553m)  For the mechanism of Pd-oxidation-KR of secondary alcohols: Sigman [*JACS* **2003**, *125*, 7005](http://dx.doi.org/10.1021/ja034262n) |
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| Stoltz and O'Brien [*ACIE* **2008**, *47*, 6367](http://dx.doi.org/10.1002/anie.200801865) |

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| - Mn(III)-Salen complex oxidative kinetic resolution |
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| Corey [*JACS* **2010**, *132*, 11165](http://dx.doi.org/10.1021/ja103103d) |

* 1. KR via nucleophilic catalysis
     1. Planar–chiral DMAP analogues

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| - First effective chiral DMAP analogue for non-enzymatic KR of alcohols was developed by Prof. Edwin Vedejs; however, the stoichiometric amount of the acyl chiral DMAP derivative was essential in their resolution.  - Based on Vedejs’ pioneering work, the Fu group developed a class of planer–chiral DMAP analogues for catalytically resolving racemic alcohols. |
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| Vedejs [*JACS* **1996**, *118*, 1809](http://dx.doi.org/10.1021/ja953631f); [*JACS* **1997**, *119*, 2584](http://dx.doi.org/10.1021/ja963666v)  Fu [*JACS* **1997**, *119*, 1492](http://dx.doi.org/10.1021/ja963835b); [*JOC* **1998***, 63,* 2794](http://dx.doi.org/10.1021/jo980183w); [*Acc. Chem. Res.* **2004**, *37*, 542](http://dx.doi.org/10.1021/ar030051b) |

* + 1. Axially Chiral DMAP Analogue

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| Spivey [*JOC* **1999**, *64*, 9430](http://dx.doi.org/10.1021/jo991011h); [*JOC* **2000***, 65, 3154*](http://dx.doi.org/10.1021/jo0000574); C2-symmetric DMAP: [*J. Chem. Soc., Perkin Trans. 1* **2000**, 3460](http://dx.doi/org/10.1039/B004704J) |

* + 1. 2,3-Dihydroimidazo[1,2-a]pyridines (Birman catalyst)

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| - Enantioselective acyl transfer catalyst |
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| Birman [*JACS* **2004**, *126*, 12226](http://dx.doi.org/10.1021/ja0491477); calculation with Houk: [*JACS* **2008**, *130*, 13836](http://dx.doi.org/10.1021/ja805275s) |

* + 1. KR via an “Induced Fit” Process

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| - Through an “induced fit” process |
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| Fuji[*JACS* **1997**, *119*, 3169](http://dx.doi.org/10.1021/ja963275g) |

* + 1. KR via peptide catalysis

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| - Catalyzed by a tetrapeptide containing an imidazole |
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| Miller [*JACS* **1998**, *120*, 1629](http://dx.doi.org/10.1021/ja973892k); [*JACS* **1999**, *121*, 11638](http://dx.doi.org/10.1021/ja9931776) |

* 1. Kinetic Resolution of Amines

- **Challenge**:

(1) high nucleophilicity of amines (compared to alcohols) leads to an increased background rate and erodes selectivity (amines react directly with most acylating reagents);

(2) there are even fewer methods for catalytic resolution of secondary amines.

* + 1. Fu’s chiral DMAP

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| - Fu: *O*-acylated azlactones as acylating reagents; they react faster with the catalyst than with the amine. |
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| Fu [*Acc. Chem. Res.* **2000***, 33,* 412](http://dx.doi.org/10.1021/ar990077w)*;* [*Acc. Chem. Res.* **2004**, *37*, 542](http://dx.doi.org/10.1021/ar030051b); the resolution of indolines: [*JACS* **2006**, *128*, 14264](http://dx.doi.org/10.1021/ja0657859) |

* + 1. Merging Nucleophilic and Hydrogen Bonding Catalysis

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| - An anion binding approach to the kinetic resolution of benzylic primary amines |
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| Seidel [*JACS* **2009**, *131*, 17060](http://dx.doi.org/10.1021/ja9079435) |

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| - An anion binding approach to the kinetic resolution of propargylic primary amines |
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| Seidel [*JACS* **2010**, *132*, 13624](http://dx.doi.org/10.1021/ja105337h) |

* + 1. Decrease Nucleophilicity of Nitrogen Lone Pair

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| - Kinetic resolution of 2-oxazolidinones via catalytic, enantioselective *N*-acylation |
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| Birman [*JACS* **2012**, *134*, 17605](http://dx.doi.org/10.1021/ja306766n) |

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| - Peptide-catalyzed kinetic resolution of formamides and thioformamides |
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| Miller [*JACS* **2010**, *132*, 2870](http://dx.doi.org/10.1021/ja9107897) |

* + 1. NHC catalyst/Chiral Hydroxamic Acid catalyzed KR

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| - Catalytic kinetic resolution of **cyclic secondary amines** (piperidines, morpholines, piperazines, azapanes) |
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| Bode [*JACS* **2011**, *133*, 19698](http://dx.doi.org/10.1021/ja209472h); expanded scope & catalyst optimization: [*Chem. Commun.* **2012**, *48*, 8892](http://dx.doi.org/10.1039/C2CC34907H) |

* 1. Kinetic Resolution of Biaryl Alcohols and Amino Alcohols

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| - Axially chiral biaryls are of great importance on asymmetric synthesis. Conventional classical resolution is still the major method to prepare their enantiopure forms; however, it requires stoichiometric use of chiral compounds to generate the separable diastereomeric materials. The Sibi group and the Zhao group currently developed different catalytic strategies to tackle this problem. |
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| Sibi[*ACIE* **2014**, *53*, 11818](http://dx.doi.org/10.1002/anie.201406684) |
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| Zhao[*ACIE* **2014**, *53*, 11041](http://dx.doi.org/10.1002/anie.201406192) |
| - Similar application with NHC **cat-B** for the KR of *trans*-cyclic diols was published earlier by Takasu and Yamada’s group. |
| Takasu & Yamada [*JACS* **2013**, *135*, 11485](http://dx.doi.org/10.1021/ja4055838) |

* 1. Kinetic Resolution of Thiols

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| - The thiol kinetic resolution is accompanied by a simultaneous desymmetrization of an achiral anhydride electrophile. |
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| Connon [*Nature Chem.* **2010**, *2*,380](http://dx.doi.org/10.1038/nchem.584) |

* 1. Kinetic Resolution of Carboxylic Acids

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| - While amino acids and lactic acid derivatives can be obtained via enzymatic kinetic resolution, alpha substituted carboxylic acids, are not so easy to prepare via this route. Most common strategy is formation of diastereomeric salts with chiral amines. An alternative selective esterification can be achieved using “Birman” catalyst, which was recently reported by the Shiina group. |
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| Shiina[*JACS* **2010,** *132*, 11629](http://dx.doi.org/10.1021/ja103490h) |

1. **Parallel Kinetic Resolution (PKR)** 
   1. Introduction

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| - To minimize the built-up of the less-reactive substrate enantiomer as the kinetic resolution approaches completion, the slow-reacting enantiomer can be simultaneously converted to a distinct product.  - PKR is powerful because the selectivity factor (s = krel = kS/kR) can be considerably lower than that needed to achieve the same result in a standard KR. |
| Vedejs [*JACS* **1997**, *119*, 2584](http://dx.doi.org/10.1021/ja963666v) |

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| - For a successful PKR:  (1) The reaction should be of no interference of the catalyst or reagents.  (2) kR and kS should be similar.  (3) The reaction should have opposite enantiocontrol with respect to the substrate.  (4) Products should be easy to separate. |
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| Walsh and Kozlowski, *Fundamentals of Asymmetric Catalysis*, C.8 |

* 1. Chemodivergent PKR

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| The products are not isomers and may have very different structure.  In this oxidative PKR NIS serves as an oxidant |
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| Onomura [*ACIE* **2008**, *47*, 9458](http://dx.doi.org/10.1002/anie.200804188) |

* 1. Regiodivergent PKR

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| - A single chiral catalyst affords products that are regioisomers via different pathways |
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| Fu [*JACS* **2003**, *125*, 8078](http://dx.doi.org/10.1021/ja035489l) |
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| Pineschi & Feringa [*ACIE* **2001**, *40*, 930](http://dx.doi.org/10.1002/1521-3773(20010302)40:5%3C930::AID-ANIE930%3E3.0.CO;2-7) |

* 1. Application of the Concept of PKR: Asymmetric Activation/Deactivation of Racemic Ru Catalysts for Enantioselective Hydrogenation

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| - In asymmetric deactivation a single enantiomer of a chiral “poison” (D\*) binds and selectively deactivates one enantiomer of the racemic catalyst, thus leaving the opposite enantiomer free to catalyze the reaction. Asymmetric activation is the opposite approach, having a single enantiomer (A\*) binding to one enantiomer of the catalyst and thus rendering it more active. These approaches can be used separately or combined. It’s a powerful method if it’s difficult to synthesize enantiopure ligands. |
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| Mikami [*ACIE* **2000**, *39*, 3707](http://dx.doi.org/10.1002/1521-3773(20001016)39:20%3C3707::AID-ANIE3707%3E3.0.CO;2-M); Lloyd-Jones [*ACIE* **2012**, *51*, 1526](http://dx.doi.org/10.1002/anie.201106836) |

1. **Dynamic Kinetic Resolution (DKR)**

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| - The DKR couples a KR with a rapid in situ racemization of the chiral substrate through an achiral intermediate or transition state. The theoretical yield of DKR is **quantitative**.  - Like KR, the rate of fast-reacting enantiomer (kfast) must be significantly faster than the slow-reacting enantiomer (kslow). Furthermore, the racemization process (kr) should proceed equally or faster than kfast.  - The DKR will give higher *ee* of the product than the classic KR because the continuous racemization will prevent the build-up of one enantiomer of the starting material that plagues the KR.  - The racemization process in a DKR does **NOT** involve the chiral catalyst. (Reminder: Don’t be confused with “dynamic kinetic asymmetric transformation, DyKAT.”) |
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| Walsh and Kozlowski, *Fundamentals of Asymmetric Catalysis*, C.8;  For reviews on DKR: Pellisier [*Adv. Synth. Catal.* **2011**, *353,* 659](http://dx.doi.org/10.1002/adsc.201000751) &[*Tetrahedron* **2008**, *64*, 1563](http://dx.doi.org/10.1016/j.tet.2007.10.080) |

* 1. Noyori’s hydrogenation DKR

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| Noyori [*Bull. Chem. Soc. Jpn.* **1995**, *68*, 36](http://dx.doi.org/10.1246/bcsj.68.36) |

* 1. Hydrolytic DKR of epoxides

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| - Usually in DKR, the mechanism of racemization proceeds via a prochiral intermediate. Direct inversion of the stereocenter of the substrate is not as common. |
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| Jacobsen [*JOC* **1998**, *63*, 6776](http://dx.doi.org/10.1021/jo981332d) |

* 1. Enzymatic DKR

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| - Biocatalyst has become an increasingly attractive method due to its mild condition and generally good turnover and great selectivity. |
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| Pellissier [*Tetrahedron* **2008**, *64*, 1563](http://dx.doi.org/10.1016/j.tet.2007.10.080)  For a review of racemization catalysts see Park [*Coord. Chem. Rev.* **2008**, *252*, 647](http://dx.doi.org/10.1016/j.ccr.2007.09.009) |

* 1. Chemoenzymatic DKR

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| - Racemizations with bio- or organocatalysts are difficult: transition metals work better. This process can then be incepted with enzymatic kinetic resolution, thus, rendering the whole process a chemoenzymatic DKR. |
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| Overman [*ACIE* **1984**, *23*, 579](http://dx.doi.org/10.1002/anie.198405791) |

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| - Chemoenzymatic DKR of -amino ester with heterogeneous catalysts: |
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| Bäckvall [*EJOC* **2011**, 1827](http://dx.doi.org/10.1002/ejoc.201001714) |

- Chemoenzymatic DKR of alcohols and amines

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| Bäckvall [*Chem. Rev.* **2003**, *103*, 3247](http://dx.doi.org/10.1021/cr020029g) & [*JACS* **2005**, *127*, 17620](http://dx.doi.org/10.1021/ja056306t) |
| - Another DKR of 1-phenylethylamine was recently carried out under the co-immobilization of an enzyme and Pd into the mesoporous silica hybrid system. |
| Bäckvall [*ACIE* **2013**, *52*, 14006](http://dx.doi.org/10.1002/anie.201306487) |

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| - Chemoenzymatic DKR of tetrahydroisoquinoline: |
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| Page [*Org. Process Res. Dev.* **2007**, *11*, 642](http://dx.doi.org/10.1021/op060233w) |

* 1. DKR in cross-coupling reaction

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| - Kumada coupling in DKR: key step relies on fast racemization of the Grignard reagent |
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| Hayashi [*JOC* **1986**, *51*, 3772](http://dx.doi.org/10.1021/jo00370a006) |

* 1. DKR of azlactones

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| - DKR along with ring-opening by allyl alcohol to afford -amino esters |
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| Berkessel [*ACIE* **2005**, *44*, 807](http://dx.doi.org/10.1002/anie.200461442); for enzymatic methods see [*ChemCatChem.* **2011**, *3*, 319](http://dx.doi.org/10.1002/cctc.201000343) |

* 1. DKR of N-carboxyanhydrides

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| - For a successful DKR, racemization needs to be faster than the kinetic resolution. In this case, racemization is slow at low temperature (normal KR works well in this system but the reaction can only proceed to <50% conversion). Racemization is accelerated when the temperature is raised and when EtOH is slowly added. |
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| Deng [*OL* **2002**, *4*, 3321](http://dx.doi.org/10.1021/ol026660l) |

* 1. DKR of a biaryl atropisomer

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| - DKR by tris-bromination  - facile racemization of starting material due to low barrier of rotation  - significantly higher barrier of rotation of the tris-brominated product (30 kcal/mol) |
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| Miller [*Science* **2010**, *328*, 1251](http://dx.doi.org/10.1126/science.1188403) |

1. **Dynamic Kinetic Asymmetric Transformations (DyKAT)**
   1. Introduction

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| - In DKR, the **racemization** occurs with an achiral catalyst via an achiral intermediate or TS  - In DyKAT, interconversion of the substrate stereochemistry occurs on a chiral (enantiomerically enriched) catalyst, which gives diastereomeric catalyst-substrate adduct (thus this is formally an epimerization)  - In type A of DyKAT, a racemic substrate binds to the chiral catalyst to give diastereomeric catalyst-substrate adducts (SRcat\* and SScat\*), epimerization occurs on the catalyst. DyKAT depends on kS/kR.  - In type B of DyKAT, a single catalyst-substrate adduct SCat\* (chiral center only at the catalyst) is formed from a racemic substrate |
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| For a review on all the terms and concepts for KR, DKR, etc: Faber [*Chem. Eur. J*. **2001**, *7*, 5004](http://dx.doi.org/10.1002/1521-3765(20011203)7:23%3C5004::AID-CHEM5004%3E3.0.CO;2-X)  For more detailed information about DyKAT, see: Steinreiber [*Chem. Eur. J*. **2008**, *14*, 8060](http://dx.doi.org/10.1002/chem.200701643) |

* 1. Type A: DyKAT with epimerization

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| - Chiral phosphines are desirable especially as ligands for transition metal-catalyzed asymmetric synthesis.  - DyKAT can be used to afford enantiomerically enriched *P*-chirogenic phosphine. |
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| Glueck [*JACS* **2002**, *124*, 13356](http://dx.doi.org/10.1021/ja0267324) |

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| - Attempt simple KR of butenolide results in low ee product at near 50% conversion.  - Base promoted epimerization of the starting material is slow and leads to low ee outcome.  - Bimetallic epimerization mechanism involved attack of a Pd0 species on the opposite face of the coordinating PdL (η3 complex). However, it was found that decreasing [cat] leads to an increase in the ee of the product – this is more consistent with the intramolecular mechanism via a Pd enolate (η1) species.  - It was also found that decreasing [base] leads to an increase in the ee. This reduces the [Nu-] and slows down the rate of the nucleophilic attack (krel < krac). |
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| Trost [*JACS* **1999**, *121*, 3543](http://dx.doi.org/10.1021/ja9844229) & [*JACS* **2003**, *125*, 3090](http://dx.doi.org/10.1021/ja020988s) |

* 1. Type B: DyKAT with desymmetrization

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| Trost [*Chem. Eur. J*. **2001**, *7*, 1619](http://dx.doi.org/10.1002/1521-3765(20010417)7:8%3C1619::AID-CHEM16190%3E3.0.CO;2-4) |

1. **Enantioconvergent synthesis**

- A special case of de-racemization in which each enantiomer is transformed through different mechanisms and converges into the same product with the same stereochemistry.

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| Trost [*ACIE* **1997**, *36*, 2635](http://dx.doi.org/10.1002/anie.199726351) |

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| Ito [*Nature Chem*. **2010**, *2*, 972](http://dx.doi.org/10.1038/nchem.801) |

1. **(Cyclic) Deracemization**
   1. Introduction

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| - In (cyclic) deracemization reactions, one enantiomer of the racemate can be converted to the other by stereoinversion processes. These reactions usually involve cyclic redox processes.  - Compared to (cyclic) deracemization, in DKR both enantiomers of a racemate are transformed to a new optically active product. If therefore the enantioenriched starting material is desired, additional steps will be required in DKR processes. |
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| Faber [*Chem. Eur. J*. **2001**, *7*, 5004](http://dx.doi.org/10.1002/1521-3765(20011203)7:23%3C5004::AID-CHEM5004%3E3.0.CO;2-X)  Steinreiber [*Chem. Eur. J*. **2008**, *14*, 8060](http://dx.doi.org/10.1002/chem.200701643)  Turner [*Curr. Opin. Chem. Biol.* **2010**, *2*, 115](http://dx.doi.org/10.1016/j.cbpa.2009.11.027) |

* 1. Enzymatic deracemization to enantiomerically pure chiral amines

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| - Enormous efforts on enzymatic deracemization of amines have been made in Turner group. In the process they have reported, the enzyme selectively oxidizes the *S*-enantiomer to the corresponding imine, which is subsequently reduced *in situ* to the racemic amine. Repeated cycles eventually will lead to the accumulation of the *R*-enantiomer in high yield and enantiopurity. To this, the catalyst must be highly selective in the oxidation step. By directed evolution screening, they were able to obtain several variants of monoamine oxidases for the deracemization of primary, secondary and tertiary amines. |
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| Turner & Carr In [*Biocatalysis in the Pharmaceutical and Biotechnology Industries (2007)*](http://www.crcnetbase.com/isbn/9781420019377), [Chapter 31, p. 743](http://www.crcnetbase.com/doi/abs/10.1201/9781420019377.ch31)  Turner & Truppo In [*Chiral Amine Synthesis: Methods, Developments and Applications (2010)*](http://onlinelibrary.wiley.com/book/10.1002/9783527629541), [Chapter 14, p. 431](http://dx.doi.org/10.1002/9783527629541.ch14)  Turner [*Chem. Rev.* **2011**, *111*, 4073](http://dx.doi.org/10.1021/cr200111v) |
| - This deracemization of amines, monitored by chiral HPLC or capillary electrophoresis, was terminated when the *ee*’s reached 99%. (Some cases with lower ee’s are noted under the substrates.) |
| - Deracemization of primary amines (with Asn336Ser variant) |
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| - Deracemization of secondary amines (with Asn336Ser/Ile246Met variant) |
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| - Deracemization of tertiary amines (with Ile246Met/Asn336Ser/Thr384Asn/Asp385Ser variant) |
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| For 1o amines: Turner [*ACIE* **2003**, *42*, 4807](http://dx.doi.org/10.1002/anie.200352100); 2o amines: [*ChemBioChem* **2005**, *6*, 637](http://dx.doi.org/10.1002/cbic.200400329); 3o amines: [*JACS* **2006**, *128*, 2224](http://dx.doi.org/10.1021/ja058536d) |

* 1. Phase transferred deracemization in single operation to indolines and tetrahydroquinolines

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| - In the redox-driven process, to combine the oxidation and reduction is a big challenge for the non-enzymatic deracemization. Recently, the Toste group realized a chemically induced “one-pot” deracemization by phase separation and a shared phosphoric acid catalyst for oxidation/reduction cycle. |
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| Toste [*JACS* **2013**, *135*, 14090](http://dx.doi.org/10.1021/ja4082827) |

1. **Desymmetrizations**

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| - Differential activity of enantiotopic atoms or groups on a meso substrate  - reaction brakes the symmetry  - similar to the kinetic resolution  - the *er* should remain constant throughout the reaction |
| Faber [*Chem. Eur. J*. **2001**, *7*, 5004](http://dx.doi.org/10.1002/1521-3765(20011203)7:23%3C5004::AID-CHEM5004%3E3.0.CO;2-X)  Diaz-de-Villegas [*Chem. Eur. J.* **2012**, *18*, 13920](http://dx.doi.org/10.1002/chem.201202264)  Connon [*ChemCatChem* **2012**, *4*, 151](http://dx.doi.org/10.1002/cctc.201100266) |

* 1. Enzymatic Desymmetrization

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| - One of the most used methods for desymmetrization is based on enzymes. (see Biocatalysis Lecture) |
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| Gotor [*Chem. Rev.* **2011**, *111*, 3998](http://dx.doi.org/10.1021/cr100287w) |

* 1. Desymmetrizations of Meso-Anhydrides

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| Deng [*PNAS* **2010**, *107*, 20625](http://dx.doi.org/10.1073/pnas.1004439107) |

* 1. Opening of Meso-Epoxides

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| - nucleophilic ring-opening |
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| Jacobsen [*JACS* **1995**,*117*, 5897](http://d.doi.org/10.1021/ja00126a048); [*JACS* **1996**, *118*, 10924](http://dx.doi.org/10.1021/ja962600x) |

* 1. Desymmetrizations of Meso-Diols

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| - Planar chiral DMAP |
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| Yamada [*JOC* **2006**, *71*, 6872](http://dx.doi.org/10.1021/jo060989t) |

* 1. Peptide-Catalyzed Desymmetrization of a Bis(phenol)

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| - Substrate is a meso diol with the stereogenic center distant from centre of reactivity  - A form of molecular recognition |
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| Miller [*JACS* **2006**, *128*, 16454](http://dx.doi.org/10.1021/ja067840j); [*JACS* **2008**, *130*, 16358](http://dx.doi.org/10.1021/ja807120z) |

* 1. Amines

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| - Desymetrization of *meso*-diamines |
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| Seidel [*JACS* **2011**, *133*, 14538](http://dx.doi.org/10.1021/ja2060462) |

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| - Chemoenzymatic approach: an oxidative Stecker reaction used by *Merck* to produce an important intermediate for synthesis of “*Boceprevir*” |
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| Li[*JACS* **2012**, *134*, 6467](http://dx.doi.org/10.1021/ja3010495) |