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Recent developments in dynamic kinetic resolution

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Contents

Abbreviations: A, amino acid; Ac, acetyl; AIBN, 2,2′-azobisisobutyronitrile; Ala, alanine; Ar, aryl; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BSA, bis-(trimethylsilyl)acetamide; Bu, butyl; Bz, benzoyl; CBS, Corey–Bakshi–Shibata; Cbz, benzyloxycarbonyl; COD, cyclooctadiene; Cp, cyclopentadienyl; Cy, cyclohexyl; DAGOH, diacetone-D-glucose; dba, (*E*,*E*)-dibenzylideneacetone; DBAB, dibenzylazodicarboxylate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N*,*N*′-dicyclohexylcarbodiimide; de, diastereomeric excess; DFT, density functional theory; DIBAL, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DKR, dynamic kinetic resolution; DMA, *N*,*N*-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMAPEN, 2-dimethylamino-1-phenylethylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; ee, enantiomeric excess; Et, ethyl; Fu, furyl; Gly, glycine; Hex, hexyl; Hept, heptyl; Ile, isoleucine; L, ligand; LDA, lithium diisopropylamide; Leu, leucine; Lys, lysine; M, metal; Me, methyl; Mes, mesyl; MOM, methoxymethyl; MTBE, methyl *tert*-butyl ether; NADP, nicotinamide adenine dinucleotide phosphate; Naph, naphthyl; nbd, norbornadiene; Non, nonyl; Nu, nucleophile; Ns, nosyl; Oct, octyl; Pent, pentyl; Ph, phenyl; Phe, phenylglycine; PMB, *p*-methoxybenzoyl; PMHS, polymethylhydrosiloxane; PMP, *p*-methoxyphenyl; Pr, propyl; Pro, proline; py, pyridine; TBAB, tetra-*n*-butylammonium bromide; TBAI, tetra-*n*-butylammonium iodide; TBDMS, *tert*-butyldimethylsilyl; TBHP, *tert*-butyl hydroperoxide; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THFA, tetrahydrofurfuryl alcohol; Thio, thiophene; TIPS, triisopropylsilyl; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; TMGA, tetramethylguanidinium azide; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl); Tyr, tyrosine; Val, valine; Xyl, xylyl.

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1. Introduction

This review updates the principal methods used to obtain dynamic kinetic resolution (DKR) by either enzymatic or non-enzymatic methods, covering the literature from 2003 to 2007. This fast-moving field was most recently reviewed in 2003.[1] Prior to that, this area has been the subject of several excellent review articles.[2] The aim of this review is to highlight examples of DKR, which have not previously been covered by the preceding articles, and demonstrate that some most important achievements, such as organocatalysed DKRs, and enzymatic or non-enzymatic transition metal-catalysed DKRs have considerably expanded the synthetic scope of the process. Moreover, a great number of novel enzymatic DKRs have been developed.

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry.[3] The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals,[4] in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation.[5] In particular, life depends on molecular chirality, in that many biological functions are inherently dissymmetric. The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis.[6] While tremendous advances have been made in asymmetric synthesis, either substrate driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. A kinetic resolution is defined as a process where the two enantiomers of a racemate are transformed into products at different rates.[7] If the kinetic resolution is efficient, one of the enantiomers of the racemic mixture is transformed into the desired product while the other is recovered unchanged (Fig. 1).

However, this procedure suffers from being limited to a maximum theoretical yield of 50%. Many efforts have been devoted to overcome this limitation and to afford compounds with the same high enantiomeric purity, but with much improved yields. It is a combination of these twin goals that has led to the evolution of classical kinetic resolution into DKR. In such a process, one can in principle obtain a quantitative yield of one of the enantiomers. Effectively, DKR combines the resolution step of kinetic resolution with an in situ equilibration or racemisation of the chirally labile substrate (Fig. 2). In DKR, the enantiomers of a racemic substrate are induced to equilibrate at a rate that is faster than that of the slow-reacting enantiomer in reaction with the chiral reagent (Curtin–Hammett kinetics). If the enantioselectivity is sufficient, then isolation of a highly enriched non-racemic product

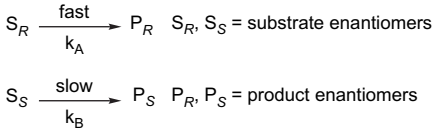


Figure 1. Classical kinetic resolution.

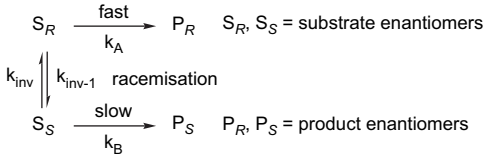


Figure 2. Dynamic kinetic resolution.

is possible with a theoretical yield of 100% based on the racemic substrate. Clearly, certain requirements have to be fulfilled in order to gain the complete set of advantages of DKR, such as the irreversibility of the resolution step, and the fact that no product racemisation should occur under the reaction conditions. In order to obtain products with high optical purity, the selectivity (k_A/k_B) of the resolution step should be at least 20. Furthermore, the rate constant for the racemisation process (k_{inv}) should be faster than the rate constant of the resolution step (k_A), otherwise a very high selectivity has to be ensured.

Indeed, in this way, all of the substrate can be converted into a single product isomer with a 100% theoretical yield. Racemisation of the substrate can be performed by a chemocatalyst, a biocatalyst or can occur spontaneously. The utility of the DKR is not limited to a selective synthesis of an enantiomer; when the reaction occurs along with the creation of a new stereogenic centre, an enantioselective synthesis of a diastereoisomer is also possible, as outlined in Figure 3.

This review highlights and updates the principal methods employed to obtain DKR by either enzymatic or non-enzymatic methods, illustrating the diversity of useful products that can be obtained through this concept.

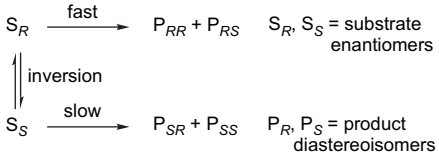


Figure 3. Enantioselective synthesis of a diastereoisomer via DKR.

2. Non-enzymatic methods

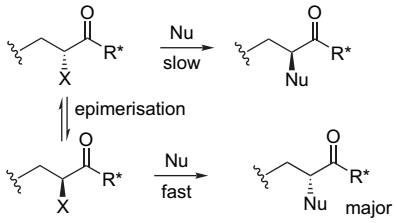
2.1. Chiral auxiliaries

There are certainly numerous ways of obtaining resolutions of chiral compounds by chemical means. The combination of these chemical kinetic resolutions with racemisation is, however, less obvious. Nevertheless, DKR processes can be exploited just as successfully for non-enzymatic reactions. Typically, chiral auxiliaries or chiral organometallic complexes are employed to achieve the desired resolution. Hence, besides metal complexes bearing chiral ligands, such as ruthenium catalysts together with a chiral ligand such as BINAP, there is also the possibility of using chiral auxiliaries for the asymmetric induction through a dynamic kinetic process.

2.1.1. Configurationally labile alkyl halides

Nucleophilic substitution on configurationally labile halides has been involved in compounds with a bromo or iodo

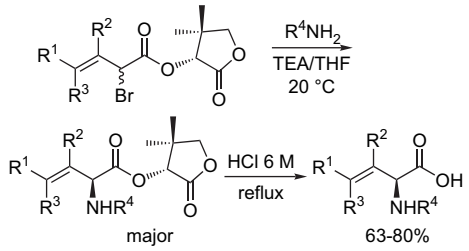
atom in the α-position with respect to a carboxylic acid derivative, in which the S_N2 reaction is governed by a chiral auxiliary placed in the carboxylic moiety.[8] Racemisation takes place by consecutive inversions at the labile centre induced by additives such as polar solvents, bases or halide salts (Scheme 1).



Scheme 1. S_N2 reactions on configurationally labile halides bearing a carboxylated function.

Extensive studies have been carried out on nucleophilic substitution of α-halocarboxylic acid derivatives containing a chiral auxiliary in the carboxylic moiety. The racemisation of the labile chiral centre in the α-position to the carbonyl, induced by additives such as polar solvents, bases or halide salts, allows a high asymmetric induction through a DKR process to be obtained. This methodology has been recently recognised as a powerful synthetic method for asymmetric syntheses of α-heteroatom-substituted carboxylic acid derivatives. As an example, Bettoni et al. have applied this methodology to α-bromo esters containing lactamides as chiral auxiliaries, allowing the synthesis of chiral analogues of antilipidemic clofibrate.[9] Hence, the displacement of the bromine with 4-chlorophenoxide was found to proceed with good-to-high diastereoselectivities to give the corresponding 4-(chlorophenoxy)butanoyl esters (Scheme 2). After hydrolysis, the (*R*)-enantiomer of antilipidemic 2-(4-chlorophenoxy)butanoic acid was obtained. In 2006, the same group improved the stereoselectivity up to 98% de by using other chiral auxiliaries such as piperidine-, morpholine-, pyrrolidine- and 4-methylpiperazine-derived lactamides (Scheme 2).[10]

This methodology was extended by Cardillo et al. to the synthesis of chiral α-benzylamino-β,γ-unsaturated acids, starting from α-bromo-α,β-unsaturated chlorides.[11] The treatment of these latter compounds with (*R*)-pantolactone in the presence of TEA allowed the in situ formation of the deconjugated ketenes and their direct transformation into the corresponding chiral esters. The substitution of bromine with benzylamine, followed by acid hydrolysis, produced enantiomerically enriched α-benzylamino-β,γ-unsaturated acids (Scheme 3). The displacement of the bromine with other nitrogen nucleophiles, such as *p*-MeO-benzylamine and allylamine, also occurred with good yield with complete diastereoselectivity.

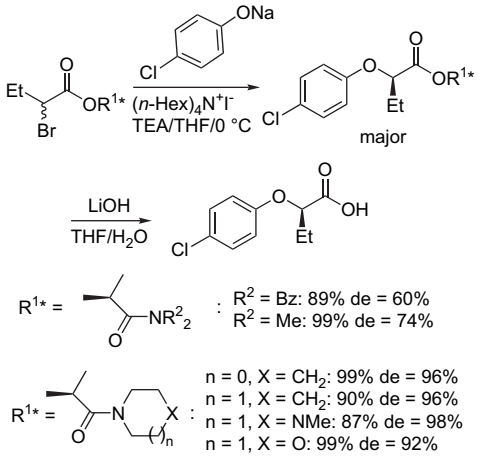


R^1 = Me, R^2 = R^3 = H, R^4 = Bn: 90% de = 24%
R^1 = R^2 = H, R^3 = Et, R^4 = Bn: 64% de = 56%
R^1 = Me, R^2 = H, R^3 = *n*-Pr, R^4 = Bn: 80% de = 44%
R^1 = Me, R^2 = R^3 = H, R^4 = PMB: 70% de = 62%
R^1 = Me, R^2 = R^3 = H, R^4 = allyl: 70% de = 60%

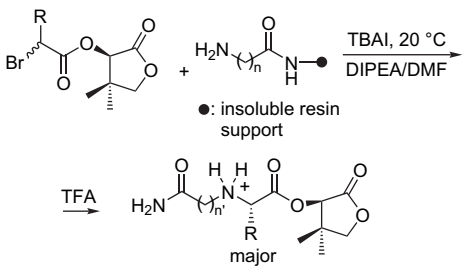
Scheme 3. Synthesis of α-alkylamino-β,γ-unsaturated acids.

In 2004, Ben et al. reported the first example of a DKR using immobilised amine nucleophiles.[12] This novel approach used a nucleophilic amine attached to a solid-phase resin via an organic spacer, giving optical purities of the *N*-substituted α-amino ester products superior to the solution-phase DKR process with des ranging from 84% to 90% and yields between 66% and 98% (Scheme 4).

The incorporation of unnatural amino acids into peptides to enhance their metabolic stability and activity is an area of major interest in peptidomimetic chemistry. In order to accomplish this goal, Park et al. have developed nucleophilic substitutions of α-bromo amides derived from L-amino acids in the presence of amine nucleophiles on the basis of DKR processes.[13] Whereas moderate stereoselectivities were obtained when using benzylamine as the nucleophile, the



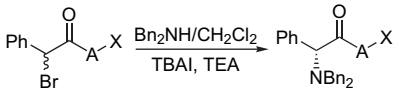
Scheme 2. DKR of α-bromo esters containing lactamides.



R = Me, n = n' = 1: 66% de = 86%
R = Ph, n = n' = 1: 91% de = 90%
R = Me, n = n' = 3: 89% de = 84%
R = Ph, n = n' = 3: 84% de = 88%
R = Me, n = 10, n' = 3: > 95% de = 82%
R = Ph, n = 10, n' = 3: > 95% de = 88%

Scheme 4. DKR using immobilised amine nucleophiles.

nucleophilic substitution reactions of various α-bromo amides with the more sterically demanding secondary amine nucleophile, dibenzylamine, allowed the stereoselectivity of the reactions to be increased remarkably. This methodology provided, in the presence of TBAI and TEA, the corresponding dipeptide analogues in up to 98% yield and 98% de (Scheme 5).

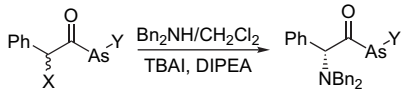


A = L-Leu, X = OMe: 83% de = 78%
A = L-Leu, X = O*t*-Bu: 63% de = 86%
A = L-Leu, X = O*t*-Bu: 68% de = 92%
A = L-Leu, X = OBn: 95% de = 88%
A = L-Pro, X = OMe: 93% de > 98%
A = L-Pro, X = O*t*-Bu: 91% de > 98%
A = L-Ala, X = OMe: 96% de = 80%
A = L-Val, X = OMe: 81% de = 90%
A = L-Ile, X = OMe: 95% de = 86%
A = L-Tyr, X = OMe: 77% de = 80%
A = L-Lys(*N*-Cbz), X = OMe: 91% de = 80%

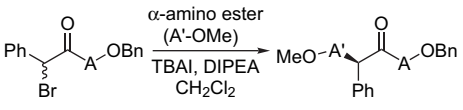
Scheme 5. Synthesis of dipeptides.

As an extension of the preceding methodology, Park et al. reported the stereoselective syntheses of tri- and tetrapeptide analogues starting from α-chloro as well as α-bromo amides (Scheme 6).[14] Mechanistic investigations suggested that α-iodo acetamides were real intermediates for the nucleophilic substitutions of both α-chloro and α-bromo amides in the presence of TBAI. The methodology was also successful for the N-terminal functionalisation of peptides, affording a generalised and practical method for the asymmetric syntheses of *N*-carboxyalkyl, *N*-aminoalkyl and *N*-hydroxyalkyl peptide analogues.

In 2006, the same group reported the synthesis of other chiral *N*-aminoethyl prolinol derivatives on the basis of a DKR of *N*-(α-bromo-α-phenylacetyl)proline methyl ester in asymmetric nucleophilic substitution and subsequent reduction (Scheme 7).[15] These peptide-derived prolinols were tested as



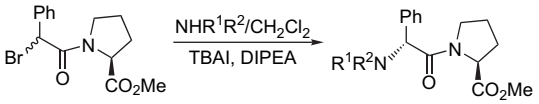
As = L-Pro-Gly, X = Br, Y = OMe: 91% de = 90%
As = L-Pro-Gly, X = Cl, Y = OMe: 84% de = 90%
As = L-Pro-L-Leu, X = Br, Y = OMe: 85% de > 98%
As = L-Pro-L-Leu, X = Cl, Y = OMe: 82% de > 98%
As = L-Pro-D-Leu, X = Cl, Y = OMe: 77% de = 92%
As = L-Pro-L-Leu-L-Ala, X = Cl, Y = OMe: 71% de = 62%
As = L-Pro-L-Leu-D-Ala, X = Cl, Y = OMe: 68% de = 52%



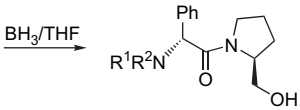
A = L-Leu, A' = D-Ala: 83% de = 82%
A = L-Leu, A' = D-Leu: 63% de = 86%
A = L-Leu, A' = D-Phe: 49% de = 84%
A = L-Pro, A' = L-Leu: 44% de = 86%

Scheme 6. Synthesis of tri- and tetrapeptides.

chiral ligands in the asymmetric addition of a Reformatsky reagent to aromatic aldehydes, providing up to 98% ee.



$R^1 = R^2$ = Bn: 93% de = 98%
R^1 = Bn, $R^2 = (CH_2)_2OH$: 69% de = 90%
R^1 = H, $R^2 = CH(Ph)_2$: 60% de = 88%

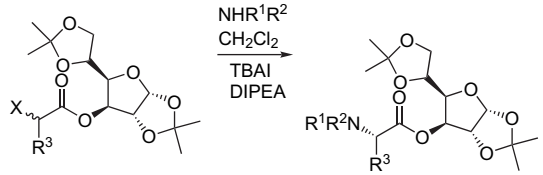


$R^1 = R^2$ = Bn: 64% de > 98%
R^1 = Bn, $R^2 = (CH_2)_2OH$: 53% de > 98%
R^1 = H, $R^2 = CH(Ph)_2$: 68% de > 98%

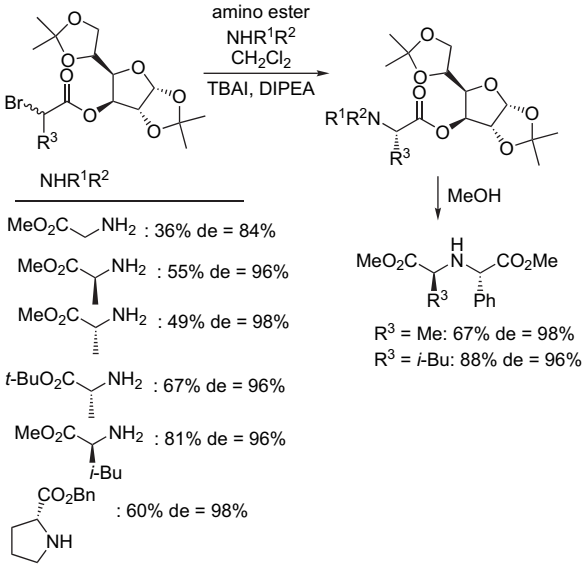
Scheme 7. Synthesis of dipeptide-derived prolinols.

Carbohydrates are readily available inexpensive natural products in which numerous functional groups and stereogenic centres are present in a molecule. A number of carbohydrate-based templates have been used as chiral auxiliaries for various strereoselective reactions. In 2005, Park et al. described the first successful example of carbohydrate-mediated DKR of α-halo esters in nucleophilic substitution for asymmetric syntheses of α-amino acid derivatives.[16] Hence, the use of diacetone-D-glucose as a chiral auxiliary allowed the substitution products to be obtained in up to 99% yield and 94% de. The procedure was generalised to various amine nucleophiles, as depicted in Scheme 8. In addition, the application of this mild and simple method to highly stereoselective preparations of 1,1′-iminodicarboxylic acid derivatives was also demonstrated on the basis of substitution with various amino ester nucleophiles (Scheme 8).[17]

Chiral imidazolidinones have been widely employed as chiral auxiliaries for more than 20 years due to their low flexibility.[18] In 2005, Caddick et al. demonstrated that diastereoselective substitution reactions of α-bromoacyl-imidazolidinones with nitrogen nucleophiles could be promoted with either retention or inversion of configuration by carrying out reactions under epimerising or non-epimerising conditions.[19] Hence, an alternative general strategy was sought in which the substitution of the (2′*R*)-bromide, depicted in Scheme 9, with a nucleophile under epimerising conditions led to the corresponding (2′*R*)-product with overall retention of configuration via DKR, in which the (2′*S*)-isomer was the most reactive. This process was complemented by classical inversion, providing access to the (2′*S*)-product under non-epimerising conditions and in the presence of tetramethylguanidinium azide (TMGA). Substitution of the diastereomerically pure bromides with benzylamine under DKR conditions was shown to proceed with a high level of stereocontrol and with retention of configuration (Scheme 9). This was consistent with a reaction involving the initial conversion of the (2′*R*)-bromide into a mixture of (2′*S*)/(2′*R*)-halides and then selective reaction of the (2′*S*)-product with inversion of configuration.



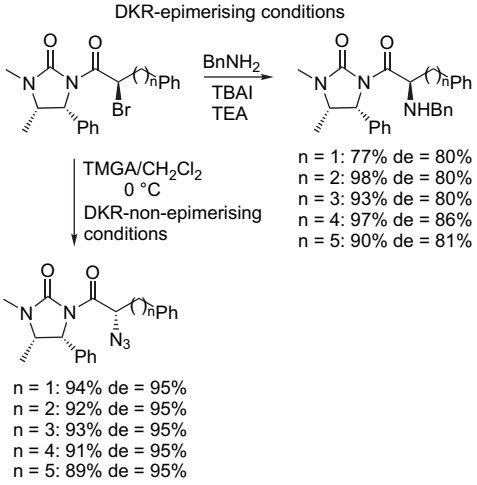
X = Cl, R^1 = H, R^2 = $CH(Ph)_2$, R^3 = Ph: 62% de = 94%
X = Cl, R^1 = H, R^2 = *i*-Pr, R^3 = Ph: 75% de = 90%
X = Cl, R^1 = H, R^2 = *n*-Bu, R^3 = Ph: 48% de = 90%
X = Cl, R^1 = H, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph: 97% de = 94%
X = Cl, R^1 = R^2 = Bn, R^3 = Ph: 61% de = 88%
X = Cl, R^1 = Me, R^2 = Bn, R^3 = Ph: 82% de = 88%
X = Cl, R^1 = R^2 = $(CH_2)_4$, R^3 = Ph: 73% de = 86%
X = Br, R^1 = H, R^2 = *i*-Pr, R^3 = Me: 70% de = 60%
X = Br, R^1 = H, R^2 = *p*-$MeOC_6H_4$, R^3 = Me: 85% de = 82%
X = Br, R^1 = H, R^2 = *p*-$MeOC_6H_4$, R^3 = *n*-Bu: 64% de = 94%
X = Br, R^1 = H, R^2 = *p*-$MeOC_6H_4$, R^3 = Et: 99% de = 40%
X = Br, R^1 = H, R^2 = Bn, R^3 = Et: 77% de = 50%
X = Br, R^1 = R^2 = Bn, R^3 = Me: 48% de = 38%
X = Br, R^1 = R^3 = Me, R^2 = Bn: 91% de = 50%



Scheme 8. DKRs of α-halo esters using diacetone-D-glucose as chiral auxiliary.

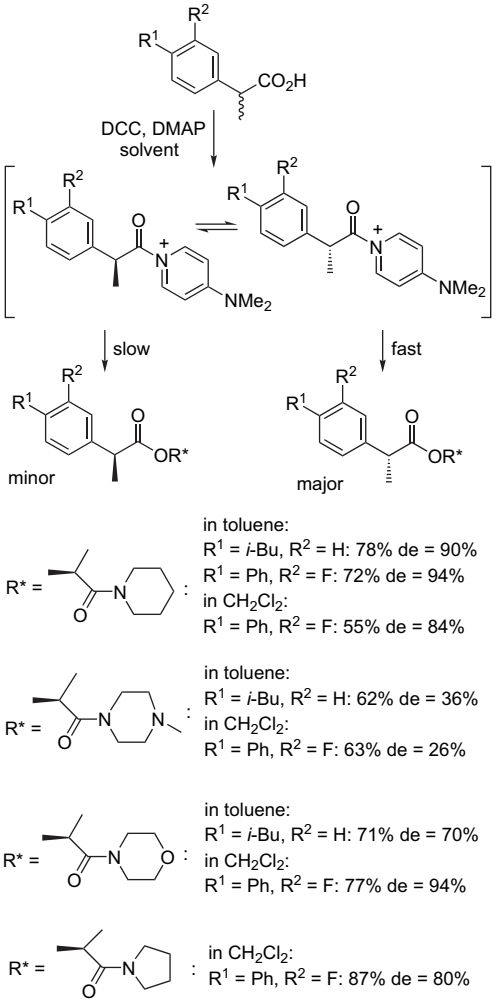
2.1.2. Miscellaneous reactions

In 2006, Amoroso et al. reported the asymmetric synthesis of several biologically active arylpropionic acids, such as ibuprofen, flurbiprofen and fenoprofen, by using lactamide chiral auxiliaries, such as piperidine-, morpholine-, pyrrolidine- and 4-methylpiperazine-derived lactamides.[10] As shown in Scheme 10, the diastereomeric mixtures of lactamic esters of ibuprofen, flurbiprofen and fenoprofen were obtained with good yields and high diastereoselectivities depending upon the solvent and the auxiliary used for the esterification process. As a general trend, the reactions performed in toluene were faster and with higher des, compared to those in CH_2Cl_2. These good stereochemical results could be attributed to the sufficiently fast equilibration with respect to the esterification rate of a pyridinium intermediate, showing that the pathway of the asymmetric induction was a DKR process.



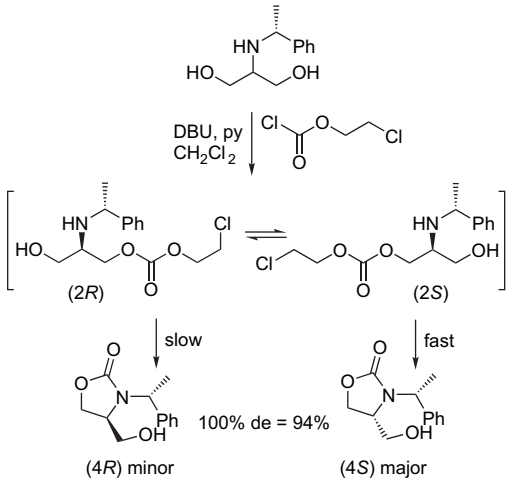
Scheme 9. Complementary DKRs and substitution approach to α-azido/amino carboxylic acid derivatives.

In 2003, Ishii et al. reported the first example of a DKR accompanied by an intramolecular transesterification.[20] This one-pot reaction allowed the synthesis of a chiral 4-hydroxymethyl-2-oxazolidinone with excellent diastereoselectivity starting from a serinol derivative. It was demonstrated that



Scheme 10. DKR esterification of arylpropionic acids with various lactamides.

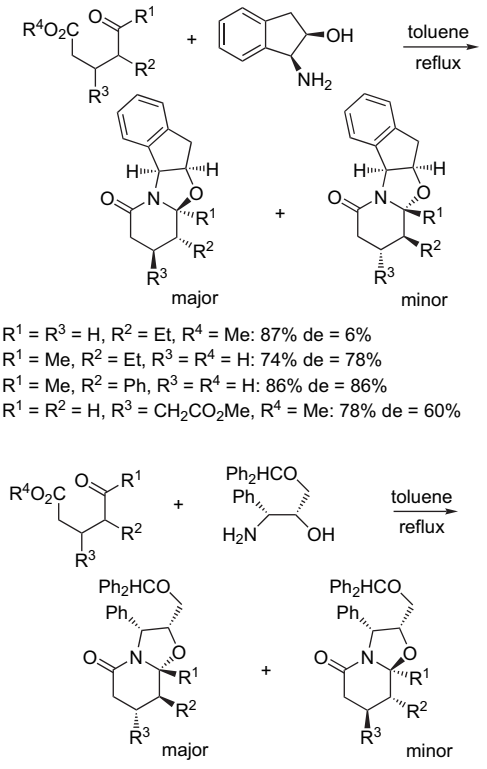
the first reaction occurred with no selectivity between the serinol derivative and 2-chloroethyl chloroformate, affording the corresponding monocarbonates. After the addition of DBU, the second reaction, consisting of an intramolecular transesterification of the monocarbonates, occurred rapidly and reached equilibrium, providing the corresponding oxazolidinones. Since the intermediate (2*S*)-monocarbonate was more reactive than the corresponding (2*R*)-monocarbonate, the (4*S*)-oxazolidinone was predominantly formed (Scheme 11).



Scheme 11. Synthesis of an oxazolidinone via DKR and intramolecular transesterification.

The development of general methods for the enantioselective synthesis of natural products has long constituted a challenging goal for synthetic organic chemists. Since the piperidine ring is a common moiety in many biologically active natural products and therapeutic agents, considerable attention has been focused on the development of general methods and strategies for the enantioselective synthesis of piperidine derivatives.[21] The piperidine ring is found in simple diversely substituted piperidine alkaloids, in bicyclic indolizidine, perhydroquinoline and quinolizidine alkaloids, as well as in many of the most complex polycyclic alkaloids. These nitrogen derivatives, which occur not only in plants, but also in insects and amphibians, constitute important targets for pharmaceutical research, with thousands mentioned as drug candidates in clinical and preclinical studies. In this context, Bosch et al. have developed highly enantioselective DKR processes on the basis of cyclocondensation reactions of chiral aminoalcohols with racemic or prochiral δ-oxoacid derivatives, providing, in a single synthetic step, the corresponding chiral bicyclic polysubstituted lactams, precursors of enantiopure piperidines.[22] The scope of the reaction was extended to a wide variety of δ-oxoacid derivatives including simple racemic aldehydes and ketones, prochiral aldehydo-diesters bearing enantiotopic ester groups and racemic aldehydo-diesters bearing diastereotopic ester groups, as shown in Scheme 12.

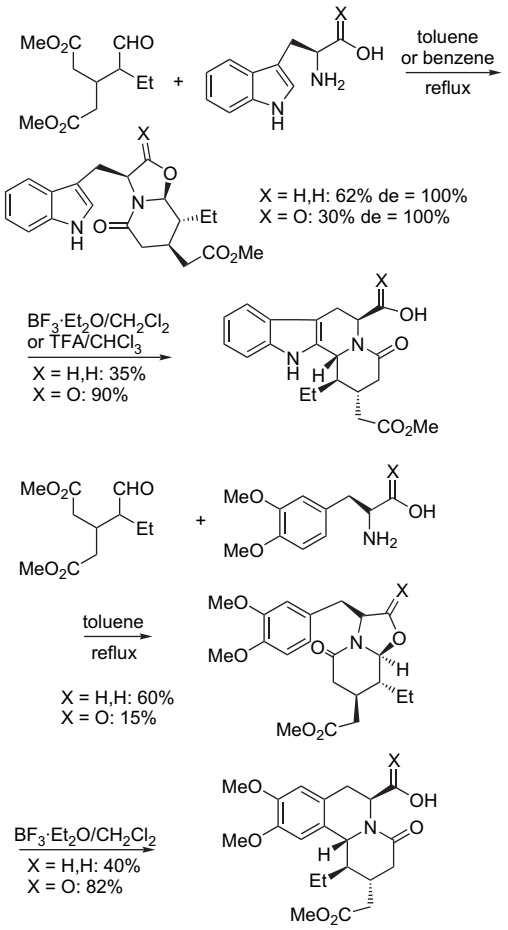
This methodology was successfully applied to the enantioselective synthesis of several biologically active natural products such as the alkaloids, (20*S*)- and (20*R*)-15,20-dihydrocleavamine, starting from (*R*)-phenylglycinol and a racemic γ-substituted δ-oxo-ester (100% yield and 40% de).[23] The scope of the methodology was extended to a biogenetically inspired enantioselective approach to indolo[2,3-*a*]- and benzo[*a*]quinolizidine alkaloids from a synthetic equivalent of secologanin, a biologically active secoiridoid glucoside.[24] Hence, a racemic oxo-diester underwent stereoselective cyclocondensation with (*S*)-tryptophanol, (*S*)-(3,4-dimethoxyphenyl)alaninol, or the corresponding amino acids, giving rise to the corresponding lactams, which were further converted into the corresponding indolo[2,3-*a*]- and benzo[*a*]quinolizidines through a subsequent cyclisation with $BF_3 \cdot Et_2O$ (Scheme 13).



Scheme 12. Cyclocondensation reactions.

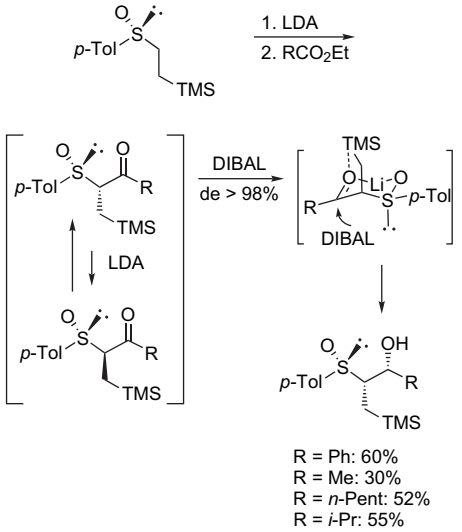
In 2003, Toru et al. reported an asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxides with DIBAL under basic conditions (Scheme 14). The stereoselective reaction was demonstrated to proceed through a DKR pathway via a six-membered cyclic transition state involving an Si–O interaction.[25]

In 2005, Shair et al. reported DKR cascade reactions occurring with racemic starting materials that contain all-carbon quaternary stereocentres.[26] Indeed, the treatment of a racemic β-keto ester with a single enantiomer of a Grignard reagent derived from a vinylstannane afforded the corresponding product of the expected cascade reaction as a single diastereomer in good yield, which was indicative of DKR (Scheme 15). These novel cascade reactions were unique because they involved DKRs that required the formation and cleavage of multiple

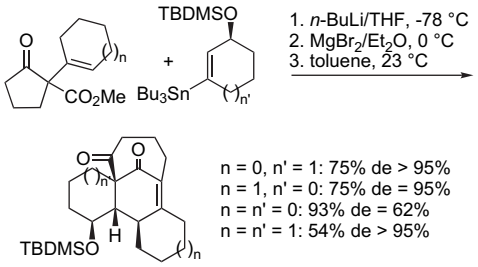


Scheme 13. Synthesis of indolo[2,3-*a*]- and benzo[*a*]quinolizidines.

C–C bonds. Moreover, DKR processes are still rare for substrates with chiral all-carbon quaternary centres. Furthermore, the products generated in these reactions were among the most complex prepared to date via DKR, suggesting that cascade reactions involving DKR may be useful for the stereoselective synthesis of complex molecules.



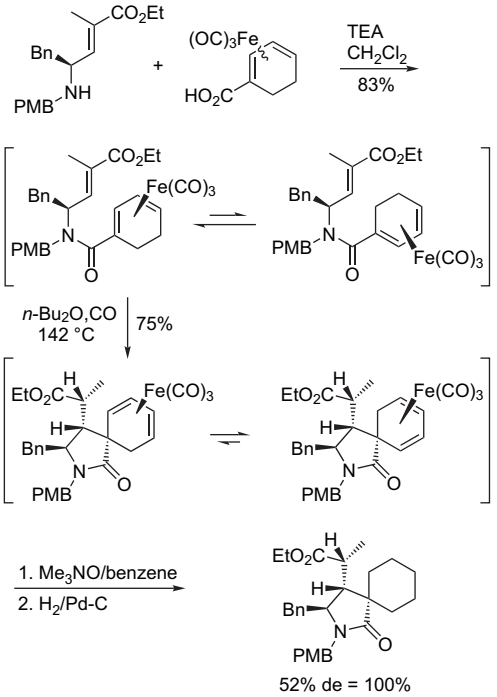
Scheme 14. Asymmetric reduction of α-(trimethylsilyl)methyl-β-ketosulfoxides.



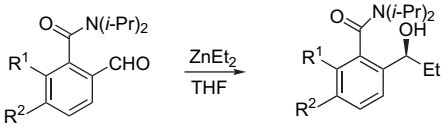
Scheme 15. Cascade reactions.

In 2005, Pearson and Wang developed a novel [6+2] ene reaction, which consisted of an intramolecular coupling reaction between a diene–$Fe(CO)_3$ complex and a pendant alkene, providing chiral spirolactams, starting from chiral amide substrates.[27] It was shown that the initial lactam product underwent a rearrangement of the diene–$Fe(CO)_3$ system via a hydride shift to afford another lactam product under the reaction conditions. Due to a significant difference in the rates of cyclisation of the two formed lactam diastereomers, compared with their rate of interconversion occurring via an iron-mediated hydride transfer, a mixture of these two complexes could afford a single product, as shown in Scheme 16.

In principle, DKR is possible if interconverting enantiomeric atropisomers are treated with enantioselective reagents.[28] In 2004, Walsh et al. observed that dialkylzinc reagents reacted rapidly with atropisomeric 2-formylarylamides relative to 2-substituted benzaldehyde derivatives. It was proposed that this large difference in reactivity was due to an internal activation of the organozinc reagent by the amide carbonyl. Additionally, with diethylzinc the products were formed with very high yields and diastereoselectivities, affording the *syn* products with up to 96% de (Scheme 17).[29]



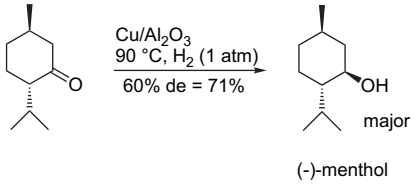
Scheme 16. [6+2] Ene-type reaction.



$R^1 = NMe_2$, R^2 = H: 99% de > 96%
$R^1 = CF_3$, R^2 = H: 96% de = 90%
R^1 = Ph, R^2 = H: 80% de > 96%
R^1 = OMe, R^2 = H: 95% de > 96%
R^1, R^2 = 1-Naph: 68% de > 96%

Scheme 17. Addition of diethylzinc to 2-formylarylamides.

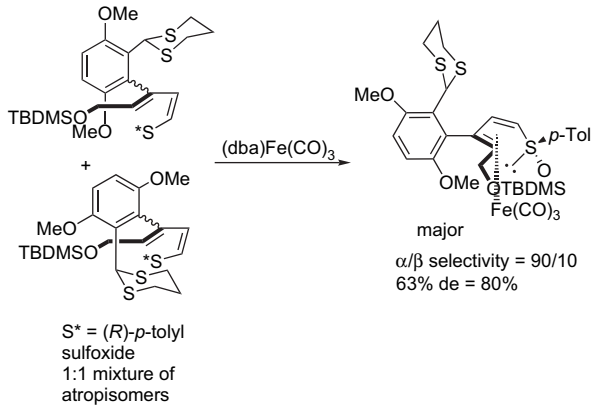
In 2006, Ravasio et al. reported a novel method of production of (−)-menthol, based on the hydrogenation of (−)-menthone over a Cu/Al_2O_3 catalyst, proceeding via DKR under very mild conditions (Scheme 18).[30]



Scheme 18. Hydrogenation of (−)-menthone.

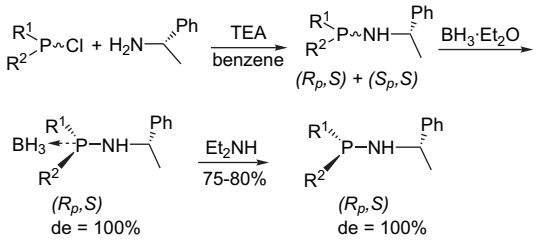
Enantiopure (1*Z*,3*E*)-1-sulfinyl dienes bearing an *o*-dithianylphenyl group have been prepared and complexed with (dba)$Fe(CO)_3$ to afford the corresponding sulfinyl diene iron(0) tricarbonyl complexes.[31] This diastereoselective complexation introduced planar and axial chiralities simultaneously, with a high degree of facial selectivity as well as atroposelectivity (Scheme 19). The origin of the atroposelectivity was explained by DKR. This explanation was supported by the discovery that stirring of each of the chromatographically separated atropoisomers of the starting sulfinyl diene in toluene afforded the same atropoisomeric mixture. Thus, the atropoisomeric sulfinyl dienes were capable of equilibration under the conditions of the complexation; the iron fragment apparently complexed with one atropoisomer faster than the other, and the less reactive could be equilibrated into the more reactive atropoisomer.

Equilibration of configuration at sulfinyl sulfur or phosphinyl phosphorus atoms can be used in DKR experiments.[32]



Scheme 19. Synthesis of sulfinyl iron diene complexes.

As an example, Kolodiazhnyi et al. have developed an asymmetric synthesis of chiral *N*-(1-methylbenzyl)aminophosphines on the basis of a DKR process.[33] Indeed, the reaction of a chlorophosphine with (*S*)-1-methylbenzylamine proceeded stereoselectively to give the corresponding *N*-(1-methylbenzyl)aminophosphine, which was isolated as a crystalline borane complex with 100% diastereomeric purity. The BH_3 group of the complex was removed by treatment with diethylamine to furnish the initial aminophosphine in 100% stereochemical purity (Scheme 20). This reaction has been demonstrated to proceed in a stereospecific manner with retention of configuration.



R^1 = *t*-Bu, R^2 = Ph: de = 80%
R^1 = *t*-Bu, R^2 = *i*-Bu: de = 40%
R^1 = Ph, R^2 = Mes: de = 50%

Scheme 20. Synthesis of aminophosphines.

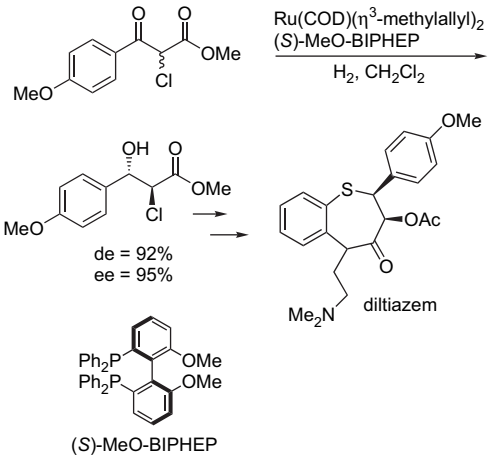
In the same context, a theoretical study on the pyramidal inversion of chiral sulfur compounds has been carried out by Maseras et al. by means of the density functional theory (DFT) method.[34] The results have revealed that, in the case of chiral sulfinyl chlorides, an organic tertiary amine such as NMe_3 could catalyse the racemisation. The base-catalysed inversion of sulfinyl chlorides was proposed as a feasible DKR mechanism for the synthesis of chiral sulfoxides by the DAG method, consisting of the reaction of a sulfinyl chloride racemate with chiral DAGOH (diacetone-D-glucose) in the presence of a nitrogenated base.

2.2. Chiral metal catalysts

Besides chiral auxiliaries, there is also the possibility of using metal complexes bearing chiral ligands for the asymmetric induction. According to a recent survey, between 70% and 90% of all chemical processes on an industrial scale are performed in a catalytic manner.[35] The development of low-molecular-weight chiral catalysts for asymmetric synthesis has been one of the major breakthroughs in organic synthesis over the last 35 years. Within this context, a significant number of enantioselective catalysts are now available that afford excellent levels of stereocontrol that could previously be achieved only using biocatalysts. Whilst the use of enzymes for the DKR of racemic substrates to afford enantiopure compounds in high ees and good yields has emerged as a popular strategy in synthesis,[36] it is only relatively recently that the widespread application of non-enzymatic chiral catalysts for DKR has gained popularity within the synthetic community.[7d]

2.2.1. Ruthenium-catalysed DKR

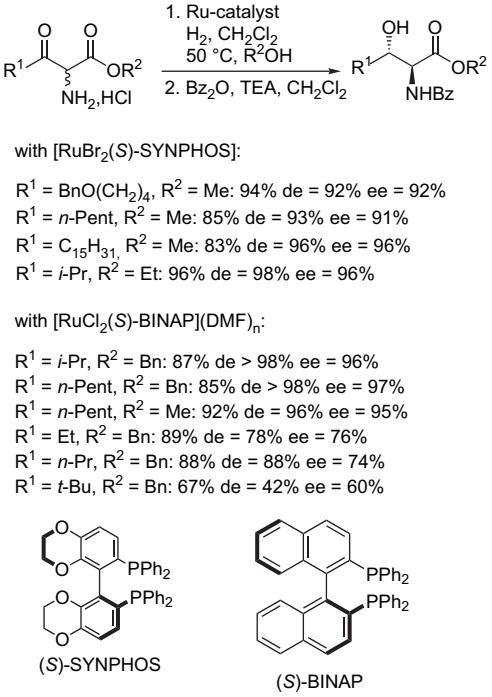
Ruthenium-catalysed hydrogenation has been widely used in the DKR of β-keto esters.[2] One of the first examples of this impressive technology, combining asymmetric hydrogenation with DKR, was reported in 1989 by Noyori's group, leading to important processes, such as that developed by Takasago for the production of acetoxyazetidinone (150 tons/year), a key intermediate in the synthesis of antibiotics.[37] At the same time, Genêt et al. have shown that the degree of selectivity was highly dependent upon the nature of the chiral ruthenium catalysts, the reaction conditions and the substrates.[38] In 2003, these latter authors applied this methodology to the synthesis of diltiazem, a potent calcium channel blocker used for the treatment of hypertension. The key step of the synthesis was the hydrogenation of a racemic α-chloro-β-keto ester via DKR in the presence of an (*S*)-MeO-BIPHEP–Ru complex, providing the corresponding *trans* β-hydroxy ester with a high level of both enantio- and diastereoselectivity (Scheme 21).



Scheme 21. Synthesis of diltiazem.

In 2003, the same group described the synthesis of SYNPHOS, a new, atropoisomeric, chiral diphosphane ligand, and its use in ruthenium-catalysed asymmetric hydrogenations, providing access to a wide range of optically active alcohols, with ee values of up to 99%.[39] As an example, this latter ligand was successfully used in the ruthenium-catalysed hydrogenation of α-amino-β-keto esters as their hydrochloride salts, affording the corresponding *anti*-α-amino-β-hydroxy esters under mild conditions with high diastereo- and enantioselectivities via DKR (Scheme 22).[40] The same reactions were also developed at the same time by Hamada et al. by using an (*S*)-BINAP–Ru(II) catalyst, which provided similar excellent results, as shown in Scheme 22.[41] These efficient and convenient methods have complemented the well-known hydrogenation of α-amido-β-keto esters, providing the *syn* isomers as major products.

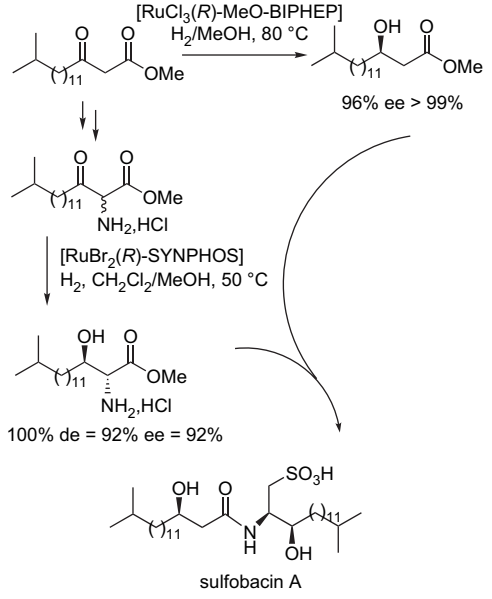
As an extension of the work developed by Genêt et al., a total synthesis of sulfobacin A, a von Willebrand factor receptor antagonist, was reported in 2004 by the same group.[42] The key steps of this short route to sulfobacin A involved ruthenium-catalysed asymmetric hydrogenation reactions of a β-keto ester and a racemic β-keto-α-amino ester hydrochloride to



Scheme 22. DKR of α-amino-β-keto ester hydrochlorides.

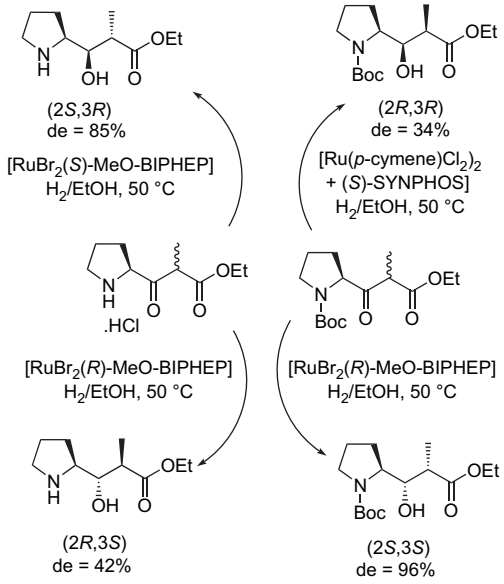
afford, respectively, the corresponding enantiomerically pure β-hydroxy ester and the enantioenriched *anti*-β-hydroxy-α-amino ester hydrochloride through DKR (Scheme 23).

In addition, the natural (2*R*,3*R*)-Boc-dolaproine and its unnatural (2*S*,3*S*)-diastereoisomer were synthesised, involving as the key transformation the ruthenium(II)-promoted hydrogenation of the β-keto-α-methyl ester derived from (*S*)-*N*-Boc-proline.[43] Interestingly, the asymmetric hydrogenation of this β-keto ester, *N*-protected as an amine hydrochloride salt, provided the corresponding *anti*-(2*S*,3*R*)- and (2*R*,3*S*)-β-hydroxy-α-methyl esters with significant levels of selectivities through DKR (Scheme 24). Hence, the protecting group



Scheme 23. Synthesis of sulfobacin A.

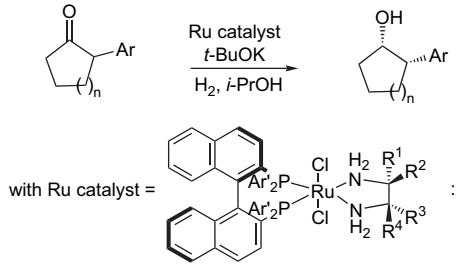
of the proline moiety turned out to play a crucial role in the stereochemical outcome of the asymmetric hydrogenation. The (2*R*,3*R*)-hydroxy-α-methyl ester was further converted into the expected natural anticancer agent, (2*R*,3*R*)-dolaproine.



Scheme 24. Ru-catalysed hydrogenations of β-keto-α-methyl esters derived from L-proline.

The application of dynamic kinetic discrimination to the ruthenium-catalysed hydrogenation of cyclic ketones, such as 2-arylated cycloalkanones, was reported by Noyori et al. in 2004.[44] Hence, the asymmetric hydrogenation of various 2-arylcycloalkanones with *trans*-$RuCl_2$(BINAP)(1,2-diamine) and *t*-BuOK in isopropanol selectively gave the corresponding *cis*-2-arylcycloalkanols in excellent enantiomeric purity and quantitative yield, as shown in Scheme 25.

Since the ketone enantiofaces are differentiated on the chiral molecular surface of the saturated RuH_2 complex, a suitable



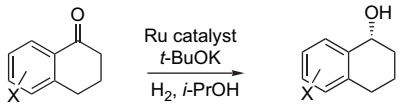
Ar = Ph, n = 1, Ar' = 3,5-$(Me)_2C_6H_3$, $R^1 = R^2$ = *p*-$MeOC_6H_4$, R^3 = H, R^4 = *i*-Pr: 100% de = 100% ee = 98%
Ar = Ph, n = 2, Ar' = *p*-Tol, $R^1 = R^4$ = Ph, $R^2 = R^3$ = H: 100% de = 100% ee = 100%
Ar = *p*-$MeOC_6H_4$, n = 2, Ar' = *p*-Tol, $R^1 = R^4$ = Ph, $R^2 = R^3$ = H: 100% de = 100% ee = 99.5%
Ar = *p*-$CF_3C_6H_4$, n = 2, Ar' = *p*-Tol, $R^1 = R^4$ = Ph, $R^2 = R^3$ = H: 100% de = 100% ee = 98%
Ar = 1-Naph, n = 2, Ar' = *p*-Tol, $R^1 = R^4$ = Ph, $R^2 = R^3$ = H: > 99% de > 98% ee > 99%
Ar = Ph, n = 3, Ar' = *p*-Tol, $R^1 = R^4$ = H, $R^2 = R^3$ = Ph: 100% de = 100% ee = 95%

Scheme 25. Ru-catalysed hydrogenation of 2-arylcycloalkanones.

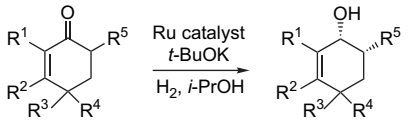
combination of the catalyst and substrate is necessary for high efficiency in this type of reactions. The enantioselectivity and reaction rate are affected by subtle changes in the electronic and steric parameters of the Ru complexes and ketones. No universal chiral catalysts exist because of the structural diversity of the ketonic substrates. Thus, as an example, the hydrogenation of 1-tetralones has remained very slow and poorly enantioselective by using the same catalyst as that depicted in Scheme 25, *trans*-$RuCl_2$(BINAP)(1,2-diamine). In 2004, Noyori et al. reported, however, that the replacement of conventional 1,2-diamine ligands by certain chiral 1,4-diamines could solve this difficult problem. Hence, a chiral $RuCl_2$-(BINAP)(1,4-diamine)/*t*-BuOK combined system promoted the hydrogenation of various 1-tetralone derivatives, affording the corresponding 1-tetralols in up to 99% ee and quantitative yield (Scheme 26).[45] Very recently, the scope of this methodology was extended to the asymmetric hydrogenation of α-amidopropiophenones catalysed by the closely related $RuCl_2$[(*S*)-TolBINAP][(*R*)-DMAPEN] (DMAPEN=2-dimethylamino-1-phenylethylamine).[46] Using these conditions, the corresponding *syn* alcohols were obtained in up to 99% ee and >98% de.

Another catalyst, such as an (*S*,*S*)-TsDPEN-based-ruthenium complex, was involved in the DKR-hydrogenation process of various ketones, providing the corresponding *syn* products with up to 97% de and 98% ee, as shown in Scheme 27.[47]

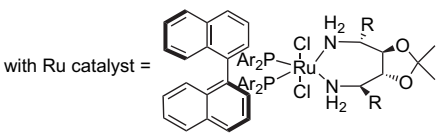
Very recently, List and Li reported the asymmetric hydrogenation of α-arylaldehydes catalysed by [$RuCl_2$(Xyl-BINAP)(DPEN)], providing the corresponding primary



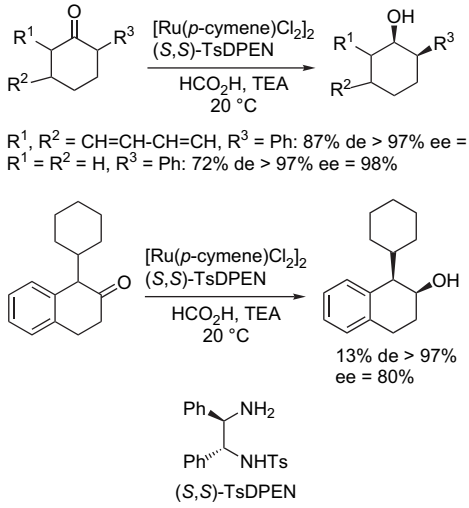
X = H, Ar = 3,5-$(Me)_2C_6H_3$, R = Me: 100% ee = 99%
X = 5-MeO, Ar = *p*-Tol, R = Me: 100% ee = 98%
X = 6-MeO, Ar = *p*-Tol, R = Me: 98% ee = 92%
X = 7-MeO, Ar = 3,5-$(Me)_2C_6H_3$, R = Me: 100% ee = 99%
X = 7-F, Ar = 3,5-$(Me)_2C_6H_3$, R = Me: 100% ee = 98%
X = 5,7-$(Me)_2$, Ar = Ph, R = Me: 100% ee = 95%
X = 4,4-$(Me)_2$, Ar = *p*-Tol, R = Me: 100% ee = 93%



R^1, R^2 = CH=CH-O, $R^3 = R^4 = R^5$ = H, Ar = *p*-Tol, R = Me: 98% ee = 96%
R^1, R^2 = CH=CH-CH=CH, $R^3 = R^4$ = H, R = R^5 = Me, Ar = Ph: 97% ee = 87%
$R^1 = R^3 = R^4$ = Me, $R^2 = R^5$ = H, Ar = *p*-Tol, R = Me: 99% ee = 96%
R = $R^1 = R^3 = R^4 = R^5$ = H, R^2 = Me, Ar = *p*-Tol: 100% ee = 80%



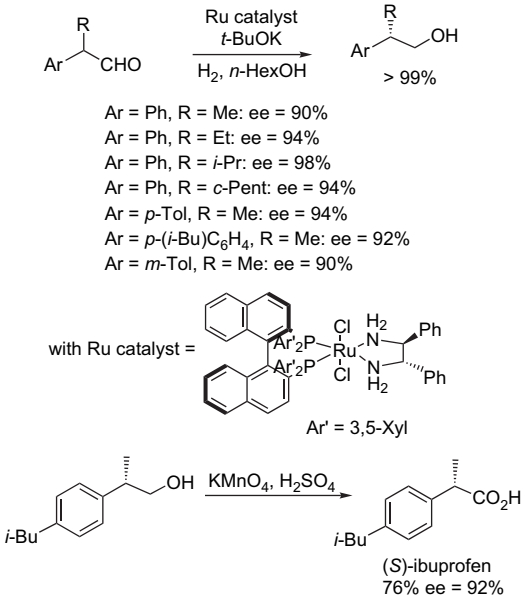
Scheme 26. Ru-catalysed hydrogenations of 1-tetralones.



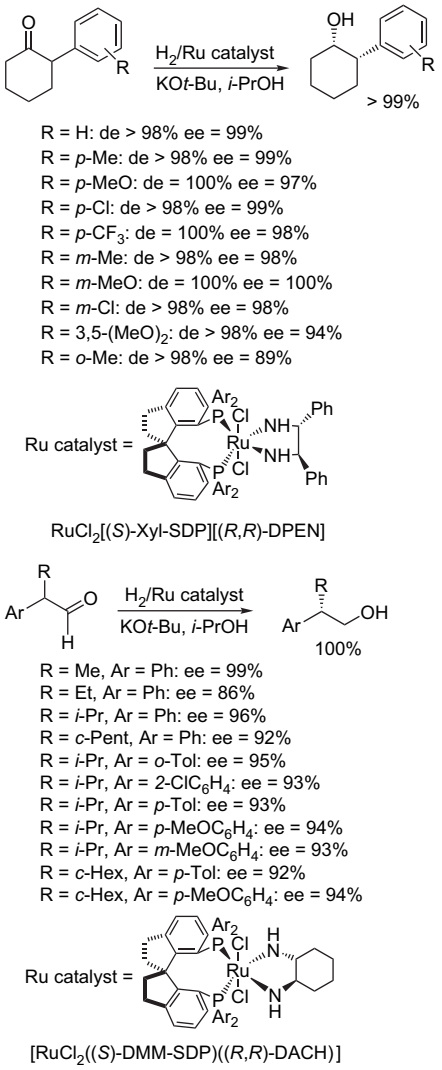
Scheme 27. Ru-catalysed hydrogenations of ketones.

alcohols in excellent enantioselectivities and yields (Scheme 28).[48] As an application of this reaction, the biologically active (*S*)-enantiomer of the non-steroidal anti-inflammatory drug, ibuprofen, could be synthesised via catalytic hydrogenation of the corresponding aldehyde followed by oxidation with potassium permanganate in 76% isolated yield and 92% ee.

A novel class of chiral spirodiphosphine (SDP) ligands has been developed by Zhou et al.[49] A chiral SDP-based Ru catalyst, such as [$RuCl_2$(Xyl-SDP)(DPEN)], was demonstrated to be a very effective catalyst for the highly enantioselective hydrogenation of α-arylcyclohexanones, providing the corresponding α-arylcycloalkanols in excellent cis/trans stereoselectivity (>98% de) and enantioselectivity (up to 100% ee), as shown in Scheme 29. As an extension of this work, another SDP-based Ru catalyst, [$RuCl_2$((*S*)-DMM-SDP)((*R*,*R*)-DACH)], was successfully applied to the enantioselective hydrogenation of α-arylaldehydes, providing an efficient synthesis of optically active primary alcohols (Scheme 29).[50]



Scheme 28. Ru-catalysed hydrogenation of α-arylaldehydes.

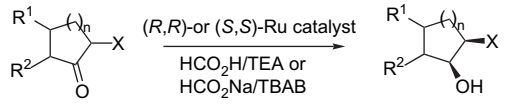


Scheme 29. Ru-catalysed hydrogenations of ketones and aldehydes.

In 2006, Lassaletta et al. extended the scope of the preceding methodology to a variety of cyclic α-haloketones, offering an efficient tool for the synthesis of chiral halohydrins, including bromo-, chloro- and even fluorohydrins in good-to-excellent yields and stereoselectivities, using either HCO_2H/TEA or HCO_2H/TBAB as the hydrogen source (Scheme 30).[51]

The highly enantioselective and quantitative hydrogenation of α-phthalimidyl ketones was studied in 2004 by Zhang et al., using a ruthenium catalyst based on the TunePhos ligand.[52] The substrate scope, summarised in Scheme 31, shows that both electron-deficient and -rich aryl ketones could be reduced with very high enantioselectivity. Moreover, the position of the substituents was also widely compatible with the highly enantioselective reduction. In addition, the compatibility of functional groups such as fluoride, chloride and even the versatile bromide was also checked.

In 2003, a highly enantioselective hydrogenation of a piperidone hydrochloride was used as the key step of an efficient enantioselective synthesis of an NMDA 2B receptor antagonist, Ro 67-8867.[53] The chiral diphosphine ligand belonged to the MeOBIPHEP family, as depicted in Scheme 32.



with (*S*,*S*)-Ru catalyst and with HCO_2H/TEA:

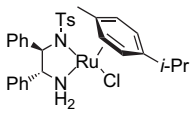
R^1, R^2 = CH=CH-CH=CH, X = Cl, n = 1: 88% de > 98% ee = 98%
$R^1 = R^2$ = H, X = Cl, n = 1: 80% de = 80% ee = 60%

with (*S*,*S*)-Ru catalyst and with HCO_2Na/TBAB:

R^1, R^2 = CH=CH-CH=CH, X = Cl, n = 1: 84% de > 98% ee > 99%
$R^1 = R^2$ = H, X = Br, n = 2: 64% de > 98% ee = 96%
$R^1 = R^2$ = H, X = Br, n = 1: 80% de > 98% ee = 45%
$R^1 = R^2$ = H, X = Br, n = 2: 84% de = 70% ee = 80%

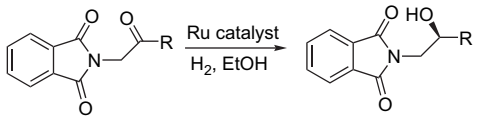
with (*R*,*R*)-Ru catalyst and with HCO_2H/TEA:

R^1, R^2 = CH=CH-CH=CH, X = Cl, n = 2: 71% de > 98% ee > 99%
$R^1 = R^2$ = H, X = F, n = 1: 92% de > 98% ee = 92%
R^1, R^2 = CH=CH-CH=CH, X = F, n = 2: 98% de = 94% ee = 97%
$R^1 = R^2$ = H, X = Cl, n = 2: 79% de = 94% ee = 90%



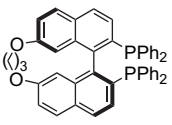
(*R*,*R*)-Ru catalyst

Scheme 30. Ru-catalysed hydrogenation of cyclic α-haloketones.



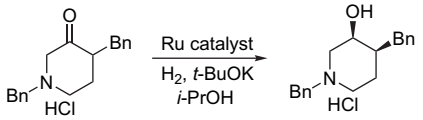
Ru catalyst = $[NMe_2H_2][\{RuCl(S)\text{-TunePhos}\}_2(\mu\text{-}Cl)_3]$

R = *p*-$MeOC_6H_4$: 100% ee = 95%
R = *p*-Tol: 100% ee > 99%
R = *p*-FC_6H_4: 100% ee > 99%
R = *p*-ClC_6H_4: 100% ee = 92%
R = *p*-BrC_6H_4: 100% ee > 99%
R = *m*-$MeOC_6H_4$: 100% ee > 99%
R = *o*-$MeOC_6H_4$: 100% ee > 99%
R = Me: 100% ee > 99%
R = Et: 100% ee > 99%

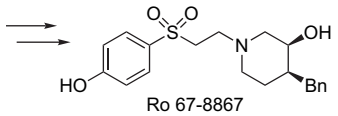


(*S*)-TunePhos

Scheme 31. Ru-catalysed hydrogenation of α-phthalimidyl ketones.

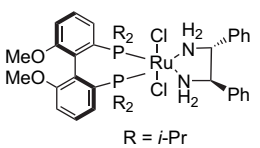


100% de > 98%
ee = 97%



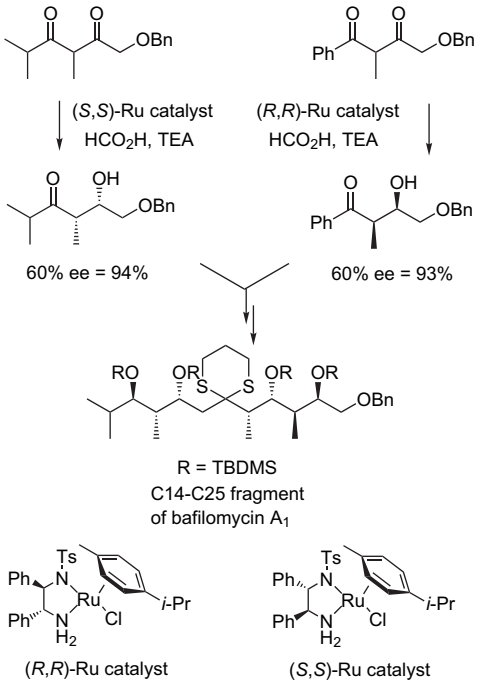
Ro 67-8867

Ru catalyst = $[RuCl_2((S)\text{-MeO-}i\text{-Pr-MeOBIPHEP})((R,R)\text{-DPEN})]$:



R = *i*-Pr

Scheme 32. Synthesis of Ro 67-8867.



Scheme 33. Synthesis of the C14–C25 fragment of bafilomycin A_1.

In the course of their study on the hydrogenation of 2-alkyl-1,3-diketones, Cossy et al. have achieved the synthesis of the C14–C25 fragment of biologically active natural bafilomycin A_1 in 11 steps in a sequence involving two enantioselective transfer-hydrogenation steps induced by chiral Ru complexes.[54] These reactions, catalysed by chiral ruthenium catalysts, set the C15, C16, C21 and C22 stereogenic centres via DKR, as depicted in Scheme 33.

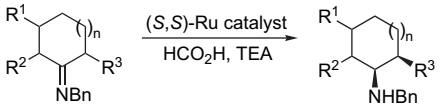
The first example of an asymmetric reduction of C=N bonds proceeding via DKR was reported in 2005 by Lassaletta et al.[55] Hence, the transfer-hydrogenation of 2-substituted bicyclic and monocyclic ketimines could be accomplished via DKR by using HCO_2H/TEA as the hydrogen source and a TsDPEN-based Ru(II) catalyst, affording the corresponding *cis*-cycloalkylamines with moderate-to-excellent levels of diastereo- and enantioselectivity (Scheme 34).

On the other hand, a chiral ruthenium catalyst, prepared from a chiral PN ligand derived from L-proline, was applied in 2005 to the asymmetric isomerisation of racemic allylic alcohols via DKR.[56] This new type of reaction was applicable to the asymmetric synthesis of muscone, as shown in Scheme 35.

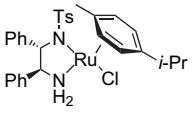
2.2.2. DKR catalysed by metals other than ruthenium

Chiral palladium complexes have also been used in the context of DKR. As an example, Trost and Toste have developed the palladium-catalysed DKR of γ-acyloxybutenolides and applied this methodology to the first enantioselective total synthesis of (−)-aflatoxins B_{2a} and B_1 (Scheme 36).[57]

Similar conditions were applied to a palladium-catalysed asymmetric allylic alkylation, effecting a DKR transformation of racemic isoprene monoepoxide and a surrogate for Nazarov's reagent in which a quaternary centre was created with

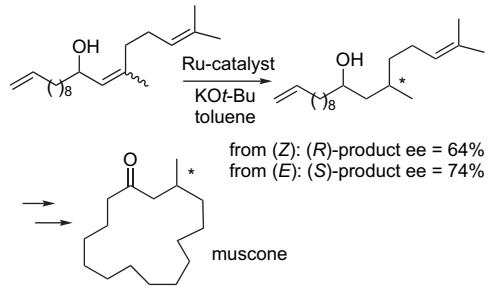


R^1, R^2 = CH=CH-CH=CH, R^3 = Me, n = 0:
70% de > 98% ee = 96%
R^1, R^2 = CH=CH-C(Me)=CH, R^3 = allyl, n = 0:
67% de > 98% ee = 92%
R^1, R^2 = CH=CH-C(Me)=CH, R^3 = Me, n = 0:
82% de > 98% ee = 97%
R^1 = R^2 = H, R^3 = allyl, n = 1:
75% de = 86% ee = 63%
R^1 = R^2 = H, R^3 = $(CH_2)_2CN$, n = 1:
60% de = 88% ee = 72%
R^1 = R^2 = H, R^3 = Ph, n = 1:
55% de > 98% ee = 50%



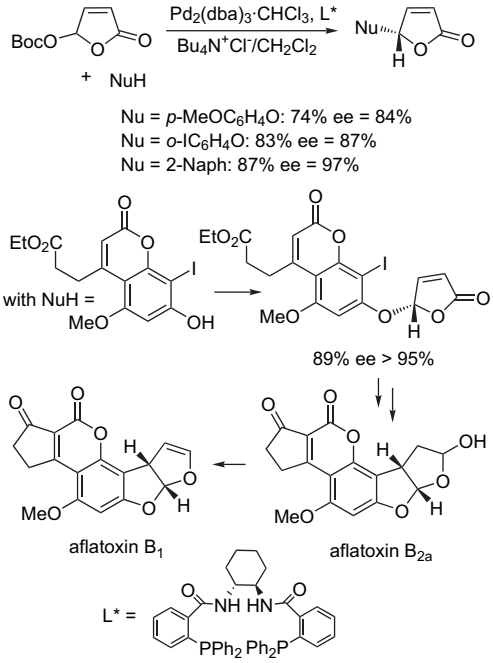
(S,S)-Ru catalyst

Scheme 34. DKR of cyclic ketimines.

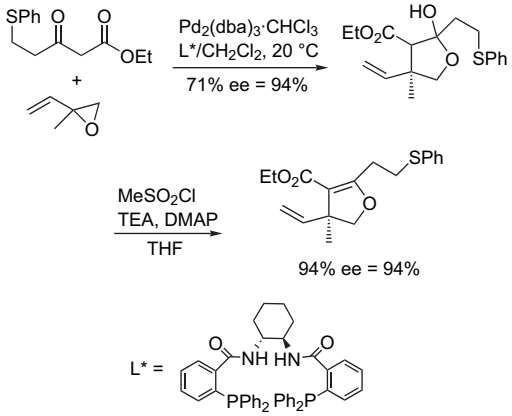


Cp*RuCl[(S)-Ph_2PCH_2-CHR^1NHR^2-k^2-P,N]
R^1, R^2 = $(CH_2)_3$, Cp* = η^5-pentamethylcyclopentadienyl

Scheme 35. Synthesis of muscone.



Scheme 36. Synthesis of aflatoxins B_1 and B_{2a}.



Scheme 37. Synthesis of cyclopentyl core of viridenomycin.

excellent ee (Scheme 37).[58] The resulting product allowed easy access to a substrate for ring-closing metathesis to form a cyclopentenone and set the stage for an 11-step synthesis of the cyclopentyl core of the antibiotic antitumour agent, viridenomycin. The scope of this methodology was extended to oxygen nucleophiles, such as unsaturated alcohols, which led, by reaction with racemic butadiene or isoprene monoepoxide, to the formation of the corresponding 3-alkoxy-4-hydroxy-1-butene or 3-alkoxy-4-hydroxy-3-methyl-1-butene, respectively, with excellent regio- and enantioselectivity (up to 96% ee).[59] These chiral oxygen heterocycles were further converted into various nucleosides, providing a further demonstration of the value of this methodology.

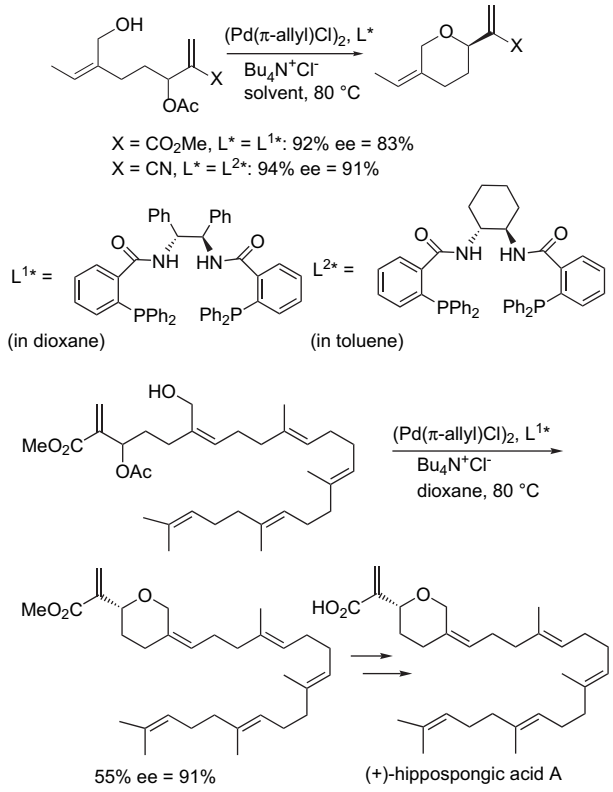
In addition, the same group has studied the ability to use aliphatic alcohols as competent nucleophiles in the palladium-catalysed dynamic kinetic asymmetric transformation of Baylis–Hillman adducts.[60] The corresponding substituted pyran products were obtained in high yields and enantioselectivities, as shown in Scheme 38. The utility of this method was further demonstrated in the context of a concise total synthesis of the gastrulation inhibitor, (+)-hippospongic acid A.

The ligand L^{2*} shown in Scheme 38 was also involved by Gais and Lüssem in palladium-catalysed enantioselective allylic alkylation[61] of thiocarboxylate ions with racemic allylic esters.[62] This novel DKR has allowed access to highly enantioenriched acyclic allylic thioesters in good-to-high yields (Scheme 39).

The same group has successfully applied similar conditions to the palladium-catalysed asymmetric synthesis of allylic alcohols from unsymmetrical and symmetrical racemic allylic carbonates and acetates (Scheme 40).[63]

In 2006, Stephenson et al. reported the involvement of a DKR process during an intramolecular asymmetric Heck reaction carried out in the presence of a BINAP-based Pd catalyst.[64] It was shown that chiral helical conformations of the starting 2-iodoanilide interconverted through internal bond rotations, leading to the proposal of a DKR mechanism to account for the switch of enantioselectivity (Scheme 41).

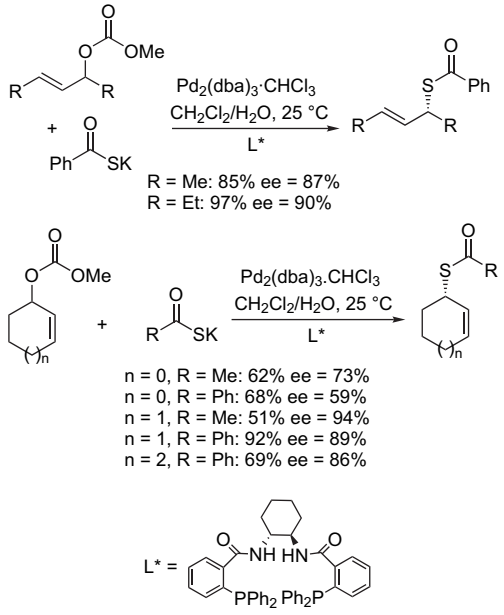
In addition, Durand et al. have very recently used an axially chiral monodentate phosphine, such as (*R*)-Ph-BINEPINE



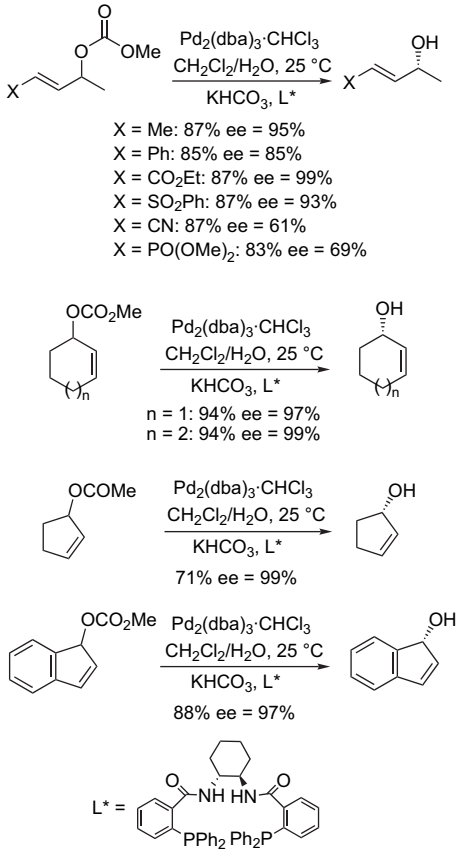
Scheme 38. DKRs of Baylis–Hillman adducts.

(Scheme 42), as a chiral resolving agent of a racemic palladium complex prepared from a 2-ferrocenyl-1,10-phenanthroline ligand.[65] The reaction evolved through a DKR process, leading after recrystallisation, to the isolation of only one of the two possible diastereoisomers.

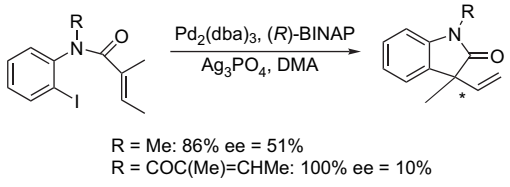
On the other hand, Hamada et al. have developed rhodium-catalysed asymmetric hydrogenation of α-amino-β-ester hydrochlorides via DKR.[66] The reaction proceeded with the catalyst derived from an Rh complex and a chiral ferrocenylphosphine under hydrogen in the presence of sodium acetate in acetic acid to afford the corresponding *anti*-β-hydroxy-α-amino esters with 58–83% ee in a diastereomeric ratio of 92:8 to 97:3 (Scheme 43).



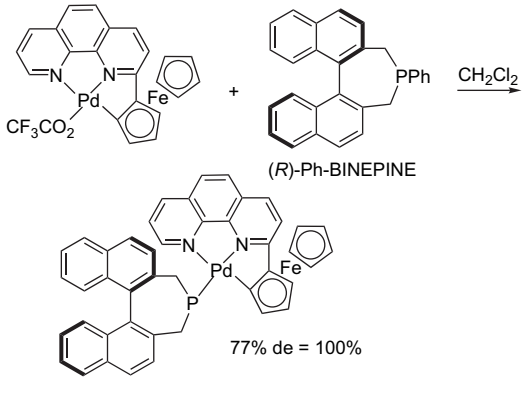
Scheme 39. DKRs of allylic esters.



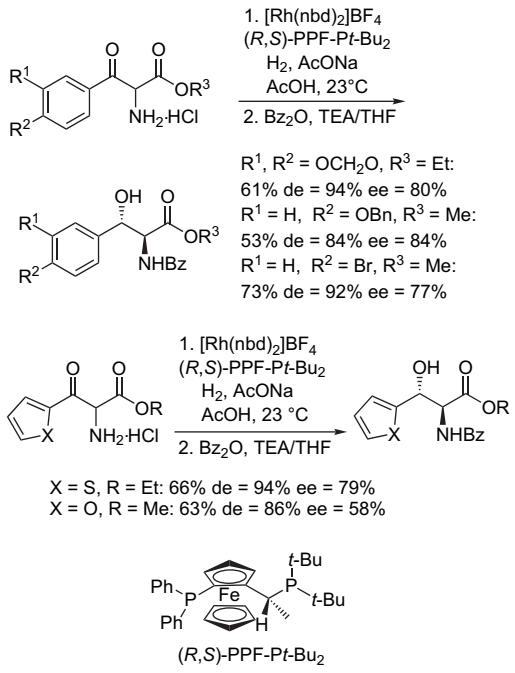
Scheme 40. DKRs of allylic carbonates and acetates.



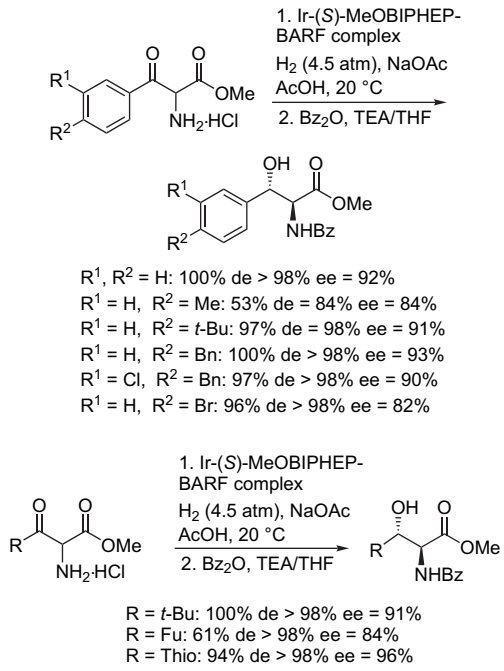
Scheme 41. Intramolecular Heck reaction.



Scheme 42. DKR of a palladium complex.



Scheme 43. Rh-catalysed hydrogenations of α-amino-β-ester hydrochlorides.

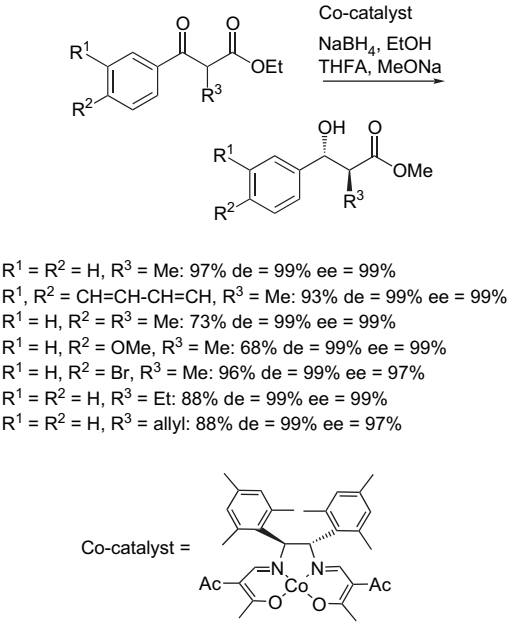


Scheme 44. Ir-catalysed hydrogenations of α-amino-β-ester hydrochlorides.

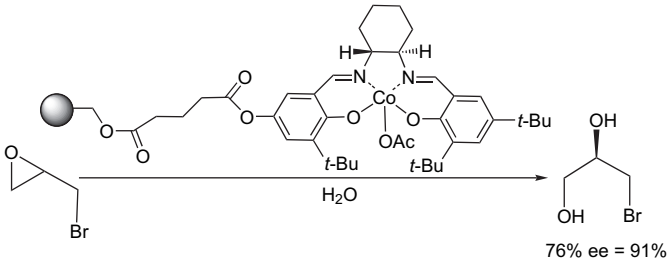
The same reactions as those depicted in Scheme 43 were previously carried out by Hamada et al. in 2004 in the presence of an Ir–MeOBIPHEP catalyst, providing excellent yields and *anti*-diastereoselectivities (>98% de) with ee values ranging from 75% to 95%.[67] However, a high hydrogen pressure (100 atm) and a tedious degasing operation by freeze–thaw cycles in the preparation of the catalyst and the stage prior to hydrogenation were essential for a smooth reaction and these conditions made it difficult to run this hydrogenation in a practical sense. The same group has more recently reported similar reactions under a low hydrogen pressure catalysed by an easily handled cationic iridium complex with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) as a counterion.[68] Scheme 44 summarises the utility of this new Ir catalyst in hydrogenation via DKR under mild conditions, allowing high diastereo- and enantioselectivities to be obtained.

In 2003, a chiral β-ketoiminato cobalt(II) complex was used by Yamada et al. to catalyse the enantioselective borohydride reduction of 2-substituted 3-keto esters via DKR.[69] High diastereo- and enantioselectivities for the produced *anti*-2-substituted-3-hydroxy esters were achieved with the addition of an alkali metal alkoxide such as MeONa (Scheme 45). The reduction was accomplished by using premodified borohydride arising from $NaBH_4$, tetrahydrofurfuryl alcohol (THFA) and ethanol.

In 2005, Kunz et al. developed new composite materials, which ideally combined polymer functionalisation with good mass-transfer properties of monolithic carriers.[70] This unique combination led to versatile materials for organic synthesis, which could be used in a flow-through mode. Based on these monolithic materials with different polymer functionalities, a wide variety of reactions were conducted, such as the example of DKR depicted in Scheme 46.

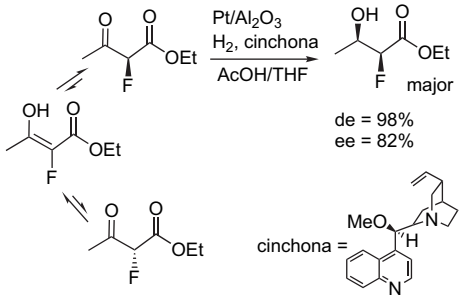


Scheme 45. Borohydride reduction of 2-substituted 3-ketoesters.



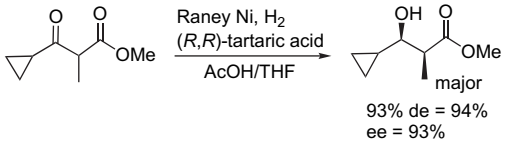
Scheme 46. Polymer-supported DKR with a cobalt catalyst.

In 2006, Szöllosi et al. reported the enantioselective hydrogenation of ethyl 2-fluoroacetoacetate performed over a cinchona alkaloid-modified supported platinum catalyst.[71] This novel method for producing chiral α-fluoro-β-hydroxy esters was the first example of DKR of a chirally labile racemic fluorinated compound over a modified heterogeneous metal catalyst carried out without using supplementary additives (bases), except the chiral modifier (Scheme 47).



Scheme 47. DKR over cinchona-modified platinum catalyst.

On the other hand, the enantiomer-differentiating hydrogenation of methyl 3-cyclopropyl-2-methyl-3-oxopropanoate was achieved by Sugimura et al. by using tartaric acid-modified nickel as the heterogeneous catalyst (Scheme 48).[72]

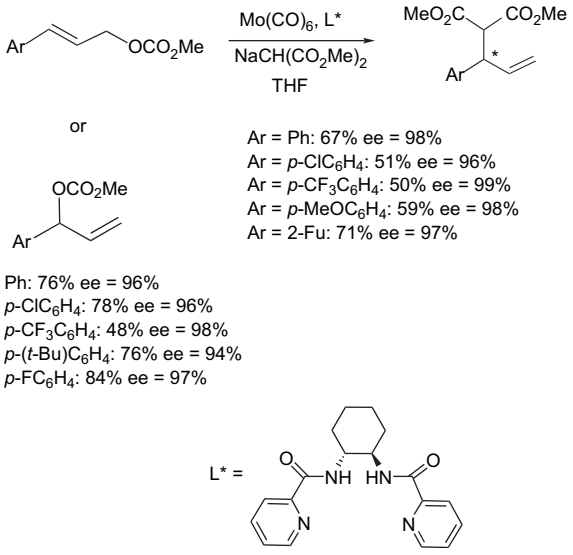


Scheme 48. DKR with a heterogeneous modified nickel catalyst.

Highly regio- and enantioselective molybdenum-catalysed allylic alkylations have become a powerful synthetic tool during the past few years. The operating mechanism for these reactions was studied by Belda and Moberg in 2004, and these workers confirmed the occurrence of a DKR.[73] High yields combined with an extremely high enantioselectivity were obtained in the presence of a chiral bis(pyridylamide) ligand and a cheap molybdenum catalyst, such as $Mo(CO)_6$ (Scheme 49). In contrast to the Pd-catalysed reaction, the Mo-catalysed reaction is characterised by its high tendency to form the more substituted products from unsymmetrical substrates. This methodology was applied to the synthesis of several biologically active compounds, such as a non-peptidic human immunodeficiency virus (HIV) protease inhibitor, tipranavir, and (*R*)-baclofen.

In 2005, Buchwald et al. reported the first total synthesis of eupomatilone-3, on the basis of a DKR of an α,β-unsaturated butenolide, submitted to an asymmetric copper-catalysed conjugate reduction.[74] This was the first example of a copper-catalysed DKR of an unsaturated lactone, which was further extended to several γ-aryl-containing α,β-unsaturated butenolides, as depicted in Scheme 50.

In 2006, Mikami et al. reported the asymmetric synthesis of the antithrombotic agents, M58163 and M58169, involving a DKR process in the amide-formation step leading to the

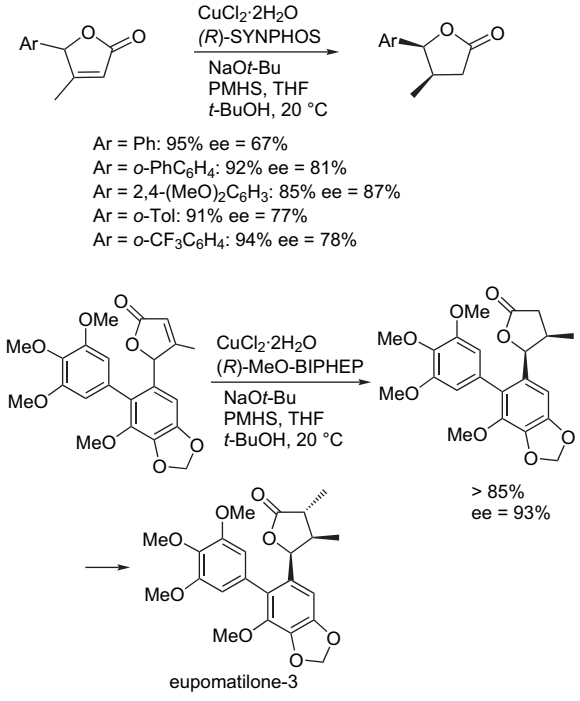


Scheme 49. Mo-catalysed allylic alkylation.

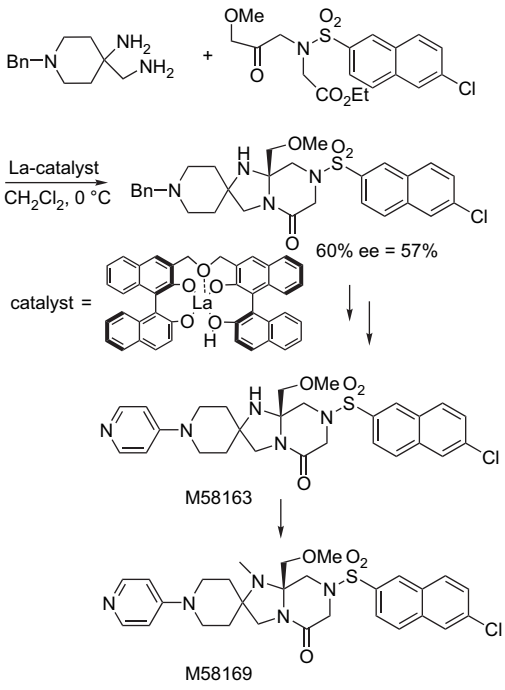
tricyclic key intermediate.[75] This step was catalysed by a La-linked BINOL complex, providing the corresponding chiral *N*,*N*-acetal, as depicted in Scheme 51.

A novel titanium(IV)-catalysed substitution of a carbon–oxygen bond by a carbon–carbon bond, which relied on a DKR process and led to products resulting from a highly enantioselective carbon allylation, was described in 2004 by Braun and Kotter.[76] By means of the chiral titanium complex depicted in Scheme 52, the substitution of a hydroxy, silyloxy, or alkoxy group by an allylic residue was possible, for the first time, in a DKR transformation.

A high level of enantioselectivity was obtained by Coldham et al. for the DKR of an *N*-Boc-2-lithiopyrrolidine in the



Scheme 50. DKRs of unsaturated lactones and synthesis of eupomatilone-3.

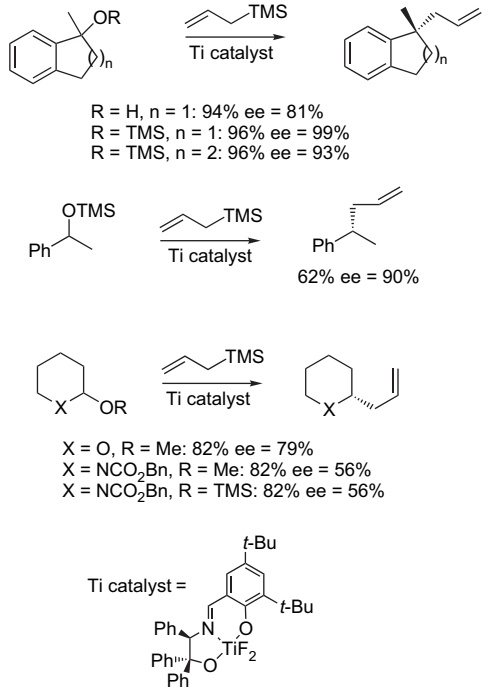


Scheme 51. La-catalysed DKR and synthesis of M58163 and M58169.

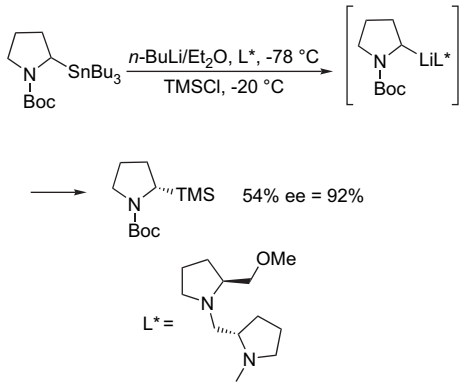
presence of *n*-butyllithium, a chiral ligand, and TMSCl as electrophile (Scheme 53).[77]

2.3. Organocatalysed DKR

While the end of the last century has been dominated by the use of metal catalysts,[78] a change in perception occurred during the last few years when several reports confirmed that relatively simple organic molecules could be highly effective and

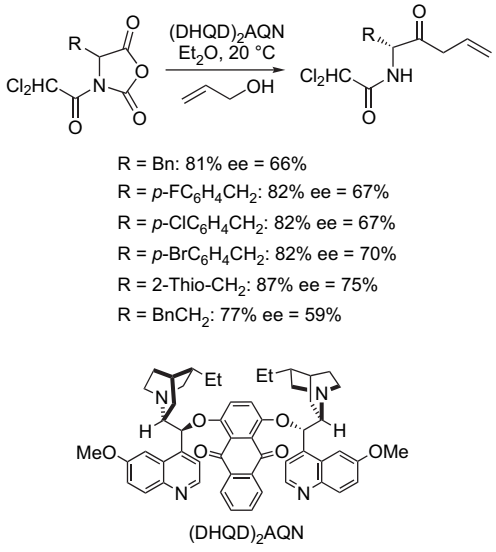


Scheme 52. Ti(IV)-catalysed DKRs of alcohols, ethers and acetals.

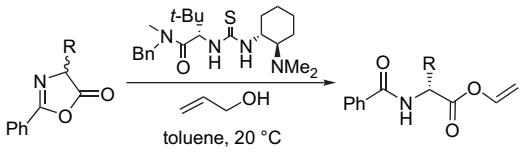


Scheme 53. DKR of an *N*-Boc-2-lithiopyrrolidine.

remarkably enantioselective catalysts of a variety of fundamentally important transformations. This rediscovery has initiated an explosive growth of research activities in organocatalysis, both in industry and in academia. Organocatalysts have several important advantages, since they are usually robust, inexpensive, readily available and non-toxic.[79,80] Enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications, regarding the applications of this type of reactions, which paint a comprehensive picture for their real possibilities in organic synthesis. Even though transition metal-catalysed enantioselective reactions will certainly continue to play a central role in synthetic organic chemistry in the future, the last few years have, however, seen an increasing trend towards the use of metal-free catalysts. Hence, the application of chiral organocatalysts has permitted the preparation of a number of very valuable chiral products with the exclusion of any trace of hazardous metals and with several advantages from an economical and environmental point of view. In recent years, the first examples of organocatalysed DKR processes have been described, such as those involving *N*-carboxyanhydrides bearing alkyl substituents under catalysis with cinchona alkaloids.[81] Indeed, modified cinchona alkaloids could be applied as dual-function catalysts to catalyse both the



Scheme 54. Cinchona alkaloid-catalysed DKR of *N*-carboxyanhydrides.

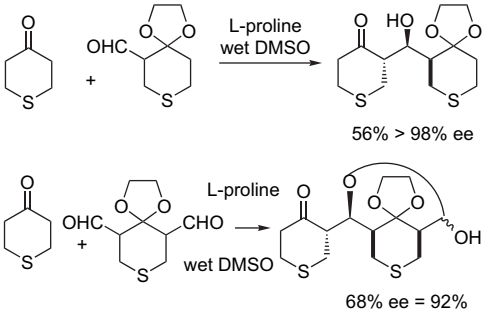


Scheme 55. Thiourea-catalysed DKR of azlactones.

racemisation and alcoholytic kinetic resolution of alkyl *N*-carboxyanhydrides bearing an electron-withdrawing *N*-protecting group, leading to a DKR converting racemic *N*-carboxyanhydrides into the corresponding amino esters in good yields and enantioselectivities (Scheme 54).

In 2005, Berkessel et al. reported the highly enantioselective alcoholytic DKR of azlactones catalysed by a thiourea-based bifunctional organocatalyst (Scheme 55).[82] This novel methodology provided a direct access to a wide range of protected natural and non-natural α-amino acids in high enantiomeric excesses. The scope of this process was extended in 2006 by the same group through the synthesis of a library of bifunctional (thio)urea-based organocatalysts and their screening in the DKR of azlactones, providing similar excellent results.[83]

An enantioselective direct aldol reaction was reported in 2005 by Ward et al., who showed that proline-catalysed reactions of tetrahydro-4*H*-thiapyranone with racemic 1,4-dioxa-8-thiaspiro[4.5]decane-6-carboxaldehyde and with *meso*/*dl* 1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde proceeded via DKR and gave single adducts with excellent enantioselectivities (Scheme 56).[84] The high enantiotopic group selectivity resulted from the high intrinsic diastereofacial selectivity of the aldehydes. Since the first reaction, depicted in Scheme 56, was complicated on a larger scale, it was carried out more recently in the presence of a more soluble catalyst derived from L-proline, such as 5-pyrrolidin-2-yltetrazole, giving rise to the same product in 75% yield and >98% ee. This reaction was the key step of an efficient synthesis of serricornin, a sex heromone.[85]

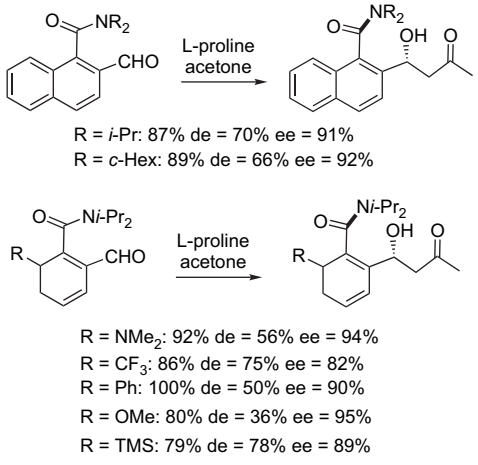


Scheme 56. L-Proline-catalysed DKRs of 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and 1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde.

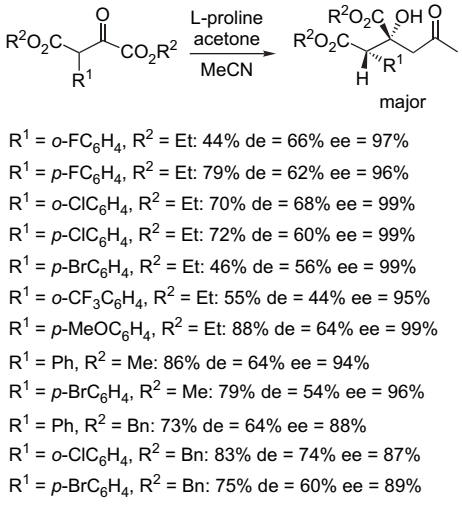
In 2004, Walsh et al. developed L-proline-catalysed aldol reactions of atropisomeric amides such as benzamides and naphthamides.[86] The DKR process simultaneously established the stereochemistry of the atropisomeric amide chiral axis and a stereogenic centre, providing high enantioselectivities (Scheme 57).

Very recently, Zhang et al. reported the DKR of 2-oxo-3-aryl-succinates by L-proline-catalysed aldol addition of acetone in acetonitrile at room temperature, providing the corresponding products in good yield with up to 74% de and high ee up to 99% (Scheme 58).[87]

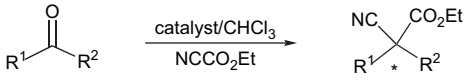
The development of the first highly enantioselective cyanocarbonation of prochiral ketones promoted by a chiral base catalyst, such as a cinchona alkaloid derivative, was reported by Deng and Tian in 2006.[88] Importantly, the reaction complemented known enzyme- and transition metal-based methods in substrate scope via its unique ability to promote highly enantioselective cyanocarbonation of sterically hindered simple dialkyl ketones. Mechanistic studies provided experimental evidence to shed significant light on the asymmetric induction step in which the modified cinchona alkaloid acted as a chiral nucleophilic catalyst. Moreover, experimental evidence supported the mechanistic proposal that the ee determination step in the cyanocarbonation was a DKR of the putative intermediates **A** and **B** via asymmetric transfer of the alkoxycarbonyl group (Scheme 59).



Scheme 57. L-Proline-catalysed DKRs of atropisomeric amides.



Scheme 58. L-Proline-catalysed DKR of 2-oxo-3-aryl-succinates.



with catalyst = $(DHQD)_2AQN$:

R^1 = *n*-Pent, R^2 = Me: 53% ee = 64%

R^1 = *i*-Pr, R^2 = Me: 51% ee = 76%

R^1 = $CH(allyl)_2$, R^2 = Me: 54% ee = 81%

R^1, R^2 = $(CH_2)_5$: 52% ee = 87%

R^1 = *t*-Bu, R^2 = Me: 55% ee = 88%

R^1, R^2 = $(Me)_2C$-$(CH_2)_4$: 62% ee = 91%

with catalyst = DHQD-PHN:

R^1 = $CH(n\text{-}Pr)_2$, R^2 = Me: 86% ee = 96%

R^1 = $CMe(OMe)_2$, R^2 = Me: 63% ee = 85%

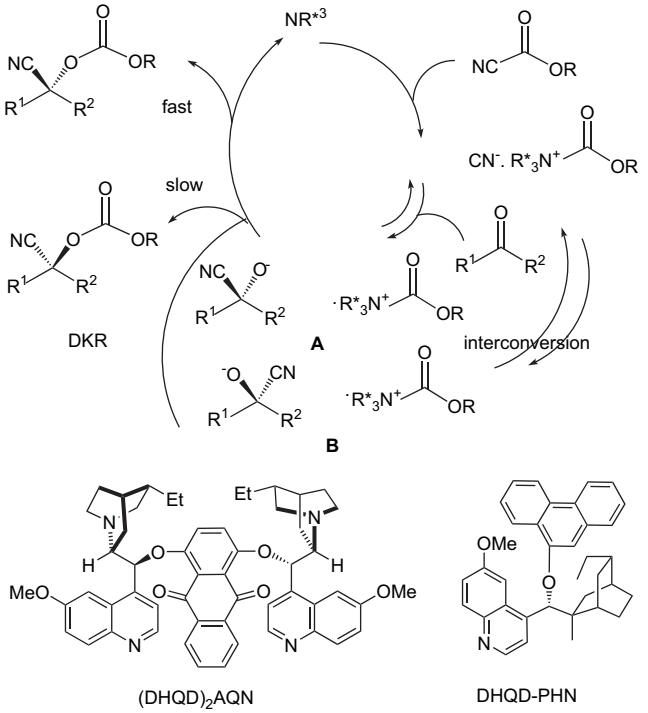
R^1 = $CMe(OEt)_2$, R^2 = Me: 65% ee = 90%

R^1, R^2 = $(Me)_2C$-$(CH_2)_3$: 80% ee = 95%

R^1, R^2 = $(EtO)_2C$-$(CH_2)_3$: 99% ee = 94%

R^1, R^2 = $(EtO)_2C$-$(CH_2)_4$: 78% ee = 96%

mechanism:



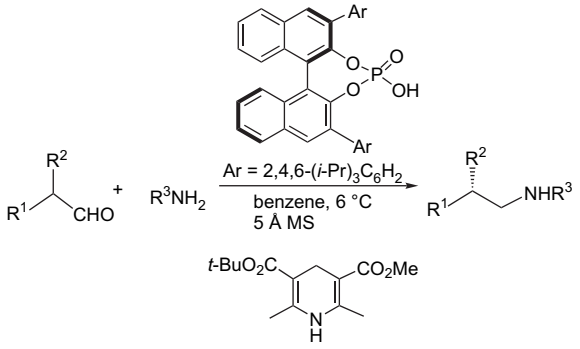
Scheme 59. Cinchona alkaloid-catalysed cyanocarbonation of ketones.

Catalytic asymmetric reductive aminations of carbonyl compounds are useful for the synthesis of chiral amines and are also powerful C–N bond-forming fragment coupling reactions.[89] Surprisingly few laboratory methods are known for enantioselective reductive amination. In 2006, List et al. reported asymmetric organocatalytic reductive aminations of aldehydes using a BINOL phosphoric acid catalyst and Hantzsch esters.[90] Hence, an efficient enantioselective reductive amination of α-branched aldehydes with aromatic amines was developed via DKR. This process was broad in scope, since both aromatic and aliphatic aldehydes could be used, although the enantiomeric ratios were typically lower with simple aliphatic aldehydes, as shown in Scheme 60.

In 2004, Krische et al. demonstrated that exposure of Morita–Baylis–Hillman acetates to tertiary phosphine catalysts in the presence of 4,5-dichlorophthalimide enabled regiospecific allylic substitution through a tandem S_N2'–S_N2' mechanism.[91] Through the use of the chiral phosphine catalyst, (*R*)-Cl-MeO-BIPHEP, the racemic Morita–Baylis–Hillman acetate depicted in Scheme 61 was converted into the corresponding enantiomerically enriched allylic amination product, thus establishing the feasibility of DKR.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides. Substance P antagonists are used to treat many ailments ranging from gastrointestinal and central nervous system disorders to inflammatory diseases, pain, and migraine. In 2006, Nugent and Seemayer developed an efficient synthesis of a pivotal precursor to substance P antagonists, which have a core structure based on the quinuclidine skeleton.[92] The key step of the synthesis was the DKR of benzhydryl quinuclidinone achieved for the first time by using L-tartaric acid, as shown in Scheme 62.

On the other hand, the first example of a catalytic enantioselective synthesis of sulfinate esters through DKR of racemic



R^1 = Ph, R^2 = Me, R^3 = PMP: 87% ee = 96%

R^1 = *p*-Tol, R^2 = Me, R^3 = PMP: 86% ee = 94%

R^1 = $p\text{-}MeOC_6H_4$, R^2 = Me, R^3 = PMP: 81% ee = 94%

R^1 = $p\text{-}BrC_6H_4$, R^2 = Me, R^3 = PMP: 92% ee = 94%

R^1 = $o\text{-}FC_6H_4$, R^2 = Me, R^3 = PMP: 89% ee = 94%

R^1 = $m\text{-}FC_6H_4$, R^2 = Me, R^3 = PMP: 84% ee = 94%

R^1 = 1-Naph, R^2 = Me, R^3 = PMP: 85% ee = 98%

R^1 = 2-Naph, R^2 = Me, R^3 = PMP: 96% ee = 96%

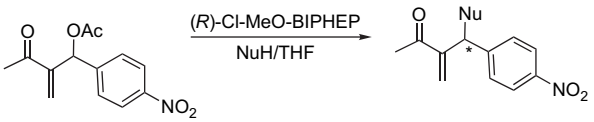
R^1 = Ph, R^2 = Et, R^3 = PMP: 92% ee = 98%

R^1 = R^3 = Ph, R^2 = Me: 78% ee = 94%

R^1 = *t*-Bu, R^2 = Me, R^3 = PMP: 77% ee = 80%

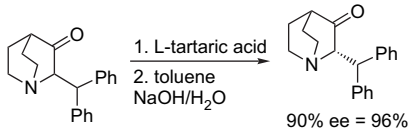
R^1 = CF_3, R^2 = Me, R^3 = PMP: 40% ee = 80%

Scheme 60. Reductive amination of aldehydes catalysed by a BINOL-derived phosphoric acid.



Nu = Phthalimide: 80% ee = 56%

Scheme 61. DKR of Morita–Baylis–Hillman acetate catalysed by (*R*)-Cl-MeO-BIPHEP.

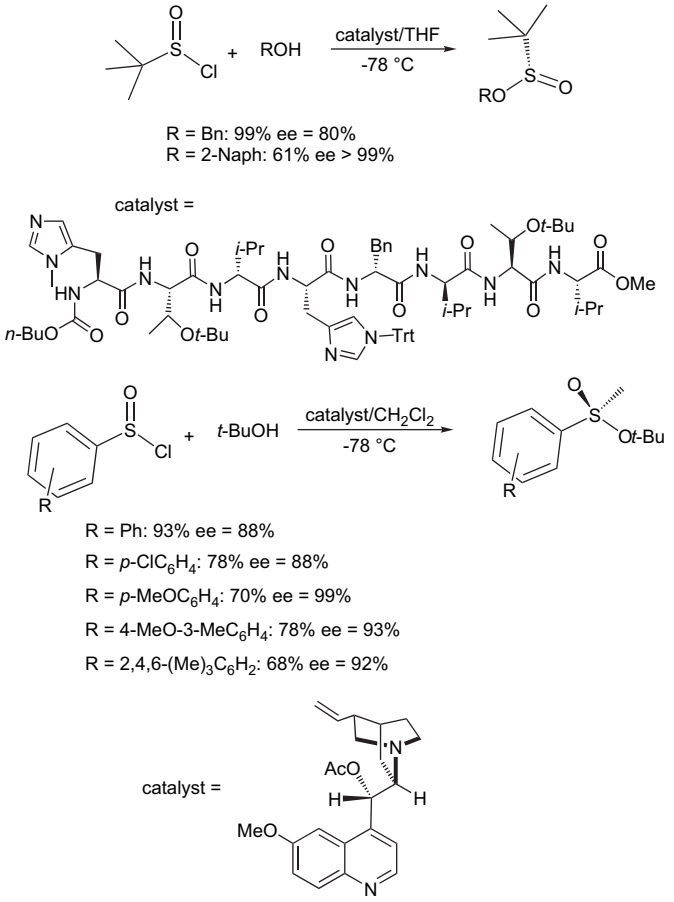


Scheme 62. DKR of benzhydryl quinuclidinone catalysed by L-tartaric acid.

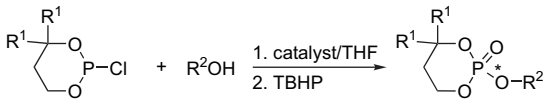
tert-butanesulfinyl chloride was reported in 2004 by Ellman et al.[93] The higher enantioselectivities for the organocatalytic enantioselective sulfinyl transfer were obtained by using an *N*-methyl imidazole-containing octapeptide as the organocatalyst (Scheme 63). In 2005, a similar reaction was performed by Toru et al. in the presence of a cinchona alkaloid as the organocatalyst.[94] The results obtained for the sulfinylation of *t*-BuOH by a combination of various arenesulfinyl chlorides in the presence of quinidine acetate as the organocatalyst are summarised in Scheme 63.

In addition, Hayakawa et al. have revealed the first example of the asymmetric synthesis of a *P*-chiral trialkyl phosphate via a trialkyl phosphite, in which the keystone was DKR in the condensation of a dialkyl phosphorochloridite and an alcohol by the catalytic assistance of a chiral amine, such as a cinchona alkaloid (Scheme 64).[95]

In the same context, Daran et al. have described the DKR of a chlorophosphine accomplished by treatment with a chiral disulfide in the presence of $Et_4N^+Cl^-$, leading to the corresponding (−)-(*S*)-phosphinoyl chloride in 70% ee, as shown in Scheme 65.[96]



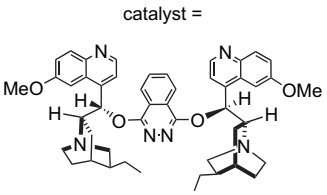
Scheme 63. Organocatalysed DKRs of sulfinyl chlorides.



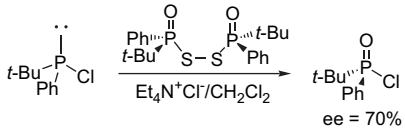
R^1 = Me, R^2 = (*E*,*E*)-(Me)CH=CH-CH=CH-CH_2: 69% ee = 64%

R^1 = Et, R^2 = (*E*,*E*)-(Me)CH=CH-CH=CH-CH_2: 49% ee = 24%

R^1 = Me, R^2 = Bn: 80% ee = 76%



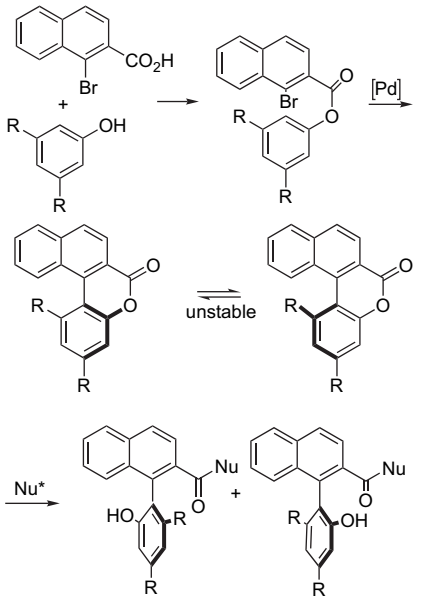
Scheme 64. Cinchona alkaloid-catalysed DKR of a phosphorochloridite.



Scheme 65. DKR of a chlorophosphine catalysed by a disulfide.

2.4. Atroposelective reactions

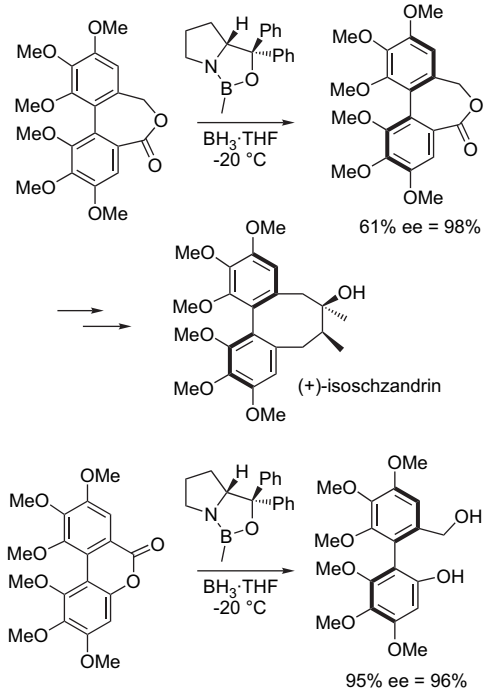
Among the few established methods for the atroposelective construction of biaryl systems, the 'lactone concept', introduced by Bringmann et al., holds a unique position, since it separates the biaryl bond-formation step from the actual introduction of stereo-information. The fundamental concept is summarised in Scheme 66. A bromoarene carboxylic acid reacts with a phenol to give the corresponding ester. This array permits the biaryl coupling to occur intramolecularly, even against strong steric hindrance, providing the corresponding lactones which are configurationally unstable. These lactones are the key intermediates in the concept, since they can be ring opened with chiral nucleophiles according to the principle of DKR, yielding the now configurationally stable biaryls.[97] The cleavage of the bridge can be achieved highly atropo-enantio- or -diastereoselectively by using a variety of possible chiral nucleophiles (O-, N-, or H-nucleophiles), establishing the axial configuration at the resulting, now configurationally stable (as it is open chained), final biaryl product. The lactone method is compatible with a variety of functional groups, proceeds under mild conditions and permits flexible and reliable access to a broad spectrum of structurally diverse biaryl species with any desired configuration at the axis. The carboxy- and phenol-derived *ortho* functions resulting from the ring opening do not necessarily have to be part of the product, as they can easily be transformed or removed. The key six-membered biaryl lactone intermediates are C_1-symmetric and thus require the availability of two different building blocks (the phenolic moiety and the acid component). Hence, the advantages of the method over other procedures are of particular significance for constitutionally unsymmetrical target



Scheme 66. Lactone concept.

molecules, whereas for simple C_2-symmetric products other procedures such as homocoupling (with subsequent racemate resolution) may be competing alternatives.

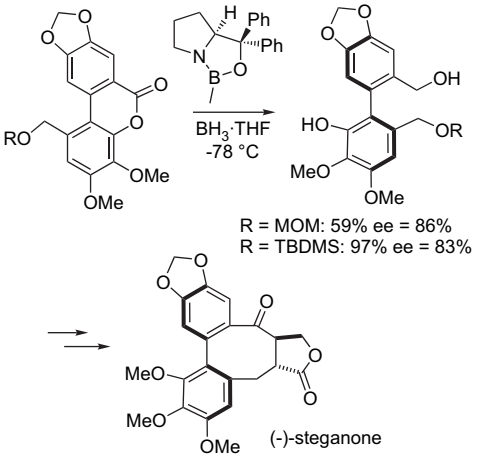
The potential and practicability of the lactone method have been demonstrated by its application in the atroposelective synthesis of several useful catalysts,[98] and more than 30 natural products, such as (+)-isoschizandrin, displaying antiulcer activity in rats.[99] The key step of the synthesis was the atropo-enantioselective reduction of a seven-membered lactone using a chiral oxazaborolidine, (*R*)-2-methyl-CBS-oxazaborolidine, providing the corresponding chiral lactone after recycling (Scheme 67). Similar conditions were also applied to the corresponding six-membered lactone, which led to the formation of the corresponding chiral diol in excellent yield and enantioselectivity (Scheme 67).



Scheme 67. Atropo-enantioselective reductions of lactones with a chiral oxazaborolidine and synthesis of (+)-isoschizandrin.

A similar methodology was applied by Harayama et al. in 2004 to the synthesis of another natural product, (−)-steganone, having antileukaemic properties.[100] Hence, the key step of the synthesis was the enantioselective lactone-opening reaction, performed with a combination of (*S*)-2-methyl-CBS-oxazaborolidine and $BH_3 \cdot THF$, providing the corresponding lactone-opened product in an enantioselective manner (Scheme 68).

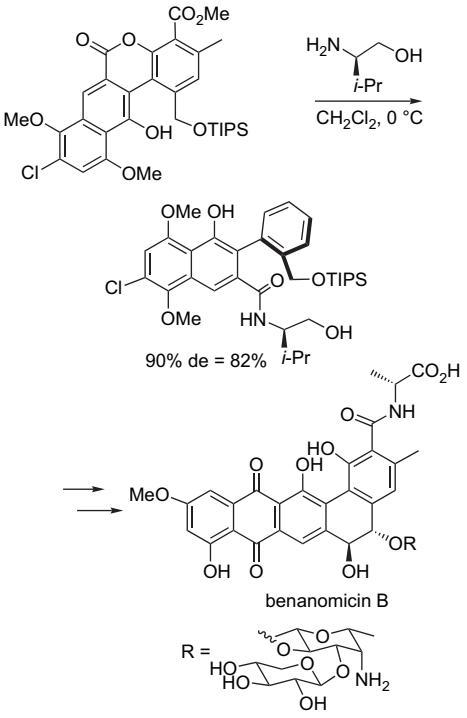
The stereoselective cleavage of the bridge can also be achieved with a chiral N-nucleophile such as D-valinol. This methodology was developed by Suzuki et al. and successfully applied to the first total synthesis of the antibiotic, benanomicin B (Scheme 69).[101]



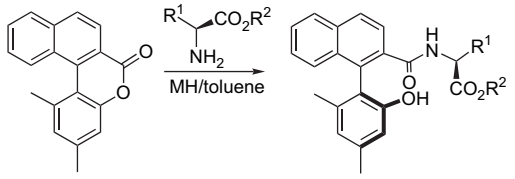
Scheme 68. Atropo-enantioselective reduction of lactones with a chiral oxazaborolidine and synthesis of (−)-steganone.

In the same context, Bringmann et al. have more recently developed atropodiastereoselective cleavage of biaryl lactones with amino acid esters as inexpensive and efficient chiral N-nucleophiles.[102] By using a broad variety of amino acid esters, the corresponding configuratively stable axially chiral biaryl amides were formed in good yields and excellent diastereoselectivities, as shown in Scheme 70.

Within the lactone concept, Uemura et al. have shown that the element of planar chirality was excellently suited for transferring chiral information to the axis.[103] Treatment of the configurationally unstable lactone depicted in Scheme 71, which bears an *R*-configured 1-hydroxyethyl substituent *ortho* to the biaryl axis, with $[CpRu(MeCN)_3]PF_6$ delivered the centro-, axial- and planar-chiral complex regio- and diastereoselectively, owing to the directing effect of the hydroxyl function. Indeed, although the δ-lactone-bridged biphenyl existed as an inseparable equilibrated atropoisomeric mixture, the corresponding ruthenium complex was obtained as a single compound with differentiated arene face complexation and fixation of the central bond. Cleavage of the lactone bridge



Scheme 69. Atropodiastereoselective ring-opening reaction with D-valinol and synthesis of benanomicin B.

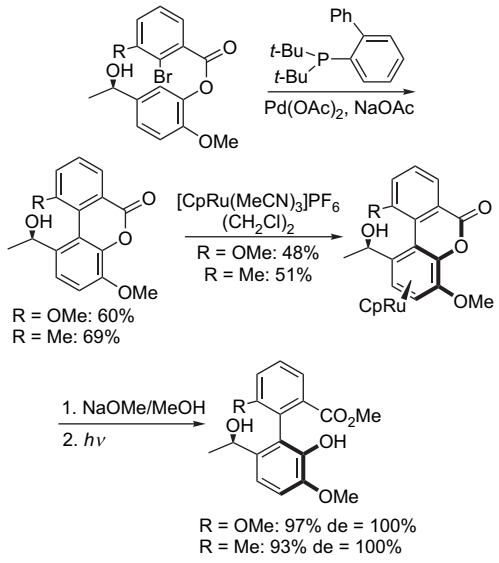


R^1 = *i*-Pr, R^2 = Me, M = K: 92% de = 99%
R^1 = *i*-Pr, R^2 = *t*-Bu, M = K: 77% de = 99%
R^1 = R^2 = Me, M = Na: 57% de = 90%
R^1 = Me, R^2 = *t*-Bu, X = Li: 99% de = 99%
R^1 = *t*-Bu, R^2 = Me, X = Li: 46% de = 99%
R^1 = Bn, R^2 = Me, X = Li: 81% de = 64%

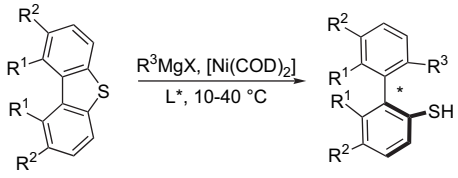
Scheme 70. Atropodiastereoselective ring-opening reaction with amino acid esters.

with sodium methoxide and subsequent decomplexation gave the corresponding axially chiral biaryl compound as a single diastereomer.

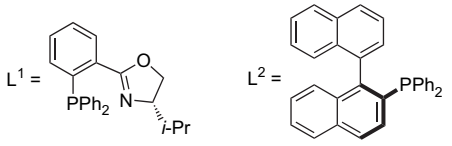
In addition, Hayashi et al. reported in 2004 an example in which a shorter bridge (five-membered ring) was cleaved atropo-enantioselectively.[104] Hence, the asymmetric nickel-catalysed cross-coupling of dibenzothiophenes with Grignard reagents in the presence of chiral phosphines delivered the corresponding biarylthiophenols (Scheme 72). In some cases, both the chemical and optical yields were excellent, but the success of this intriguing reaction varied both with the size of the Grignard reagent employed and the nature of the original *ortho* substituents. It was believed that the nickel catalyst first inserted into the C–S bond, with the stereochemically determining step being the transmetallation of the Grignard reagent or the following reaction.



Scheme 71. Atropodiastereoselective biaryl lactone formation with subsequent ring cleavage and conversion into the metal-free biaryl product.



with L* = L^1:
R^1, R^2 = CH=CH-CH=CH, R^3 = *p*-Tol, X = Br: 97% ee = 95%
R^1, R^2 = CH=CH-CH=CH, R^3 = Ph, X = Br: 92% ee = 95%
R^1, R^2 = CH=CH-CH=CH, R^3 = Me, X = I: 88% ee = 45%
with L* = L^2:
R^1, R^2 = CH=CH-CH=CH, R^3 = Me, X = I: 97% ee = 68%
R^1 = Me, R^2 = H, R^3 = *p*-Tol, X = Br: 85% ee = 82%



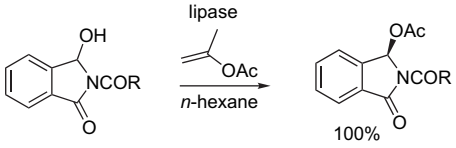
Scheme 72. Atropo-enantioselective ring-cleaving biaryl synthesis by Ni-catalysed C-alkylation or -arylation with chiral phosphines.

3. Enzymatic methods

In recent years, the use of biocatalysts for organic transformations has become an increasingly attractive alternative to conventional chemical methods.[36,105] The use of an enzyme, rather than a transition-metal catalyst, represents an attractive option for DKRs, in view of the likely mild conditions associated with enzyme-catalysed racemisation processes. In recent years, impressive examples using new enzymes and major progress in DKR have taken place, demonstrating that biocatalysis is rapidly developing and is still a growing field.

3.1. Enzymatic hydrolysis and esterification reactions

The enzymatic DKR of *N*-acylhemiaminals by various lipases, namely lipase PS (*Pseudomonas cepacia*) and lipase



R = Me, lipase = AK: ee = 63%
R = Et, lipase = AK: ee > 99%
R = *n*-Pr, lipase = PS: ee > 99%
R = *i*-Pr, lipase = PS: ee > 99%
R = *t*-Bu, lipase = PS: ee > 99%
R = Ph, lipase = PS: ee > 99%

Scheme 73. DKR of *N*-acylhemiaminals.

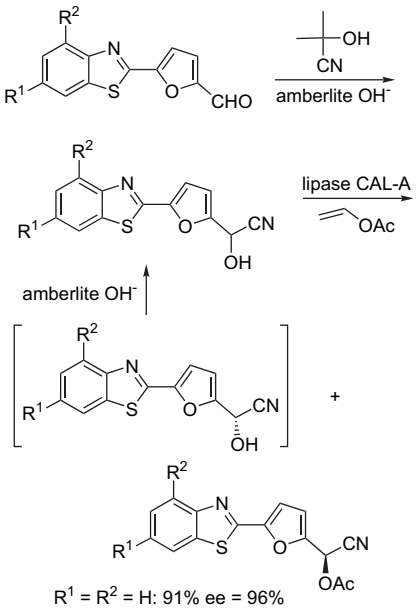
AK (*Pseudomonas fluorescens*), was investigated by Kaga et al. in 2003.[106] These authors have shown that the acetylation of racemic *N*-acylhemiaminals with lipases exclusively produces the (*R*)-enantiomers in enantiomerically pure form in quantitative yields via DKR (Scheme 73).

In 2003, Kanerva et al. reported the preparation of novel (*R*)-furylbenzothiazole-based cyanohydrin acetates from the corresponding furancarbaldehydes and acetone cyanohydrin through effective lipase-catalysed DKR of cyanohydrins with vinyl acetate in the presence of a basic resin.[107] This useful method exploited the reversible nature of the base-catalysed cyanohydrin formation from the corresponding aldehydes and hydrogen cyanide and the base-catalysed cyanohydrin decomposition to the aldehyde and hydrogen cyanide, leading to the effective racemisation of the cyanohydrins at the same time as the (*R*)-enantiomer was selectively acylated in the CAL-A-catalysed acylation (CAL-A=*Candida antarctica* lipase A). The method exploited acetone cyanohydrin as an in situ source of hydrogen cyanide. Everything took place in one pot, allowing at least 99% of the original aldehyde to be transformed into the corresponding cyanohydrin ester with high ee (Scheme 74). Moreover, the possibility of avoiding the separate preparation and purification of the relatively labile cyanohydrins and the handling of hydrogen cyanide constitute the great advantages of this methodology.

A similar methodology was applied by the same authors to the preparation of novel phenylfuran-based cyanohydrin esters by using *P. cepacia* lipase and vinyl butanoate as the acylating agent.[108] The results are summarised in Scheme 75.

In addition, DKR was used for the preparation of a series of novel (+)-10-alkyl-phenothiazin-3-ylcyanomethyl acetates on the basis of a similar methodology to that used in Scheme 75.[109] The use of *C. antarctica* lipase A allowed excellent enantioselectivities to be obtained, as depicted in Scheme 76.

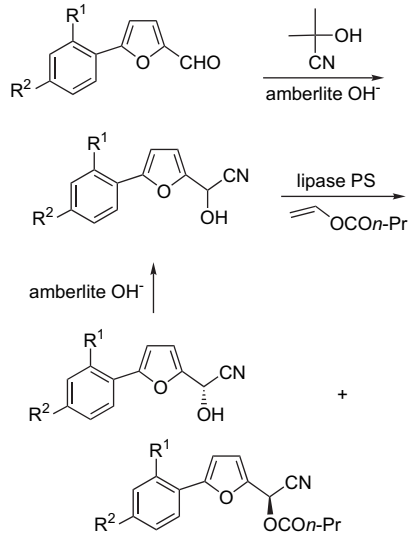
When the preceding conditions for the enantioselective synthesis of cyanohydrin acetates via DKR were applied to aliphatic substrates, only a kinetic resolution was observed. However, Hanefeld et al. have shown that, by exchanging the base (amberlite) against NaCN, quantitative conversions and good enantioselectivities were obtained in the presence of *C. antarctica* lipase B (Scheme 77).[110] In addition, by using NaCN, the reaction also became less sensitive towards water that was present in the reaction mixture. However, the ees of the products were lower than expected, most likely due to a small degree of base-catalysed chemical acylation.



$R^1 = R^2 = H$: 91% ee = 96%
R^1 = Cl, R^2 = H: 92% ee = 84%
R^1 = Me, R^2 = H: 93% ee = 95%
R^1 = H, R^2 = Cl: 92% ee = 96%

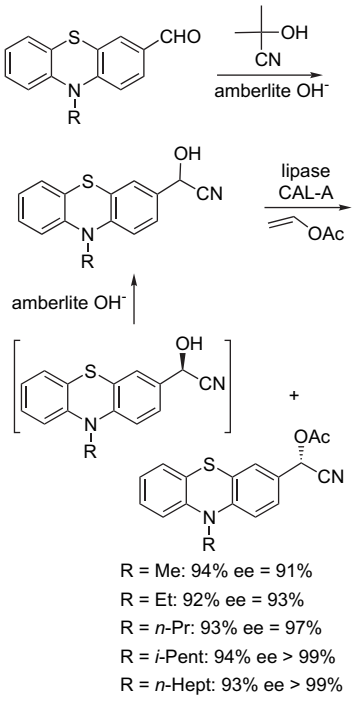
Scheme 74. DKR of furylbenzothiazole-based cyanohydrins.

In the context of these studies, the same authors have demonstrated that the synthesis of cyanohydrin esters via DKR was highly dependent upon the carrier of the enzyme. The carrier influences the amount of water available in the reaction mixture, suppressing or enhancing the undesired hydrolysis of the acyl donor and the final product.[111] Indeed, the DKR proved to be prone to residual water. However, when the lipase was immobilised on Celite as a carrier, the Celite absorbed the

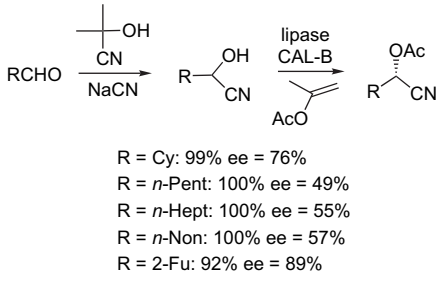


R^1 = H, R^2 = CO_2Et: 72% ee = 80%
R^1 = Cl, R^2 = H: 94% ee = 96%
R^1 = H, R^2 = Br: 93% ee = 95%
R^1 = H, R^2 = NO_2: 92% ee = 91%
R^1 = Me, R^2 = NO_2: 93% ee = 96%

Scheme 75. DKR of phenylfuran-based cyanohydrins.

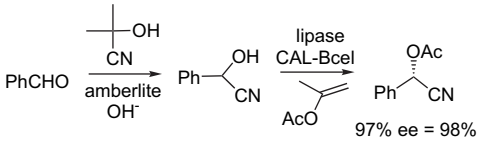


Scheme 76. DKR of phenothiazine-based cyanohydrins.



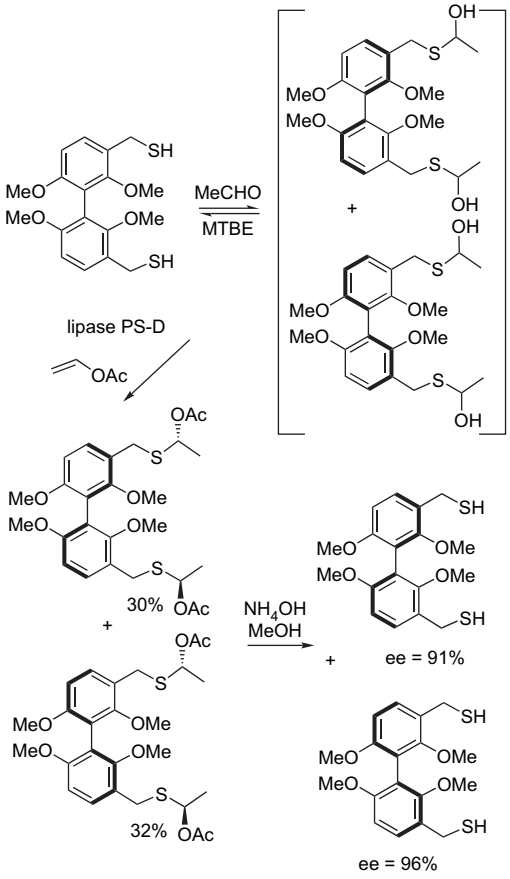
Scheme 77. DKR of aliphatic cyanohydrins.

water and suppressed the water-induced side reactions. Thereby, the enantioselectivity and the reaction times (3–10 days without Celite) for this DKR were improved, enabling a nearly enantiospecific and high-yielding synthesis of mandelonitrile acetate (Scheme 78).



Scheme 78. Synthesis of mandelonitrile acetate with Celite-immobilised CAL-B.

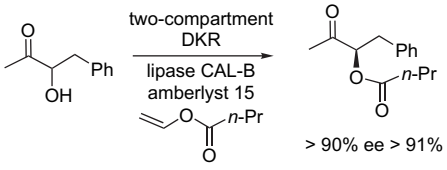
Although lipases have been used to catalyse the enantioselective esterification of different atropoisomeric binaphthyls, little attention has been paid to biphenyls. In 2005, however, Delogu et al. reported the synthesis of both atropoisomers of a racemic thiobiphenyl, 2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol, by using lipase-catalysed procedures.[112] The esterification reaction of the racemic thiobiphenyl in the presence of vinyl acetate and *P. cepacia* (PS-D) gave, in



Scheme 79. DKR of 2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol.

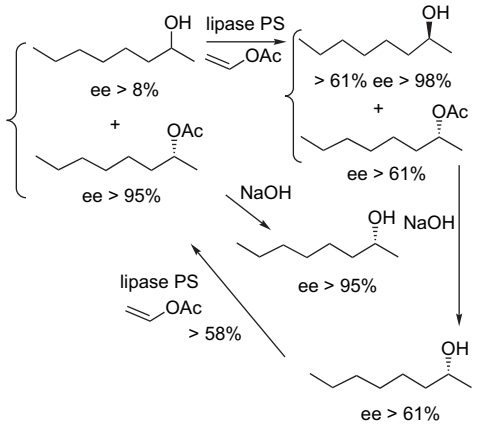
a one-pot reaction, the two corresponding enantiopure atropoisomers via a lipase-assisted DKR of epimerising hemithioacetal intermediates (Scheme 79).

In 2005, Bornscheuer et al. studied the DKR of acyloins, which constitute important building blocks in organic synthesis, e.g., for the total synthesis of epothilones.[113] No combination of base and solvent was found that could selectively racemise the acyloins or the corresponding esters under the conditions needed for a DKR. In contrast to bases, an acidic resin, such as Amberlyst 15, was found to racemise the acyloins selectively in *n*-hexane and in water. Unfortunately, the acidic resin deactivated the lipase (CAL-B), preventing a one-pot DKR. However, an efficient DKR was made possible by the spatial separation of lipase and ion exchanger, with enzymatic transesterification and resin-catalysed racemisation taking place simultaneously in two compartments connected by a pump loop. In these conditions, the conversion and selectivity were approaching excellent, as was the enantiomeric purity of the product (*S*)-acyloin butyrate ester, as depicted in Scheme 80.



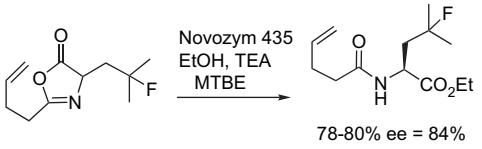
Scheme 80. Two-compartment DKR of an acyloin.

In 2005, Cong et al. developed a new method for the resolution of 2-octanol by combining a DKR with a double kinetic resolution.[114] Indeed, the method was based on the feasibility of using the residue of one double kinetic resolution as the substrate of the next double kinetic resolution, etc., and recycling them to DKR. In these conditions, an 80% racemic substrate could be converted to enantiopure products as depicted in Scheme 81.



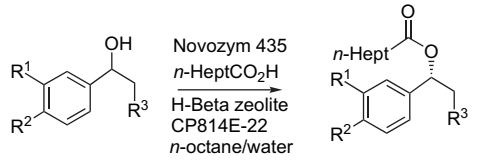
Scheme 81. DKR of 2-octanol.

In 2005, Limanto et al. reported an efficient approach to (*S*)-γ-fluoroleucine ethyl ester, which involved, as the key step, a lipase-catalysed dynamic ring opening of a 2-(3-butenyl)azlactone with EtOH to give the corresponding amide ester in high ee.[115] The use of an immobilised lipase, Novozym 435, in organic media allowed this transformation, providing the corresponding *N*-pentenamide ester in good yield and enantioselectivity (Scheme 82).



Scheme 82. Ring opening of a 2-(3-butenyl)azlactone.

In 2005, Jacobs et al. investigated the potential value of acid zeolites as heterogeneous alcohol-racemisation catalysts for the racemisation of benzylic alcohols.[116] In this context, H-beta zeolites were applied in DKR of various benzylic alcohols in the presence of carboxylic acids as acylating agents and Novozym



$R^1 = R^2 = R^3$ = H: 78% ee = 98%
$R^1 = R^3$ = H, R^2 = OMe: 13% ee = 79%
$R^1 = R^3$ = H, R^2 = Me: 84% ee > 99%
$R^1 = CF_3$, $R^2 = R^3$ = H: 39% ee > 99%
$R^1 = R^3$ = H, R^2 = Br: 74% ee = 98%
$R^1 = R^2$ = H, R^3 = Me: 79% ee = 97%

Scheme 83. DKR of benzylic alcohols with zeolites.

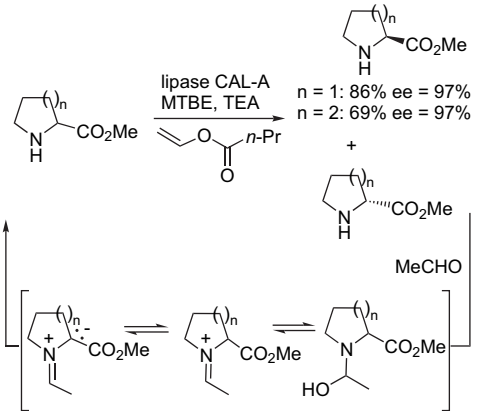
435, which were conducted by means of a two-phase approach, providing the corresponding esters in yields well above 50% with excellent enantioselectivities, as shown in Scheme 83. Very recently, Jaenicke et al. have also applied zeolites to promote the DKR of secondary alcohols in the presence of Novozym 435 and vinyl octanoate as the acyl donor.[117] In this case, a single non-aqueous liquid phase (toluene) was employed in the presence of the two heterogeneous catalysts, providing the corresponding octanoyl ester in 72% yield and 98% ee, when 1-phenylethanol was involved as the starting material in the presence of zeolite beta Al-150. In addition, zeolite Zr-beta was found to be a good racemisation catalyst of 1-phenylethanol in the presence of 2′,2′,2′-trifluoroethanol 1*H*,1*H*,2*H*,2*H*-perfluoundecanoate as the acyl donor. In order to facilitate the separation of the product, a fluorous phase-switching technique coupled with fluorous extraction was employed, allowing 95% conversion and 75% ee to be obtained.[118]

In 2006, Vaultier et al. reported the first continuous DKR of 1-phenylethanol in ionic liquids and ionic liquid/supercritical carbon dioxide systems, using a combination of the immobilised lipase, Novozym 435, and an acid chromatographic support (silica modified with benzenesulfonic acid groups; SCX) as catalysts.[119] The simultaneous action of both chemical and enzymatic catalysts was demonstrated by providing yields of (*R*)-1-phenylethyl propionate of up to 70% with 98% ee in the presence of vinyl propionate as the acylating agent. On the other hand, Kamaruddin et al. have developed a currently economical technology in the production of biologically active (*S*)-ketoprofen, based on a combination of lipase and membrane technology in an enzymatic membrane reactor.[120]

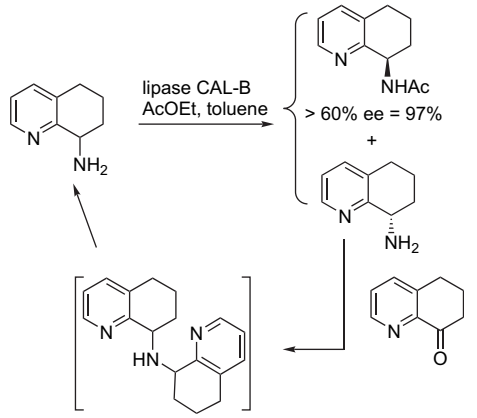
Although the enzymatic DKR methodology has been exhaustively applied to different secondary alcohols through enzymatic hydrolysis or transesterification, relatively few examples are known in the case of amines, probably because this type of DKR implies the formation of imino compounds as intermediates, which are less stable than carbonyl compounds.[121] However, in the last few years, some examples of DKR of amines have appeared in the literature. As an example, Kanerva et al. reported in 2004 the DKR of the methyl esters of proline and pipecolic acid on the basis of the acylation of the secondary amino group of the amino esters with vinyl butanoate by *C. antarctica* lipase A.[122] Acetaldehyde, used as a racemising agent, was released in situ from vinyl butanoate in the presence of triethylamine, allowing proline and pipecolic acid methyl esters to be acylated in the form of highly enantiopure butanamides (Scheme 84).

Very recently, Crawford et al. observed a spontaneous enzymatically mediated DKR of 8-amino-5,6,7,8-tetrahydroquinoline in the presence of *C. antarctica* lipase B, in which a >60% yield of the expected enantiopure (*R*)-acetamide was isolated from the racemic amine.[123] The spontaneous formation of 5,6,7,8-tetrahydroquinolin-8-one as a side product, followed by a condensation/hydrolysis sequence with the remaining (*S*)-8-amino-5,6,7,8-tetrahydroquinoline, via the corresponding enamine, provided the necessary racemisation pathway (Scheme 85).

Very recently, the performance of a DKR process associating a lipase-catalysed enzymatic resolution and an in situ

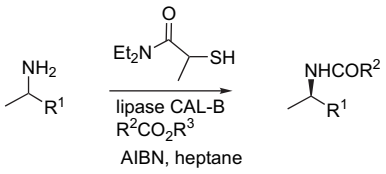


Scheme 84. DKR of proline and pipecolic acid methyl esters.



Scheme 85. DKR of 8-amino-5,6,7,8-tetrahydroquinoline.

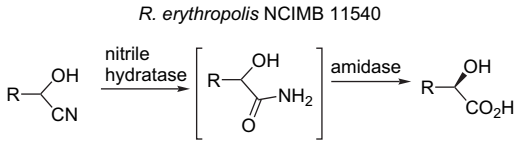
racemisation involving a thiyl radical-mediated process was developed by Bertrand et al. for the first time.[124] This process, compatible with remote functionalities, has led to various (*R*)-amides with high enantioselectivities, as depicted in Scheme 86.



$R^1 = BnCH_2$, $R^2 = Me$, $R^3 = Et$: 31% ee = 74%
$R^1 = BnCH_2$, $R^2 = C_{11}H_{23}$, $R^3 = Et$: 70% ee = 99%
$R^1 = BnCH_2$, $R^2 = C_{11}H_{23}$, $R^3 = H$: 71% ee > 99%
$R^1 = n$-Hex, $R^2 = C_{11}H_{23}$, $R^3 = Et$: 81% ee > 99%
$R^1 = Cy$, $R^2 = C_{11}H_{23}$, $R^3 = Et$: 81% ee > 99%
$R^1 = t$-BuOCOCH$_2$, $R^2 = C_{11}H_{23}$, $R^3 = Et$: 47% ee = 92%
$R^1 = (Me)_2C{=}CH(CH_2)_2$, $R^2 = C_{11}H_{23}$, $R^3 = Et$: 68% ee = 94%
$R^1 = Et$, $R^2 = C_{11}H_{23}$, $R^3 = H$: 57% ee = 86%

Scheme 86. DKR of amines.

On the other hand, various biocatalytic hydrolysis methods have been developed in the last few years on the basis of DKR. As an example, Griengl et al. reported in 2003 the hydrolysis of cyanohydrins by treatment with bacterial cells of *Rhodococcus erythropolis* NCIMB 11540, which have a highly active nitrile hydratase/amidase enzyme system.[125] In this manner, (*R*)-2-chloromandelic acid and (*R*)-2-hydroxy-4-phenylbutyric acid, two important pharmaceutical intermediates, could be

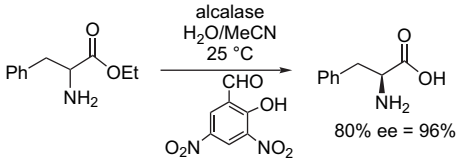


R = *o*-ClC$_6$H$_4$: 98% ee > 99%
R = BnCH$_2$: 98% ee = 98%

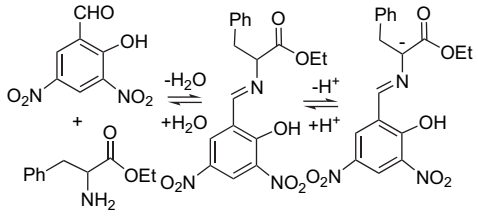
Scheme 87. DKR of cyanohydrins.

prepared in high optical and chemical yields after short reaction times (3 h and 1.5 h, respectively) (Scheme 87).

In 2006, Kragl et al. developed the DKR of α-amino acid esters, such as phenylalanine ethyl ester, in a water/acetonitrile mixture, leading to the corresponding optically active α-amino acids in good yields and optical purity (Scheme 88).[126] The alcalase-catalysed hydrolysis of the ester was combined with an in situ racemisation catalysed by 3,5-dinitrosalicylaldehyde.

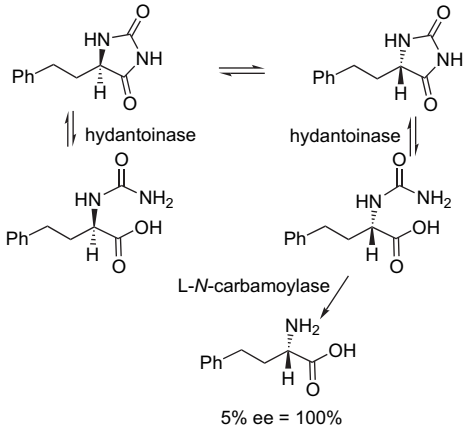


mechanism of racemisation:



Scheme 88. DKR of phenylalanine ethyl ester.

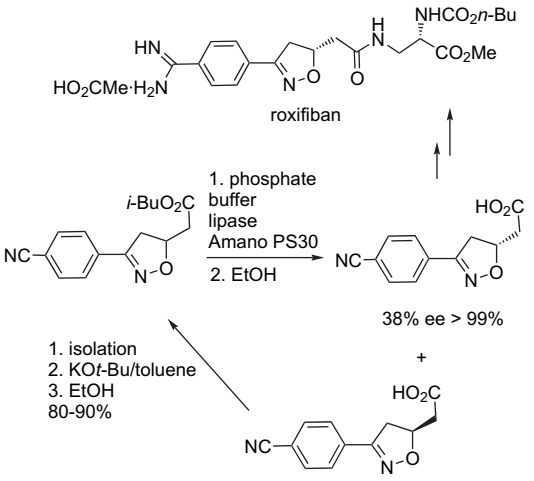
An enantioselective synthesis of (*S*)-2-amino-4-phenylbutanoic acid by the hydantoinase method was developed in 2003 by Hsu et al.[127] This methodology was based on the use of a combination of *Bacillus caldolyticus* hydantoinase and *Bacillus kaustophilus* L-*N*-carbamoylase, using racemic 5-(2-phenylethyl)-imidazolidine-2,4-dione as a substrate. In spite of giving total enantioselectivity, the yield was quite low, as shown in Scheme 89.



Scheme 89. DKR of 5-(2-phenylethyl)-imidazolidine-2,4-dione.

In addition, Asano and Yamaguchi have reported the DKR of amino acid amides catalysed by a combination of two enzymes, D-aminopeptidase and α-amino-ε-caprolactam racemase, yielding the corresponding D-amino acids.[128]

A lipase-catalysed hydrolysis has constituted the key step of a total synthesis of roxifiban, a potent antagonist of the platelet glycoprotein IIb/IIIa receptor.[129] The DKR of an isobutyl ester to form the corresponding acid in high yield and ee is depicted in Scheme 90.

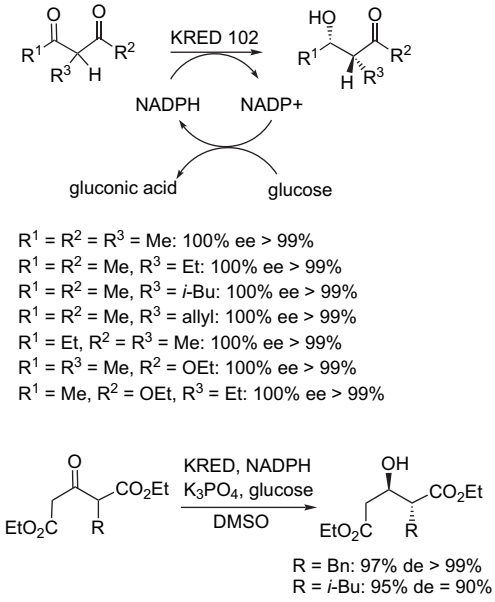


Scheme 90. Synthesis of roxifiban.

In 2006, another lipase-catalysed hydrolysis process under in situ racemisation of the remaining (*R*)-ibuprofen ester substrate with sodium hydroxide as the catalyst was developed by Kamaruddin et al. for the production of (*S*)-ibuprofen from racemic ibuprofen ester in isooctane.[130] Through this method, enantiopure (*S*)-ibuprofen could be obtained in 86% yield and >99% ee. In the same context, Tsai et al. have recently developed the dynamic kinetic hydrolytic resolution of 2,2,2-trifluoroethyl α-chlorophenylacetate in water-saturated isooctane containing lipase MY(I), producing (*R*)-α-chlorophenylacetic acid in 93% yield and 90% ee, in the presence of trioctylamine acting as the racemisation catalyst and enzyme activator.[131] These authors have also reported the DKR of naproxen 2,2,2-trifluoroethyl ester via lipase-catalysed hydrolysis in micro-aqueous isooctane.[132] In this method, *Candida rugosa* lipase was immobilised on polypropylene powder, and an organic base, such as 1,5,7-triazabicyclo[4,4,0]-dec-5-ene bound to polystyrene crosslinked with 2% divinylbenzene, was added as an in situ racemisation catalyst. In these conditions, a 96% yield of the desired (*S*)-naproxen was obtained with a disappointing ee of 58%. Better results were, however, obtained by the same group for the DKR of suprofen 2,2,2-trifluoroethyl thioester using a hollow-fibre membrane.[133] Similar conditions to those described above were applied, but, in this case, a hollow-fibre membrane was also integrated with the DKR process, in order to continuously extract the desired (*S*)-suprofen into an aqueous solution containing NaOH. In this context, 86% ee could be obtained.

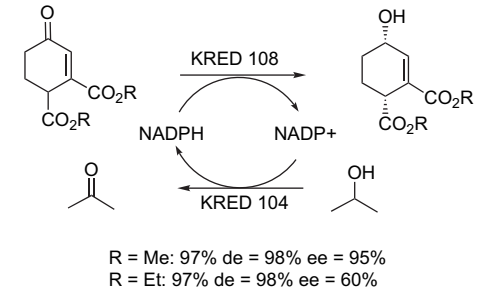
3.2. Miscellaneous enzymatic reactions

In 2005, Kambourakis et al. reported the biocatalytic reduction of α-alkyl-1,3-diketones and α-alkyl-β-keto esters, employing isolated NADPH-dependent ketoreductases (KREDs).[134] The corresponding optically pure single keto alcohols and hydroxy esters were obtained in quantitative yields (Scheme 91). The same authors have previously reported the total synthesis of a new class of triterpene derivatives with anti-HIV activity, statine and statine analogues, based on a diastereoselective reduction of a 2-alkyl-substituted 3-ketoglutarate by a KRED.[135] The results are summarised in Scheme 91.



Scheme 91. Reduction of α-alkyl-1,3-diketones and α-alkyl-β-keto esters by KRED enzymes.

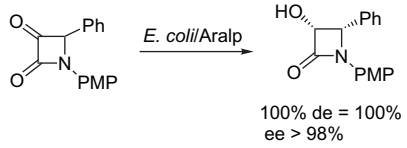
In 2006, Kosjek et al. reported a similar methodology for the biocatalytic reduction of α,β-unsaturated ketones, providing the corresponding chiral allylic alcohols in both high enantio- and diastereoselectivities, as depicted in Scheme 92.[136] The method employed the enzyme KRED 108 including an NADPH cofactor recycling system using KRED 104/2-propanol.



Scheme 92. Reduction of α,β-unsaturated ketones by KRED enzymes.

Using a recombinant *Escherichia coli* (*E. coli*) strain overexpressing yeast reductase Ara1p, Kayser et al. have reduced

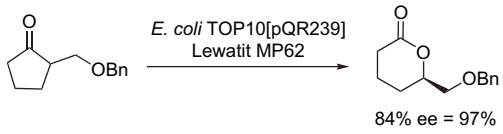
a racemic 3-oxo-4-phenyl-β-lactam to the corresponding enantiomerically pure 3-hydroxy-β-lactam (Scheme 93).[137] The DKR occurred over the course of fermentation at pH 7. Unfortunately, other lactams, such as 3-oxo-4-(2-thiophenyl)-β-lactam and 3-oxo-4-(2-furyl)-β-lactam, could not be resolved under the same conditions.



Scheme 93. Reduction of a 3-oxo-4-phenyl-β-lactam by *E. coli*/Aralp.

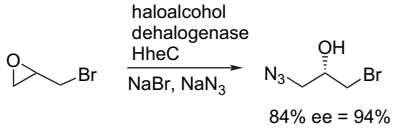
In 2006, Blanchard et al. demonstrated that intact cells from the cut portions of plants, such as *Daucus carota*, could mediate the bioreduction of 2-hydroxycyclohexanone.[138] In these conditions, the (*S*)-enantiomer was converted faster than the (*R*)-enantiomer, leading to a 67:33 ratio of C_2-symmetric:-*meso*-cyclohexan-1,2 diols with 23% ee and >95% ee, respectively. In addition, Howdle et al. have reported the simultaneous DKR of a secondary alcohol in combination with lipase-catalysed ring-opening polymerisation of ε-caprolactone.[139] 1-Phenylethanol was used as a model secondary alcohol and incorporated into poly(ε-caprolactone) under DKR conditions. A total of 75% of 1-phenylethanol was incorporated as (*R*)-1-phenylethanol-poly(ε-caprolactone) with >99% ee. This methodology could provide a simple one-step approach to prepare enantiopure sustained release polymeric formulations of chiral species such as drugs or drug precursors bearing a secondary hydroxyl group.

On the other hand, Alphand et al. have developed an enantioconvergent microbial Baeyer–Villiger oxidation, achieved by combining a whole cell-based kinetic resolution and an anion exchange resin-catalysed in situ racemisation.[140] The choice of a suitable resin, Lewatit MP62, was the key point of this work. When the process was applied to racemic 2-benzyloxymethylcyclopentanone, a nearly enantiopure lactone, (*R*)-6-benzyloxymethyltetrahydro-2-pyrone, was obtained in excellent yield (Scheme 94).



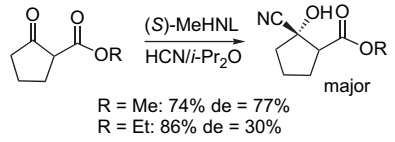
Scheme 94. Microbial Baeyer–Villiger oxidation.

Another type of enzymatic reaction, proceeding via DKR of epihalohydrins, was described by Janssen et al. in 2004.[141] The haloalcohol dehalogenase from *Agrobacterium radiobacter* AD1 was shown to catalyse the reversible ring closure of vicinal haloalcohols to produce epoxides and halides. In the ring of epoxides, non-halide nucleophiles such as N_3^- are accepted. The enantioselective irreversible ring opening of an epihalohydrin by N_3^-, combined with racemisation caused by a reversible ring opening by a halide, resulted in an enzymatic DKR, yielding the optically active (*S*)-1-azido-3-halo-2-propanol. With an epibromohydrin as the substrate, the racemisation rate was higher than the rate of ring opening, resulting in an efficient DKR (Scheme 95).



Scheme 95. DKR of an epibromohydrin.

The stereoselectivity of the hydroxynitrile lyase(HNL)-catalysed cyanohydrin formation of monosubstituted cyclic ketones is of general interest for the synthesis of biologically active compounds. In the course of a systematic investigation of the stereoselectivity of hydroxynitrile lyase-catalysed addition of HCN to a variety of monosubstituted cyclopentanones, Effenberger and Kobler observed a DKR for the addition of HCN to alkyl 2-oxocyclopentanecarboxylates catalysed by (*S*)-MeHNL from cassava (*Manihot esculenta*).[142] Continuous equilibration via keto–enol tautomerism and the preferred enzymatic conversion of the (*R*)-enantiomers of the ketones resulted in the preferred formation of the *cis*-(1*R*,2*S*)-diastereomers (Scheme 96).

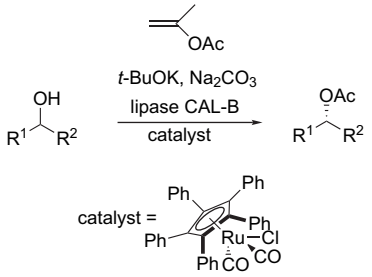


Scheme 96. (*S*)-MeHNL-catalysed addition of HCN to 2-substituted cyclopentanones.

4. Chemoenzymatic methods

The use of transition metal–enzyme combinations to effect tandem in situ racemisation and resolution, highlighted in 1997 by Stürmer,[143] has widely extended the scope of DKRs.[144] Since the demonstration of the compatibility of enzymes with metal complexes in one pot,[2e,145,146] this powerful concept has recently attracted much attention. In this approach, the enzyme acts as an enantioselective resolving catalyst and the metal serves as a racemising catalyst for the efficient DKR. Three major types of enzyme–metal combinations, lipase–ruthenium, subtilisin–ruthenium and lipase combined with a metal other than ruthenium, have been developed primarily as the catalysts not only for the DKRs of various secondary alcohols but also for diols, amines and esters. Meanwhile, the lipase–ruthenium combination has been the most used method up to the present time. As an example, Bäckvall et al. have demonstrated that pentaphenylcyclopentadienylruthenium complexes and lipases in tandem were highly performing for the DKR of a wide variety of functionalised secondary alcohols including heteroaromatic alcohols,

leading, for many of the latter, to the corresponding enantiopure acetates prepared for the first time via DKR (Scheme 97).[147] The reaction took place in very short times, and isoprenyl acetate was employed as the acyl donor, which made the purification of the products very easy. A study of the racemisation of (*S*)-1-phenylethanol indicated that the racemisation took place within the coordination sphere of the ruthenium catalyst.

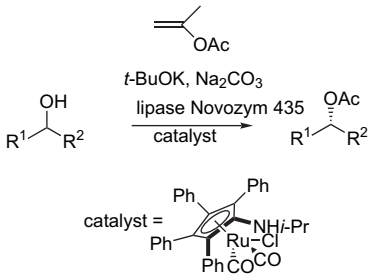


R^1 = Ph, R^2 = Me: 98% ee > 99%
R^1 = 2-Naph, R^2 = Me: 93% ee > 99%
R^1 = *p*-PhC_6H_4, R^2 = Me: 96% ee > 99%
R^1 = Ph, R^2 = Et: 92% ee > 99%
R^1 = *p*-MeOC_6H_4, R^2 = Me: 96% ee > 99%
R^1 = *p*-(*n*-Pr)C_6H_4, R^2 = Me: 96% ee = 99%
R^1 = *p*-$O_2NC_6H_4$, R^2 = Me: 99% ee > 99%
R^1 = *p*-NCC_6H_4, R^2 = Me: 98% ee > 99%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 98% ee > 99%
R^1 = C_6F_5, R^2 = Me: 98% ee > 99%
R^1 = Cy, R^2 = Me: 98% ee > 99%
R^1 = *n*-Hex, R^2 = Me: 93% ee > 98%
R^1 = $BnCH_2$, R^2 = Me: 91% ee = 96%
R^1 = Bn, R^2 = Me: 99% ee = 91%
R^1 = $PhOCH_2$, R^2 = Me: 98% ee > 92%
R^1 = 2-Fu, R^2 = Me: 93% ee = 96%
R^1 = 2-Thio, R^2 = Me: 98% ee > 99%
R^1 = 4-py, R^2 = Me: 97% ee = 99%
R^1 = Ph, R^2 = CH_2Cl: 83% ee > 99%
R^1 = Ph, R^2 = CH_2CN: 85% ee = 97%
R^1 = PhCH=CH, R^2 = Me: 89% ee > 99%
R^1 = $(Bn)_2NCH_2$, R^2 = CH_2Cl: 97% ee > 97%
R^1 = $(Me)_2C$=CH-$(CH_2)_2$, R^2 = Me: 92% ee = 98%

Scheme 97. DKR of various alcohols in the presence of a ruthenium catalyst and lipases.

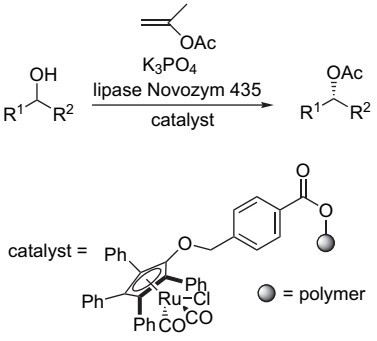
In 2004, Park et al. obtained similar results in the presence of novel aminocyclopentadienylruthenium complexes as racemisation catalysts.[148] Not only simple alcohols, but also functionalised alcohols, such as allylic alcohols, alkynyl alcohols, diols, hydroxyl esters and chlorhydrins, were successfully transformed into chiral acetates, as depicted in Scheme 98.

In the same context, another racemisation ruthenium catalyst, bearing a benzyloxy function, was synthesised by the same group and was successfully applied to similar reactions to those described above, providing the DKR of a wide range of functionalised alcohols in excellent yields and enantioselectivities (>99% ee).[149] The corresponding polymer-supported derivative was also synthesised and tested as a recyclable catalyst for the aerobic DKR of alcohols (Scheme 99) and its catalytic activity was found to be practically the same as that of the non-polymeric catalyst.



R^1 = Ph, R^2 = Me: 95% ee > 99%
R^1 = *p*-ClC_6H_4, R^2 = Me: 94% ee > 99%
R^1 = *p*-MeOC_6H_4, R^2 = Me: 90% ee > 99%
R^1 = Cy, R^2 = Me: 86% ee > 99%
R^1 = *n*-Hex, R^2 = Me: 89% ee = 91%
R^1 = PhCH=CH, R^2 = Me: 93% ee = 98%
R^1 = Ph-Ph-CH=CH, R^2 = Me: 90% ee > 99%
R^1 = Cy, R^2 = CH=CH_2: 90% ee > 99%
R^1 = Ph, R^2 = CH=CH_2: 62% ee = 81%
R^1 = PhOPh-CH=CH, R^2 = CH=CH_2: 93% ee > 99%
R^1 = PhC≡C, R^2 = CH=CH_2: 95% ee > 99%
R^1 = Ph_3COCH_2, R^2 = Me: 97% ee = 99%
R^1 = $Ph_3CO(CH_2)_2$, R^2 = Me: 94% ee > 99%
R^1 = *m*-(MeCHOH)C_6H_4, R^2 = Me: 95% ee > 99%
R^1 = *p*-(MeCHOH)C_6H_4, R^2 = Me: 94% ee > 99%
R^1 = Ph, R^2 = CH_2Cl: 75% ee = 95%
R^1 = $PhOCH_2$, R^2 = CH_2Cl: 62% ee = 87%

Scheme 98. DKR of various alcohols in the presence of a ruthenium catalyst and lipases.

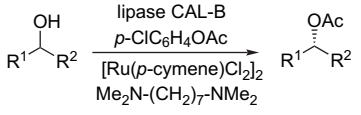


R^1 = Ph, R^2 = Me: 99% ee > 99%
R^1 = *p*-Tol, R^2 = Me: 99% ee > 99%
R^1 = *p*-ClC_6H_4, R^2 = Me: 99% ee > 99%
R^1 = 2-Naph, R^2 = Me: 99% ee > 99%
R^1 = Cy, R^2 = Me: 95% ee > 99%
R^1 = *n*-Hex, R^2 = Me: 94% ee = 97%
R^1 = $BnCH_2$, R^2 = Me: 86% ee = 92%

Scheme 99. DKR of various alcohols in the presence of a polymer-bound ruthenium catalyst and lipases.

In 2005, Trauthwein et al. reported the synthesis of an easy-to-handle and stable racemisation catalyst for secondary alcohols by an in situ mixture of readily available [Ru(*p*-cymene)Cl_2]$_2$ with chelating aliphatic amines.[150] Optimisation of the reaction revealed that *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine as ligand racemised aromatic alcohols completely within 5 h. The combination of this catalyst with lipase showed a good performance for the DKR of various alcohols in the presence of *p*-chlorophenyl acetate as the acyl donor (Scheme 100).

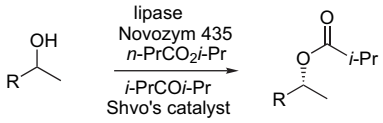
In the same context, Livingston et al. have studied the efficiency of ruthenium *p*-cymene catalyst combined with



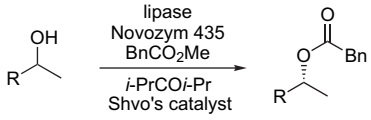
R^1 = Ph, R^2 = Me: 80% ee = 98%
R^1= *p*-$MeOC_6H_4$, R^2 = Me: 66% ee = 97%
R^1, R^2 = 1-indane: 93% ee = 98%
R^1 = 2-Naph, R^2 = Me: 64% ee = 96%

Scheme 100. DKR of various alcohols in the presence of a ruthenium catalyst and lipases.

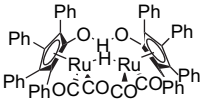
Novozym 435, in the presence of a number of different bases, for the DKR of allylic alcohols.[151] Using this method, the DKR of methyl styryl carbinol, performed in the presence of a base, such as TEA, or trioctylamine, and vinyl acetate as the acyl donor, led to the corresponding chiral acetate in yields above 68% and 80–97% ee. In 2006, Wolfson et al. reported the DKR of 1-phenylethanol by hydrated ruthenium chloride in an aqueous medium using Novozym 435 as the lipase.[152] This novel process, involving phenyl acetate as the acyl donor, led to the formation of the corresponding chiral acetate in 82% yield and 98% ee. Besides its low price and ideal environmental impact, performing the reaction in an aqueous medium, allowed an easy separation of the product. In 2005, Verzijl et al. demonstrated that the continuous removal of the acyl donor residue during the reaction allowed the use of simple alkyl esters as acyl donors for the DKR of various secondary alcohols in the presence of Novozym 435 and a dinuclear ruthenium catalyst, Shvo's ruthenium catalyst,[153] as depicted in Scheme 101.[154] The addition of a ketone, such as 2,4-dimethyl-3-pentanone, sped up the racemisation process and allowed the amounts of enzyme and ruthenium catalyst to be reduced. Hence, various benzylic and aliphatic alcohols were reacted using isopropyl butyrate or methyl phenyl acetate as the acyl donor and, in most cases, the ester was isolated in >95% yield and 99% ee.



R = Ph: 96% ee = 99%
R = Ph: 94% ee > 99%
R = *p*-ClC_6H_4: 96% ee = 99%
R = *p*-$MeOC_6H_4$: 93% ee > 99%
R = *m*-$CF_3C_6H_4$: 91% ee > 99%
R = *p*-FC_6H_4: 98% ee = 99%
R = $PhOCH_2$: 75% ee = 84%
R = 2-Fu: 87% ee = 95%
R = *n*-Hex: 90% ee = 95%
R = *t*-Bu: 75% ee = 97%
R = Cy: 97% ee > 99%



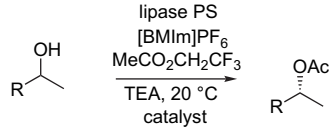
R = Ph: 93% ee > 99%
R = $PhOCH_2$: 88% ee > 99%
R = 2-Fu: 94% ee = 99%
R = *n*-Hex: 84% ee > 99%



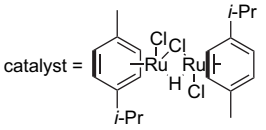
Shvo's catalyst

Scheme 101. DKR of various alcohols in the presence of Shvo's ruthenium catalyst and lipases.

In addition, the activated hydride form of a cymene–ruthenium complex was shown to be effective as a racemising catalyst in ionic liquids, such as $[EMIm]BF_4$ and $[BMIm]PF_6$ ([EMIm]=1-ethyl-3-methylimidazolium and [BMIm]=1-butyl-3-methylimidazolium).[155] In these conditions, the DKR of various secondary alcohols occurred in the ionic liquids at room temperature, allowing the catalyst and enzyme in the ionic liquid layer to be re-usable after extracting the products with ether (Scheme 102).



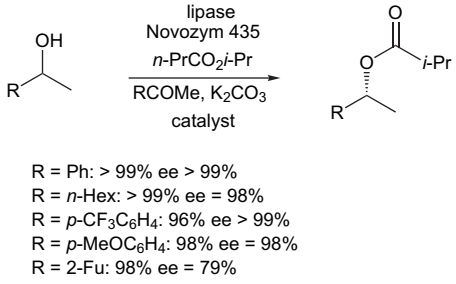
R = Et: 85% ee = 99%
R = *n*-Pr: 85% ee = 99%
R = *p*-Tol: 87% ee = 99%
R = *m*-Tol: 87% ee = 98%
R = *p*-$MeOC_6H_4$: 85% ee = 99%
R = *p*-ClC_6H_4: 87% ee = 99%
R = *p*-BrC_6H_4: 92% ee = 99%
R = *p*-(MeCHOH)C_6H_4: 87% de = 99% ee = 99%
R = *m*-(MeCHOH)C_6H_4: 86% de = 97% ee = 99%

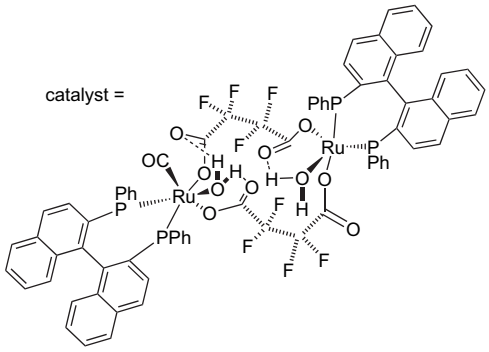


Scheme 102. DKR of various alcohols in the presence of a ruthenium catalyst and lipases in ionic liquids.

In 2006, Hulshof et al. reported the synthesis of a novel dinuclear ruthenium catalyst, bearing tetrafluorosuccinate and racemic BINAP ligands.[156] This catalyst was applied to the DKR of various secondary alcohols in the presence of isopropyl butyrate as the acyl donor and Novozym 435 as the enzyme (Scheme 103). Activation of the ruthenium catalyst with K_2CO_3 was necessary. When the reaction was performed in the presence of the ketone corresponding to the substrate, it was complete within 10 h with an excellent ee, whereas, without this ketone, the complete reaction was achieved in 23 h, also giving an excellent ee.

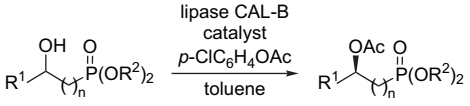
The combination of a lipase and a ruthenium catalyst has also been applied to the deracemisation of α- and β-hydroxyphosphonates.[157] Hydroxyphosphonates are an important class of substrates, with applications in medicinal chemistry (haptens of catalytic antibodies, phosphonic acid-based antibiotics), biochemistry (enzyme inhibitors) and organic synthesis. Under typical conditions, Bäckvall and Pamies have shown that the DKR of several dimethyl- and diethyl-α-hydroxyphosphonates proceeded with excellent ees and moderate-to-good yields (Scheme 104). This was attributed to the coordination of the phosphonate moiety to the ruthenium catalyst at a low alcohol concentration. This DKR



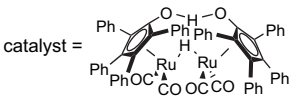


Scheme 103. DKR of various alcohols in the presence of a BINAP-based ruthenium catalyst and lipases.

procedure was also applied to the deracemisation of diethyl β-hydroxyphosphonates. However, in contrast to the DKR results on the α-hydroxyphosphonates, the formation of large amounts of the corresponding ketone was observed. To increase the efficiency of the process by reducing the amount of ketone, the authors completely suppressed the ketone formation by adding 2,4-dimethyl-3-pentanol as a hydrogen source after 24 h. Under these conditions, the DKR of β-hydroxyphosphonates proceeded with excellent ees and moderate yields and without ketone formation.

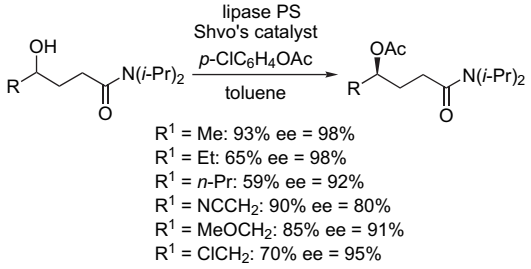


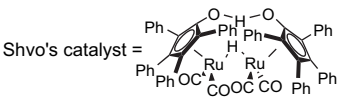
$R^1 = R^2 = Me$, n = 0: 83% ee > 99%
R^1 = Me, R^2 = Et, n = 0: 86% ee > 99%
$R^1 = R^2 = Me$, n = 1: 62% ee > 99%
R^1 = Me, R^2 = Et, n = 1: 69% ee > 99%



Scheme 104. Ruthenium-catalysed DKR of dimethyl- and diethyl-α-hydroxyphosphonates.

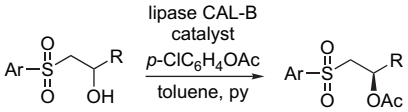
A similar methodology was applied to the DKR of functionalised γ-hydroxy amides by using Shvo's ruthenium catalyst in combination with *P. cepacia* lipase (lipase PS).[158] This enzyme tolerated both variations in the chain length and different functionalities, giving good-to-high enantioselectivities, as shown in Scheme 105. The synthetic utility of this procedure was illustrated by the practical synthesis of the versatile intermediate γ-lactone, (*R*)-5-methyltetrahydrofuran-2-one.



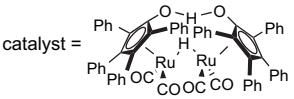


Scheme 105. DKR of functionalised γ-hydroxy amides.

Other functionalised alcohols have been submitted to DKR in similar conditions, such as aryl β-hydroxyalkyl sulfones, which have been successfully transformed into the corresponding optically active *O*-acetyl derivatives in high yields and ees by using *C. antarctica* lipase B combined with Shvo's ruthenium catalyst (Scheme 106).[159]

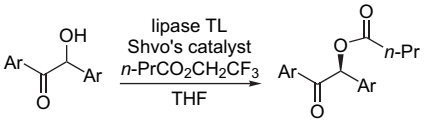


Ar = Ph, R = Me: 70% ee > 99%
Ar = p-Tol, R = Me: 79% ee > 99%
Ar = p-Tol, R = Et: 42% ee > 99%



Scheme 106. DKR of β-hydroxyalkyl sulfones.

In 2006, Alcantara et al. reported the first DKR of different benzoins using *Pseudomonas stutzeri* lipase (lipase TL) and Shvo's ruthenium catalyst in organic solvents, obtaining the corresponding *S*-acylated products with yields of up to 87% and ee values >99% (Scheme 107).[160] In all cases, the particular stereobias of the lipase towards the racemic substrates allowed the production of the opposite enantiomer to that prepared through a different enzymatic methodology.

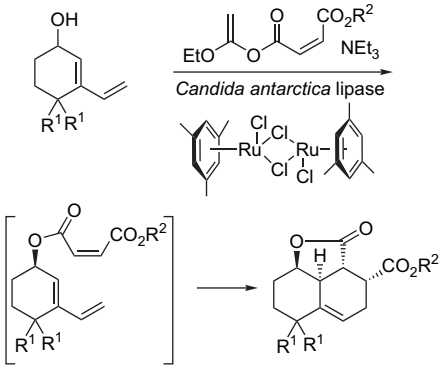


Ar = Ph: 87% ee > 99%
Ar = 2-Fu: 78% ee > 99%
Ar = 3-Thio: 76% ee > 99%

Scheme 107. DKR of benzoins.

In 2004, Kita et al. reported a combination of the domino reaction concept and the DKR protocol,[161] comprising the first lipase-catalysed domino process that combined the DKR of racemic alcohols by using 1-ethoxyvinyl esters and the Diels–Alder reaction of the intermediates. The finding that ruthenium

catalysts produced a rapid racemisation of the slow-reacting (*S*)-enantiomers was the key to the success of this process, which provided useful chiral intermediates for natural products, such as compactin and forskolin (Scheme 108).

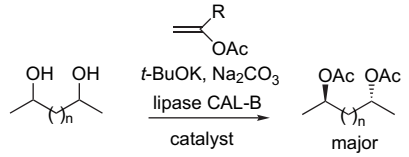


R^1 = H, R^2 = Et: 86% ee = 95%
R^1 = H, R^2 = Me: 83% ee = 93%
R^1 = R^2 = Me: 81% ee = 91%
R^1, R^1 = $S(CH_2)_3S$, R^2 = Et: 69% ee = 93%

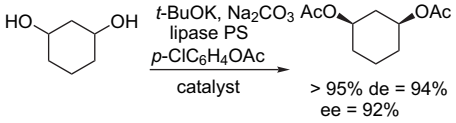
Scheme 108. Enzyme-triggered Diels–Alder reaction combined with DKR.

The lipase–ruthenium-catalysed DKR of other functionalised alcohols such as diols has been widely studied by Bäckvall et al. in recent years. These authors have developed a highly efficient synthesis of enantiopure diacetates of the symmetric diols, 2,4-pentanediol and 2,5-hexanediol, by combining a ruthenium catalyst with lipase CAL-B, in the presence of vinyl acetate or isoprenyl acetate as the acyl donor, respectively.[162] Excellent yields, and diastereo- and enantioselectivities were obtained in both cases, as shown in Scheme 109. The scope of the methodology was extended to 1,3-cyclohexanediol, providing the corresponding diacetate with high *syn*-diastereoselectivity and enantioselectivity (Scheme 109).[163] Moreover, the DKR of a series of 1,2-diols was achieved in similar conditions, affording enantioenriched *syn*-diacetates as the main diastereomers (Scheme 109).[164] This procedure provided a useful alternative to the Sharpless asymmetric dihydroxylation, since the costs of the ruthenium catalyst and the CAL-B lipase are not very high. In addition, a similar methodology was applied to the synthesis of a *cis*-3,5-piperidine diacetate with excellent yield and diastereo- and enantioselectivities (Scheme 109).[165] This product was further converted into various interesting 3,5-disubstituted piperidines.

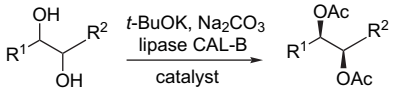
In 2003, Bäckvall et al. employed Shvo's catalyst for the lipase-catalysed acylation of unsymmetrical alkanediols.[166] Hence, enantiomerically pure *syn*-1,3-diacetates, containing one large and one small group, could be prepared, starting from the corresponding racemic 1,3-diols (Scheme 110). Surprisingly, when a similar methodology was extended to unsymmetrical 1,4-diols, the authors observed the formation of the corresponding enantiomerically enriched γ-acetoxy ketones (Scheme 110).[167] The least hindered alcohol was acetylated, whereas oxidation of the second hydroxyl group took



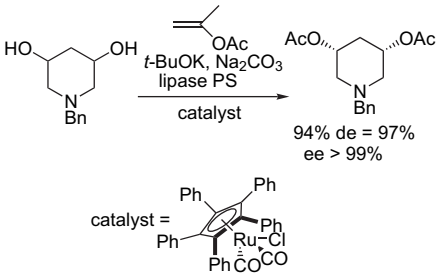
R = Me, n = 1: 96% de = 94% ee > 99%
R = H, n = 2: > 99% de > 99% ee > 99%



> 95% de = 94%
ee = 92%

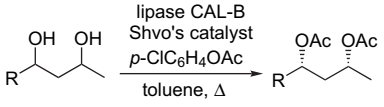


R^1 = Ph, R^2 = Me: 95% de = 34% ee = 98 and 99%
R^1 = *n*-Pent, R^2 = Me: 95% de = 34% ee = 96 and 99%
R^1 = *n*-Bu, R^2 = Et: 87% de = 82% ee > 99%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 77% de = 34% ee = 98 and 99%
R^1 = *p*-BrC_6H_4, R^2 = Me: 71% de = 10% ee = 81%

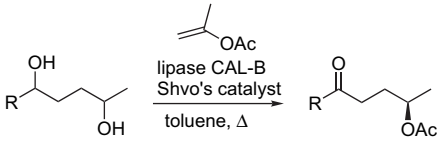


94% de = 97%
ee > 99%

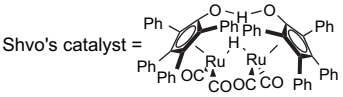
Scheme 109. DKRs of diols.



R = Ph: 73% de = 86% ee > 99%
R = *n*-Pent: 58% de = 80% ee > 99%



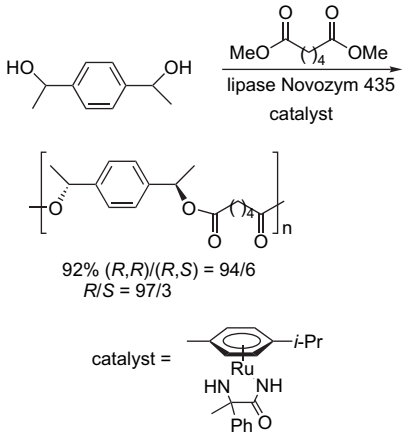
R = Ph: 75% ee = 84%
R = *i*-Pr: 93% ee = 86%
R = Cy: 73% ee = 90%
R = *n*-Pent: 82% ee = 48%
R = Bn: 70% ee = 74%
R = 2-Naph: 82% ee = 79%
R = *p*-BrC_6H_4: 81% ee = 88%
R = *p*-FC_6H_4: 75% ee = 86%
R = *p*-$MeOC_6H_4$: 96% ee = 21%



Scheme 110. DKRs of unsymmetrical diols with Shvo's catalyst and lipases.

place under the reaction conditions. This procedure constituted a new method for the synthesis of chiral γ-hydroxy ketones, which are precursors of versatile building blocks, such as tetrahydrofurans and dihydrofurans.

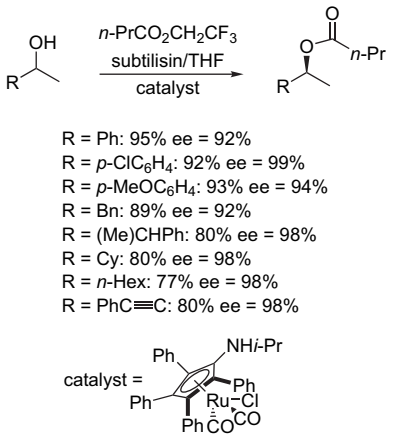
In 2006, Heise et al. reported a novel concept for the synthesis of chiral polyesters based on a lipase-catalysed DKR polymerisation of racemic diols.[168] As shown in Scheme 111, a mixture of stereoisomers of a secondary diol was enzymatically polymerised with a difunctional acyl donor (dicarboxylic acid derivative) and, because of its enantioselectivity, the lipase converted only the hydroxyl groups at the *R*-configured centres. In situ racemisation of the hydroxyl-substituted stereocentres from the *S* to the *R* configuration allowed the polymerisation to proceed to high conversion. This combination of a DKR with a polymerisation was performed in the presence of lipase Novozym 435, a Noyori-type ruthenium catalyst, and dimethyl adipate as the acyl donor, providing chiral polyesters from non-natural monomers.



Scheme 111. Synthesis of chiral polyesters via DKR polymerisation.

In order to obtain (*S*)-selective DKR of secondary alcohols, an enzyme with a complementary (*S*)-stereoselectivity was needed, since the lipase-catalysed DKR provides only (*R*)-products. In this context, Park et al. reported in 2003 the use of subtilisin instead of lipase, but the commercial form of subtilisin was not applicable to DKR, due to its low enzymatic activity and instability in non-aqueous medium.[169] However, these authors succeeded in enhancing its activity and stability by treating it with a surfactant before use. Hence, the combination of subtilisin with a ruthenium catalyst and trifluoroethyl butanoate as the acylating agent allowed the (*S*)-products to be obtained in good yields with high optical purities (Scheme 112). More recently, Bäckvall et al. have optimised the DKR of 1-phenylethanol by using a specially treated subtilisin, subtilisin Carlsberg, which was activated by two surfactants, octyl β-D-glycopyranoside and Brij 56.[170] This latter enzyme was about 4-to5-fold faster than the previously reported DKR, providing the corresponding chiral butanoate in 96% yield and 95% ee.

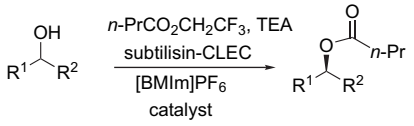
In addition, the (*S*)-selective DKR of alcohols with subtilisin was also possible in ionic liquids at room temperature.[155] In this case, a cymene–ruthenium complex was used as the



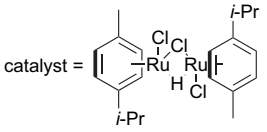
Scheme 112. DKR of secondary alcohols by subtilisin–ruthenium combination.

catalyst, and the optical purities of the final (*S*)-esters were lower than those of the (*R*)-esters obtained by using lipases, as shown in Scheme 102 (Scheme 113).

Metals other than ruthenium also have the potential to produce diverse DKR methods. However, although some rhodium, iridium, ruthenium and aluminium complexes are known to catalyse the racemisation of alcohols, only a few have proved to be compatible with enzymatic reactions. In this context, Akai et al. have recently developed a novel DKR process of allylic alcohols promoted by the combined use of lipases with [VO(O-SiPh$_3$)$_3$].[171] This complex catalysed the 1,3-transposition of the starting allylic alcohol, resulting in a thermodynamic equilibrium of two regioisomers, which underwent highly enantio- and chemoselective esterification under the action of the lipases (Scheme 114). Because the [VO(OSiPh$_3$)$_3$]-catalysed 1,3-transposition reactions were not sensitive to oxygen and moisture, this DKR method offered the advantage of a facile experimental procedure without the need for special apparatus (anaerobic conditions, as for ruthenium-catalysed reactions). Furthermore,

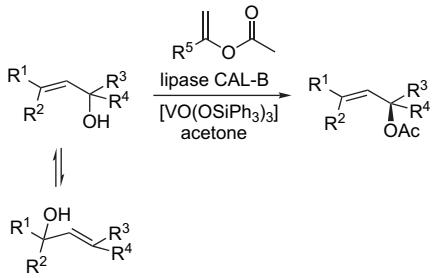


R^1 = Ph, R^2 = Et: 89% ee = 97%
R^1 = Ph, R^2 = *n*-Pr: 90% ee = 97%
R^1 = *m*-Tol, R^2 = Me: 90% ee = 85%
R^1 = *p*-Tol, R^2 = Me: 90% ee = 85%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = Me: 80% ee = 99%
R^1 = *p*-ClC$_6$H$_4$, R^2 = Me: 92% ee = 87%
R^1 = *p*-BrC$_6$H$_4$, R^2 = Me: 91% ee = 82%
R^1 = *p*-(HOCH$_2$CH$_2$)C$_6$H$_4$, R^2 = Me: 78% ee = 86%
R^1 = *m*-(HOCH$_2$CH$_2$)C$_6$H$_4$, R^2 = Me: 83% ee = 96%

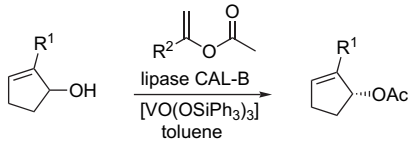


Scheme 113. DKR of secondary alcohols by subtilisin–ruthenium combination in ionic liquids.

it featured a unique preparation of chiral esters of secondary alcohols from the corresponding ketones via the readily available tertiary alcohols.



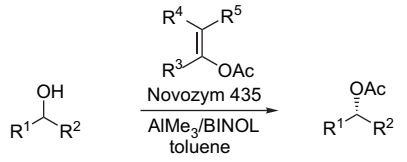
R^1, R^2 = $(CH_2)_2$-C(Me)$_2$-$(CH_2)_2$, R^3 = Me, R^4 = H,
R^5 = OEt: 88% ee = 97%
R^1, R^2 = $(CH_2)_2$-C(Me)$_2$-$(CH_2)_2$, R^3 = Me,
R^4 = R^5 = H: 94% ee = 98%
R^1, R^2 = $(CH_2)_6$, R^3 = Me, R^4 = H,
R^5 = OEt: 88% ee = 97%
R^1, R^2 = $(CH_2)_6$, R^3 = Me, R^4 = R^5 = H:
80% ee = 98%
R^1 = R^2 = *n*-Pr, R^3 = Me, R^4 = H,
R^5 = OEt: 93% ee = 98%
R^1 = R^2 = *n*-Pr, R^3 = Me, R^4 = R^5 = H:
93% ee = 99%



R^1 = Ph, R^2 = OEt: 91% ee = 97%
R^1 = Ph, R^2 = H: 96% ee = 99%
R^1 = C≡C-TMS, R^2 = OEt: 81% ee = 91%

Scheme 114. DKRs of allylic alcohols catalysed by a combination of lipases and $[VO(OSiPh_3)_3]$.

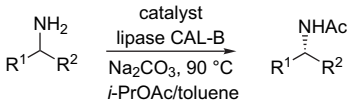
In addition, Berkessel et al. have demonstrated that aluminium could also be highly efficiently combined with lipases to afford the DKR of various secondary alcohols.[172] The best results were obtained when the inexpensive aluminium species was readily prepared by the reaction of $AlMe_3$ with a bidentate ligand such as BINOL, as shown in Scheme 115.



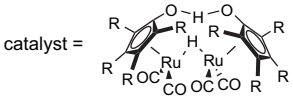
R^1 = R^3 = Ph, R^2 = Me, R^4 = R^5 = H: 96% ee = 96%
R^1 = R^3 = Cy, R^2 = Me, R^4 = R^5 = H: 98% ee = 99%
R^1 = *n*-Hex, R^2 = R^3 = Me, R^4 = *n*-Pent, R^5 = H: 93% ee = 80%
R^1 = Ph, R^2 = Et, R^3 = R^4 = R^5 = H: 99% ee = 98%
R^1 = *n*-Pent, R^2 = Et, R^3 = R^4 = R^5 = H: 95% ee = 95%

Scheme 115. DKR of secondary alcohols catalysed by a combination of lipases and $AlMe_3$/BINOL.

Enantiomerically pure chiral amines are particularly important to the pharmaceutical and agrochemical industries. Their production via DKR is more challenging than that of alcohols, since only a few practical procedures have been developed. Generally, the occurrence of this type of DKR requires a high temperature combined with a long reaction time.[173] In these harsh reaction conditions, most enzymes would be denaturated, making them unsuitable for DKR. Recently, milder conditions for amine racemisation have been developed through the use of ruthenium-, palladium- and iridium-based catalysts. As an example, Bäckvall and Paetzold developed in 2005 a highly efficient process for the DKR of a variety of unfunctionalised primary amines, which used a combination of a ruthenium catalyst and a lipase, leading to the corresponding amides in high yields and ees (Scheme 116).[174]



R^1 = Ph, R^2 = Me: 90% ee = 98%
R^1 = *m*-Tol, R^2 = Me: 69% ee = 98%
R^1 = *p*-FC_6H_4, R^2 = Me: 83% ee = 99%
R^1 = *p*-BrC_6H_4, R^2 = Me: 78% ee = 99%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me: 95% ee = 99%
R^1 = 2-Naph, R^2 = Me: 80% ee > 99%
R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 91% ee = 99%
R^1 = *n*-Hex, R^2 = Me: 85% ee = 93%
R^1 = $BnCH_2$, R^2 = Me: 78% ee = 95%
R^1 = Ph, R^2 = Et: 85% ee = 99%

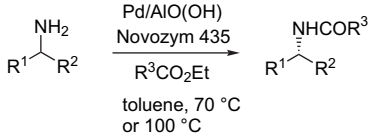


Scheme 116. DKR of primary amines catalysed by a combination of lipases and a ruthenium catalyst.

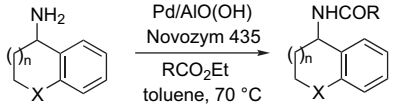
Very recently, Kim et al. have reported another DKR of primary amines using a recyclable Pd nanocatalyst combined with a lipase in the presence of ethyl acetate or ethyl methoxyacetate as the acyl donor.[175] As shown in Scheme 117, a series of primary amines and one amino acid amide have been efficiently resolved with good yields and high ees. The catalyst, Pd/AlO(OH), was prepared as palladium nanoparticules entrapped in aluminium hydroxide. Because this catalyst was highly thermostable, the DKR reactions could be operated at 100 °C with multiple recycling of the catalyst.

In addition, Jacobs et al. have developed the DKR of benzylic amines in the presence of a combination of palladium supported on an alkaline earth-type support such as $BaSO_4$ with a lipase.[176] Hence, this heterogeneous catalytic system has allowed various benzylic amines to be transformed into their corresponding enantiomerically pure amides with excellent yields and ees, as shown in Scheme 118.

The use of ruthenium- and palladium-based catalysts has significant limitations that restrict their industrial applicability including high catalyst loading, limited substrate scope and high substrate dilution. In this context, Page et al. reported in 2007 an efficient process for the DKR of a secondary amine using a novel iridium-based amine racemisation catalyst under significantly milder conditions than those described

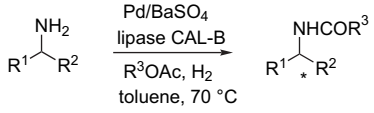


$R^1 = R^3 = Me$, $R^2 = p$-Tol: 91% ee = 97%
$R^1 = Ph$, $R^2 = p$-Tol, $R^3 = CH_2OMe$: 85% ee = 99%
$R^1 = R^3 = Me$, $R^2 = p$-$MeOC_6H_4$: 93% ee = 98%
$R^1 = Me$, $R^2 = p$-$MeOC_6H_4$, $R^3 = CH_2OMe$: 85% ee = 98%
$R^1 = R^3 = Me$, $R^2 = p$-$CF_3C_6H_4$: 95% ee = 98%
$R^1 = Me$, $R^2 = p$-$CF_3C_6H_4$, $R^3 = CH_2OMe$: 99% ee = 99%
$R^1 = Et$, $R^2 = Ph$, $R^3 = Me$: 90% ee = 98%
$R^1 = Et$, $R^2 = Ph$, $R^3 = CH_2OMe$: 96% ee = 99%
$R^1 = R^3 = Me$, $R^2 = CH_2Bn$: 95% ee = 98%
$R^1 = R^3 = Me$, $R^2 = Cy$: 93% ee = 99%
$R^1 = R^3 = Me$, $R^2 = n$-Hex: 92% ee = 98%
$R^1 = Bn$, $R^2 = CONH_2$, $R^3 = Me$: 96% ee = 98%



X = CH_2, n = 0, R = Me: 88% ee = 99%
X = CH_2, n = 0, R = CH_2OMe: 87% ee = 97%
X = CH_2, n = 1, R = Me: 86% ee = 97%
X = CH_2, n = 1, R = CH_2OMe: 84% ee = 99%
X = O, n = 1, R = Me: 94% ee = 98%
X = O, n = 1, R = CH_2OMe: 92% ee = 99%

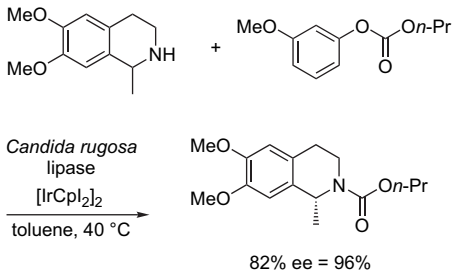
Scheme 117. DKRs of primary amines catalysed by a combination of lipases and a palladium nanocatalyst.



$R^1 = Ph$, $R^2 = Me$, $R^3 = i$-Pr: 91% ee > 99%
$R^1 = p$-$MeOC_6H_4$, $R^2 = Me$, $R^3 = Et$: 90% ee > 99%
$R^1 = 2$-Naph, $R^2 = Me$, $R^3 = i$-Pr: 89% ee = 99%
$R^1 = 1$-Naph, $R^2 = Me$, $R^3 = i$-Pr: 64% ee = 99%
$R^1 = p$-Tol, $R^2 = Me$, $R^3 = Et$: 73% ee > 99%

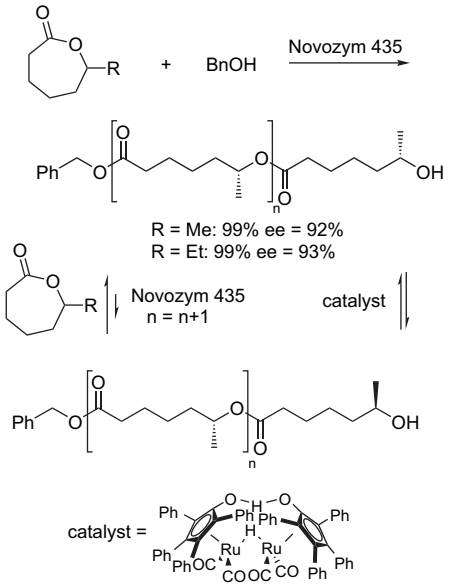
Scheme 118. DKRs of benzylic amines by a combination of $Pd/BaSO_4$ and lipases.

previously.[177] Hence, the combination of $[IrCpI_2]_2$ with *C. rugosa* lipase at 40 °C in toluene allowed the DKR of the racemic secondary amine, depicted in Scheme 119, in high yield and ee. The reaction was performed in 23 h on a 3 g scale in the presence of 3-methoxyphenylpropyl carbonate, providing the corresponding chiral product carbonate.



Scheme 119. DKR of a secondary amine by a combination of $[IrCpI_2]_2$ and lipases.

The scope of the combination catalysts has been extended to the asymmetric transformations of various substrates. As an example, Meijer et al. have recently developed a particularly elegant example of DKR applied to the synthesis of chiral polymers by iterative tandem catalysis.[178] Hence, these authors have shown that racemic ω-substituted caprolactones could be completely converted into chiral polyesters of remarkably high MW and high ee by combining lipase-catalysed ring-opening polymerisation with Ru-catalysed racemisation. Actually, Novozym 435 catalysed *S*-selectively the ring opening of the ω-substituted caprolactone, yielding an *S*-secondary alcohol, which is the slower-reacting enantiomer in lipase-catalysed reactions. The in situ Ru-catalysed racemisation of the terminal secondary alcohol was, therefore, required for propagation, and iterative operation of these two reactions enabled polymerisation. Both 6-methyl- and 6-ethyl-ε-caprolactones were successfully converted into the chiral polymer by using this methodology, as shown in Scheme 120.



Scheme 120. Synthesis of chiral polymers.

5. Conclusions

This review updates the principle methods employed to obtain DKR, reported in the literature since 2003, by either enzymatic or non-enzymatic methods and illustrates the diversity of useful products that can be obtained through this powerful concept. The last four years have witnessed significant developments in the efficiency and scope of the application of DKRs. Indeed, impressive examples using new enzymes and major progress in the DKRs of racemates have taken place over the past few years. The powerful combination of enzyme catalysis (for the resolution of a racemate) and metal catalysis (for the racemisation of the slow-reacting enantiomer) has also been the subject of spectacular development. In addition, a new type of DKRs, involving organocatalysts, has appeared

in the last few years, providing an impressive and steadily increasing number of publications. Even though transition-metal catalysis will certainly continue to play a central role in the DKR concept in the future, the last few years have, however, seen an increasing trend towards the use of metal-free catalysts. The reasons for this trend are the often high costs of transition metals and the problems that their residues, mainly in pharmaceutical products, can cause. Although asymmetric catalysis has undergone development during the last two decades, the most common process in industry today to obtain enantiomerically pure compounds is still via resolution of racemic mixtures, despite the major disadvantage that only a maximum of 50% product yield can be obtained. It is therefore not surprising that DKR, which solves the problem of the limitation in yield, has attracted an increasing amount of interest from both the industrial and the academic perspectives over the past few years.

References and notes

1. Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327.
2. (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56; (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490; (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447–456; (d) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, 321–331; (e) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11–15; (f) Azerad, R.; Buisson, D. *Curr. Opin. Chem. Biol.* **2000**, *11*, 565–571; (g) Stecher, H.; Faber, K. *Synthesis* **1997**, 1–16; (h) Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587.
3. Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1995.
4. Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
5. Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15–32.
6. (a) Koskinen, A. *Asymmetric Synthesis of Natural Products*; John Wiley and Sons: New York, NY, 1993; (b) Atkinson, S. C. *Stereoselective Synthesis*; John Wiley and Sons: New York, NY, 1995.
7. (a) Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011–3030; (b) Vedejs, E.; Jure, M. *Angew Chem., Int. Ed.* **2005**, *44*, 3974–4001; (c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824; (d) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446.
8. (a) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700–7706; (b) Nunami, K.-i.; Kubota, H.; Kubo, A. *Tetrahedron Lett.* **1994**, *35*, 8639–8642; (c) Devine, P. N.; Dolling, U. H.; Heid, R. M.; Tschaen, D. M. *Tetrahedron Lett.* **1996**, *37*, 2683–2686.
9. Ammazzalorso, A.; Amoroso, R.; Bettoni, G.; De Filippis, B.; Giampietro, L.; Maccallini, C.; Tricca, M. L. *Arkivoc* **2004**, *V*, 375–381.
10. Ammazzalorso, A.; Amoroso, R.; Bettoni, G.; De Filippis, B.; Fantacuzzi, M.; Giampietro, L.; Maccallini, C.; Tricca, M. L. *Eur. J. Org. Chem.* **2006**, 4088–4091.
11. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2004**, *15*, 593–601.
12. Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545–2549.
13. (a) Nam, J.; Chang, J.-Y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727–7730; (b) Nam, J.; Chang, J.-Y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60*, 6311–6318.
14. Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Park, Y. S. *Tetrahedron* **2005**, *61*, 2743–2750.
15. Shin, E.-k.; Kim, H. J.; Kim, Y.; Kim, Y.; Park, Y. S. *Tetrahedron Lett.* **2006**, *47*, 1933–1935.
16. Kim, H. J.; Shin, E.-k.; Chang, J.-y.; Kim, Y.; Park, Y. S. *Tetrahedron Lett.* **2005**, *46*, 4115–4117.
17. Kim, H. J.; Kim, Y.; Choi, E. T.; Lee, M. H.; No, E. S.; Park, Y. S. *Tetrahedron* **2006**, *62*, 6303–6311.
18. Gil Santos, A.; Pereira, J.; Afonso, C. A. M.; Frenking, G. *Chem.—Eur. J.* **2005**, *11*, 330–343.
19. Treweeke, N. R.; Hitchcock, P. B.; Pardoe, D. A.; Caddick, S. *Chem. Commun.* **2005**, 1868–1870.
20. Sugiyama, S.; Watanabe, S.; Inoue, T.; Kurihara, R.; Itou, T.; Ishii, K. *Tetrahedron* **2003**, *59*, 3417–3425.
21. (a) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80; (b) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191; (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729.
22. (a) Amat, M.; Bassas, O.; Pericas, M. A.; Pasto, M.; Bosch, J. *Chem. Commun.* **2005**, 1327–1329; (b) Amat, M.; Bassas, O.; Llor, N.; Canto, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 7872–7881; (c) Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, J. *Org. Lett.* **2005**, *7*, 3653–3656.
23. Amat, M.; Escolano, C.; Lozano, O.; Llor, N.; Bosch, J. *Org. Lett.* **2003**, *5*, 3139–3142.
24. (a) Bassa, O.; Llor, N.; Santos, M. M. M.; Griera, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817–2820; (b) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207.
25. Nakamura, S.; Nakayama, J.-i.; Toru, T. *J. Org. Chem.* **2003**, *68*, 5766–5768.
26. Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D. *Angew Chem., Int. Ed.* **2005**, *44*, 2259–2261.
27. Pearson, A. J.; Wang, X. *Tetrahedron Lett.* **2005**, *46*, 3123–3126.
28. Chan, V.; Kim, J. G.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2004**, *6*, 2051–2053.
29. Jimeno, C.; Rios, R.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2004**, *60*, 4543–4548.
30. Ravasio, N.; Zaccheria, F.; Fusi, A.; Psaro, R. *Appl. Catal., A* **2006**, *315*, 114–119.
31. Paley, R. S.; Liu, J. M.; Lichtenstein, B. R.; Knoedler, V. L.; Sanan, T. T.; Adams, D. J.; Fernandez, J.; Rablen, P. R. *Org. Lett.* **2003**, *5*, 309–312.
32. Khiar, N.; Araujo, C. S.; Alcudia, F.; Fernandez, I. *J. Org. Chem.* **2002**, *67*, 345–356.
33. Kolodiazhnyi, O. I.; Gryshkun, E. V.; Andrushko, N. V.; Freytag, M.; Jones, P. G.; Schmutzler, R. *Tetrahedron: Asymmetry* **2003**, *14*, 181–183.
34. (a) Balcells, D.; Maseras, F.; Khiar, N. *Org. Lett.* **2004**, *6*, 2197–2200; (b) Balcells, D.; Ujaque, G.; Fernandez, I.; Khiar, N.; Maseras, F. *J. Org. Chem.* **2006**, *71*, 6388–6396.
35. Dingerdissen, U.; Riermeier, T.; Wolf, D.; Zanthoff, H. W.; Trauthwein, H. *Elements, Degussa Sci. Newslett.* **2003**, *3*, 14–18.
36. (a) Turner, N. J. *Curr. Opin. Biotechnol.* **2003**, *14*, 401–406; (b) Turner, N. J. *Trends Biotechnol.* **2003**, *21*, 474–478; (c) Alexeeva, M.; Carr, R.; Turner, N. J. *Org. Biomol. Chem.* **2003**, *1*, 4133–4137; (d) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114–119; (e) Schnell, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2003**, *345*, 653–666; (f) Bornscheuer, U. T. *Adv. Biochem. Eng. Biotechnol.* **2005**, *100*, 181–203; (g) Gadler, P.; Glueck, S. M.; Kroutil, W.; Nestl, B. M.; Larissegger-Schnell, B.; Ueberbacher, B. T.; Wallner, S. R.; Faber, K. *Biochem. Soc. Trans.* **2006**, *34*, 296–300.
37. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.
38. (a) Genêt, J.-P.; Mallart, S.; Jugé, S. French patent 8,911,159, 1989; (b) Genêt, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908–918.
39. Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931–1941.
40. (a) Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Chem. Commun.* **2004**, 1296–1297; (b) Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, 3017–3026.
41. Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882–884.
42. Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2004**, *15*, 1899–1908.

43. Mordant, C.; Reymond, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* **2004**, *60*, 9715–9723.
44. Ohkuma, T.; Li, J.; Noyori, R. *Synlett* **2004**, 1383–1386.
45. Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681–2683.
46. Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939–941.
47. Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864–1876.
48. Li, X.; List, B. *Chem. Commun.* **2007**, 1739–1741.
49. Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 2967–2973.
50. Xie, J.-H.; Zhou, Z.-T.; Kong, W.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1868–1869.
51. Ros, A.; Magriz, A.; Dietrich, H.; Fernandez, R.; Alvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127–130.
52. Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626–1627.
53. Scalone, M.; Waldmeier, P. *Org. Process Res. Dev.* **2003**, *7*, 418–425.
54. (a) Eustache, F.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2003**, *68*, 9994–10002; (b) Eustache, F.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2003**, *44*, 8823–8826.
55. Ros, A.; Magriz, A.; Dietrich, H.; Ford, M.; Fernandez, R.; Lassaletta, J. M. *Adv. Synth. Catal.* **2005**, *347*, 1917–1920.
56. Ito, M.; Kitahara, S.; Ikariya, T. *J. Am. Chem. Soc.* **2005**, *127*, 6172–6173.
57. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090–3100.
58. Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563–1565.
59. Trost, B. M.; Brown, B. S.; McEachern, E. J.; Kuhn, O. *Chem.—Eur. J.* **2003**, *9*, 4442–4451.
60. Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014–7024.
61. Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837.
62. Lüssem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041–4052.
63. (a) Gais, H.-J.; Bondarev, O.; Hetzer, R. *Tetrahedron Lett.* **2005**, *46*, 6279–6283; (b) Gais, H.-J. *Asymm. Synth.* **2007**, 84–89.
64. McDermott, M. C.; Stephenson, G. R.; Hughes, D. L.; Walkington, A. J. *Org. Lett.* **2006**, *8*, 2917–2920.
65. Durand, J.; Gladiali, S.; Erre, G.; Zangrando, E.; Milani, B. *Organometallics* **2007**, *26*, 810–818.
66. Makino, K.; Fujii, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 481–485.
67. Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785.
68. Makino, K.; Iwasaki, M.; Hamada, Y. *Org. Lett.* **2006**, *8*, 4573–4576.
69. Yamada, T.; Nagata, T.; Sugi, K. D.; Yorozu, K.; Ikeno, T.; Ohtsuka, Y.; Miyazaki, D.; Mukaiyama, T. *Chem.—Eur. J.* **2003**, *9*, 4485–4509.
70. Kunz, U.; Kirschning, A.; Wen, H.-L.; Solodenko, W.; Cecilia, R.; Kappe, C. O.; Turek, T. *Catal. Today* **2005**, *105*, 318–324.
71. Szori, K.; Szöllosi, G.; Bartok, M. *Adv. Synth. Catal.* **2006**, *348*, 515–522.
72. Sugimura, T.; Watanabe, J.; Nakagawa, S.; Okuyama, T. *J. Mol. Catal., A* **2006**, *248*, 233–236.
73. Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159–167.
74. Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew Chem., Int. Ed.* **2005**, *44*, 6177–6180.
75. (a) Saitoh, F.; Nishida, H.; Mukaihira, T.; Aikawa, K.; Mikami, K. *Eur. J. Org. Chem.* **2006**, 5454–5457; (b) Saitoh, F.; Nishida, H.; Mukaihira, T.; Aikawa, K.; Mikami, K. *Adv. Synth. Catal.* **2007**, *349*, 617–628.
76. Braun, M.; Kotter, W. *Angew Chem., Int. Ed.* **2004**, *43*, 514–517.
77. Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943–10951.
78. Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208.
79. Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
80. Dalko, P. I.; Moisan, L. *Angew Chem., Int. Ed.* **2004**, *43*, 5138–5175.
81. Hang, J.; Deng, L. *Synlett* **2003**, 1927–1930.
82. (a) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898–1900; (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew Chem., Int. Ed.* **2005**, *44*, 807–811; (c) Berkessel, A. *Pure Appl. Chem.* **2005**, *77*, 1277–1284.
83. Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J.-M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4*, 4319–4330.
84. Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184.
85. Ward, D. E.; Jheengut, V.; Beye, G. E. *J. Org. Chem.* **2006**, *71*, 8989–8992.
86. See Ref. 28.
87. Wang, Y.; Shen, Z.; Li, B.; Zhang, Y.; Zhang, Y. *Chem. Commun.* **2007**, 1284–1286.
88. Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320–11330.
89. Tararov, V. I.; Börner, A. *Synlett* **2005**, 203–211.
90. Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074–13075.
91. Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337–1339.
92. Nugent, T. C.; Seemayer, R. *Org. Process Res. Dev.* **2006**, *10*, 142–148.
93. Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134–8135.
94. Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2005**, *127*, 1374–1375.
95. Hayakawa, Y.; Hyodo, M.; Kimura, K.; Kataoka, M. *Chem. Commun.* **2003**, 1704–1705.
96. Perlikowska, W.; Gouygou, M.; Mikolajczyk, M.; Daran, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3519–3529.
97. (a) Bringmann, G.; Tasler, S.; Pfeifer, R.-M.; Breuning, M. *J. Organomet. Chem.* **2002**, *661*, 49–65; (b) Bringmann, G.; Breuning, M.; Pfeifer, R.-M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2002**, *661*, 31–47; (c) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew Chem., Int. Ed.* **2005**, *44*, 5384–5427.
98. (a) Bringmann, G.; Breuning, R.-M.; Schreiber, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2225–2228; (b) Bringmann, G.; Pfeifer, R.-M.; Rummey, C.; Hartner, K.; Breuning, M. *J. Org. Chem.* **2003**, *68*, 6859–6863; (c) Bringmann, G.; Pfeifer, R.-M.; Schreiber, P.; Hartner, K.; Schraut, M.; Breuning, M. *Tetrahedron* **2004**, *60*, 4349–4360.
99. Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533–9540.
100. Abe, H.; Takeda, S.; Fujita, T.; Nishioka, K.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2004**, *45*, 2327–2329.
101. Ohmori, K.; Tamiya, M.; Kitamura, M.; Kato, H.; Oorui, M.; Suzuki, K. *Angew Chem., Int. Ed.* **2005**, *44*, 3871–3874.
102. Bringmann, G.; Scharl, H.; Maksimenka, K.; Radacki, K.; Braunschweig, H.; Wich, P.; Schmuck, C. *Eur. J. Org. Chem.* **2006**, 4349–4361.
103. Kamikawa, K.; Norimura, K.; Furusyo, M.; Uno, T.; Sato, Y.; Konoo, A.; Bringmann, G.; Uemura, M. *Organometallics* **2003**, *22*, 1038–1046.
104. Cho, Y.-H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, *69*, 3811–3823.
105. Sukumaran, J.; Hanefeld, U. *Chem. Soc. Rev.* **2005**, *34*, 530–542.
106. Sharfuddin, M.; Narumi, A.; Iwai, Y.; Miyazawa, K.; Yamada, S.; Kakuchi, T.; Kaga, H. *Tetrahedron: Asymmetry* **2003**, *14*, 1581–1585.
107. Paizs, C.; Tosa, M.; Majdik, C.; Tähtinen, P.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 619–627.
108. Paizs, C.; Tähtinen, P.; Lundell, K.; Poppe, L.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron: Asymmetry* **2003**, *14*, 1895–1904.
109. Paizs, C.; Tähtinen, P.; Tosa, M.; Majdik, C.; Irimie, F. D.; Kanerva, L. T. *Tetrahedron* **2004**, *60*, 10533–10540.
110. (a) Veum, L.; Hanefeld, U. *Synlett* **2005**, 2382–2384; (b) Veum, L.; Kanerva, L. T.; Halling, P. J.; Maschmeyer, T.; Hanefeld, U. *Adv. Synth. Catal.* **2005**, *347*, 1015–1021.
111. Veum, L.; Hanefeld, U. *Tetrahedron: Asymmetry* **2004**, *15*, 3707–3709.
112. Sanfilippo, C.; Nicolosi, G.; Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **2005**, *16*, 1079–1084.
113. Odman, P.; Wessjohann, L. A.; Bornscheuer, U. T. *J. Org. Chem.* **2005**, *70*, 9551–9555.
114. Cong, F.-D.; Wang, Y.-H.; Ma, C.-Y.; Yu, H.-F.; Han, S.-P.; Tao, J.; Cao, S.-G. *Enzyme Microb. Technol.* **2005**, *36*, 595–599.
115. Limanto, J.; Shafiee, A.; Devine, P. N.; Upadhyay, V.; Desmond, R. A.; Foster, B. R.; Gauthier, D. R.; Reamer, R. A.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 2372–2375.

116. (a) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. *Chem.—Eur. J.* **2005**, *11*, 386–397; (b) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. *Chem. Commun.* **2003**, 1928–1929.
117. Zhu, Y.; Fow, K.-L.; Chuah, G.-K.; Jaenicke, S. *Chem.—Eur. J.* **2007**, *13*, 541–547.
118. Teo, E.-L.; Chuah, G.-K.; Huguet, A. R. J.; Jaenicke, S.; Pande, G.; Zhu, Y. *Catal. Today* **2004**, *97*, 263–270.
119. Lozano, P.; De Diego, T.; Larnicol, M.; Vaultier, M.; Iborra, J. L. *Biotechnol. Lett.* **2006**, *28*, 1559–1565.
120. Ong, A. L.; Kamaruddin, H.; Bhatia, S. *Process Biochem.* **2005**, *40*, 3526–3535.
121. Gotor-Fernandez, V.; Gotor, V. *Curr. Org. Chem.* **2006**, *10*, 1125–1143.
122. Liljeblad, A.; Kiviniemi, A.; Kanerva, L. T. *Tetrahedron* **2004**, *60*, 671–677.
123. Crawford, J. B.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2007**, *72*, 669–671.
124. Gastaldi, S.; Escoubet, S.; Vanthuyne, N.; Gil, G.; Bertrand, M. P. *Org. Lett.* **2007**, *9*, 837–839.
125. Osprian, I.; Fechter, M. H.; Griengl, H. *J. Mol. Catal., B* **2003**, *24–25*, 89–98.
126. Zimmermann, V.; Beller, M.; Kragl, U. *Org. Process Res. Dev.* **2006**, *10*, 622–627.
127. Lo, H.-H.; Kao, C.-H.; Lee, D.-S.; Yang, T.-K.; Hsu, W.-H. *Chirality* **2003**, *15*, 699–702.
128. Asano, Y.; Yamaguchi, S. *J. Am. Chem. Soc.* **2005**, *127*, 7696–7697.
129. Pesti, J. A.; Yin, J.; Zhang, L.-h.; Anzalone, L.; Waltermire, R. E.; Ma, P.; Gorko, E.; Confalone, P. N.; Fortunak, J.; Silverman, C.; Blackwell, J.; Chung, J. C.; Hrytsak, M. D.; Cooke, M.; Powell, L.; Ray, C. *Org. Process Res. Dev.* **2004**, *8*, 22–27.
130. Fazlena, H.; Kamaruddin, A. H.; Zulkali, M. M. D. *Bioprocess Biosyst. Eng.* **2006**, *28*, 227–233.
131. Wen, W.-Y.; Ng, I.-S.; Tsai, S.-W. *J. Chem. Technol. Biotechnol.* **2006**, *81*, 1715–1721.
132. Lin, H.-Y.; Tsai, S.-W. *J. Mol. Catal., B* **2003**, *24–25*, 111–120.
133. Wang, L. W.; Cheng, Y. C.; Tsai, S. W. *Bioprocess Biosyst. Eng.* **2004**, *27*, 39–49.
134. Kalaitzakis, D.; Rozzell, J. D.; Kambourakis, S.; Smonou, I. *Org. Lett.* **2005**, *7*, 4799–4801.
135. Kambourakis, S.; Rozzell, J. D. *Adv. Synth. Catal.* **2003**, *345*, 699–705.
136. Kosjek, B.; Tellers, D. M.; Biba, M.; Farr, R.; Moore, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2798–2803.
137. Yang, Y.; Drolet, M.; Kayser, M. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2748–2753.
138. Blanchard, N.; van de Weghe, P. *Org. Biomol. Chem.* **2006**, *4*, 2348–2353.
139. Zhou, J.; Wang, W.; Thurecht, K. J.; Villarroya, S.; Howdle, S. M. *Macromolecules* **2006**, *39*, 7302–7305.
140. Gutiérrez, M.-C.; Furstoss, R.; Alphand, V. *Adv. Synth. Catal.* **2005**, *347*, 1051–1059.
141. Spelberg, J. H. L.; Tang, L.; Kellogg, R. M.; Janssen. *Tetrahedron: Asymmetry* **2004**, *15*, 1095–1102.
142. Kobler, C.; Effenberger, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3731–3742.
143. Stürmer, R. *Angew Chem., Int. Ed.* **1997**, *36*, 1173–1174.
144. (a) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261; (b) Pamies, O.; Bäckvall, J.-E. *Curr. Opin. Biotechnol.* **2003**, *14*, 407–413; (c) Pamies, O.; Bäckvall, J.-E. *Trends Biotechnol.* **2004**, *22*, 130–135; (d) Martin-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232; (e) Bäckvall, J.-E. *Asymm. Synth.* **2007**, 171–175.
145. Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669.
146. Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Korean Chem. Soc.* **2005**, *26*, 515–522.
147. (a) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825; (b) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J.-E. *Angew Chem., Int. Ed.* **2004**, *43*, 6535–6539; (c) Ell, A. H.; Johnson, J. B.; Bäckvall, J.-E. *Chem. Commun.* **2003**, 1652–1653.
148. Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972–1977.
149. Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526.
150. Riermeier, T. H.; Gross, P.; Monsees, A.; Hoff, M.; Trauthwein, H. *Tetrahedron Lett.* **2005**, *46*, 3403–3406.
151. Roengpithya, C.; Patterson, D. A.; Gibbins, E. J.; Taylor, P. C.; Livingston, A. G. *Ind. Eng. Chem. Res.* **2006**, *45*, 7101–7109.
152. Wolfson, A.; Yehuda, C.; Shokin, O.; Tavor, D. *Lett. Org. Chem.* **2006**, *3*, 107–110.
153. Karvembu, R.; Prabhakaran, R.; Natarajan, K. *Coord. Chem. Rev.* **2005**, *249*, 911–918.
154. Verzijl, G. K. M.; de Vries, J. G.; Broxterman, Q. B. *Tetrahedron: Asymmetry* **2005**, *16*, 1603–1610.
155. Kim, M.-J.; Kim, H. M.; Kim, D.; Ahn, Y.; Park, J. *Green Chem.* **2004**, *6*, 471–474.
156. Van Nispen, S. F. G. M.; van Buijtenen, J.; Vekemans, J. A. J. M.; Meuldijk, J.; Hulshof, L. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2299–2305.
157. Pamies, O.; Bäckvall, J. E. *J. Org. Chem.* **2003**, *68*, 4815–4818.
158. Fransson, A.-B. L.; Boren, L.; Pamies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2005**, *70*, 2582–2587.
159. Kielbasinski, P.; Rachwalski, M.; Mikolajczyk, M.; Moelands, M. A. H.; Zwanenburg, B.; Rutjes, F. P. J. T. *Tetrahedron: Asymmetry* **2005**, *16*, 2157–2160.
160. Hoyos, P.; Fernandez, M.; Sinisterra, J. V.; Alcantara, A. R. *J. Org. Chem.* **2006**, *71*, 7632–7637.
161. Akai, S.; Tanimoto, K.; Kita, Y. *Angew Chem., Int. Ed.* **2004**, *43*, 1407–1410.
162. Martin-Matute, B.; Edin, M.; Bäckvall, J.-E. *Chem.—Eur. J.* **2006**, *12*, 6053–6061.
163. Fransson, A.-B. L.; Xu, Y.; Leijondahl, K.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 6309–6316.
164. Edin, M.; Martin-Matute, B.; Bäckvall, J.-E. *Tetrahedron: Asymmetry* **2006**, *17*, 708–715.
165. Olofsson, B.; Bogar, K.; Fransson, A.-B. L.; Bäckvall, J.-E. *J. Org. Chem.* **2006**, *71*, 8256–8260.
166. (a) Edin, M.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 2216–2222; (b) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761–5766.
167. Martin-Matute, B.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 9191–9195.
168. Hilker, I.; Rabani, G.; Verzijl, G. K. M.; Palmans, A. R. A.; Heise, A. *Angew Chem., Int. Ed.* **2006**, *45*, 2130–2132.
169. Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494–11495.
170. Boren, L.; Martin-Matute, B.; Xu, Y.; Cordova, A.; Bäckvall, J.-E. *Chem.—Eur. J.* **2006**, *12*, 225–232.
171. Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew Chem., Int. Ed.* **2006**, *45*, 2592–2595.
172. Berkessel, A.; Sebastian-Ibarz, M. L.; Müller, T. N. *Angew Chem., Int. Ed.* **2006**, *45*, 6567–6570.
173. Kim, W.-H.; Karvembu, R.; Park, J. *Bull. Korean Chem. Soc.* **2004**, *25*, 931–933.
174. Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621.
175. Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159.
176. (a) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309; (b) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034–2043.
177. Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247–1250.
178. (a) van As, B. A. C.; van Buijtenen, J.; Heise, A.; Broxterman, Q. B.; Verzijl, G. K. M.; Palmans, A. R. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 9964–9965; (b) van Buijtenen, J.; van As, B. A. C.; Meuldijk, J.; Palmans, A. R. A.; Vekemans, J. A. J. M.; Hulshof, L. A.; Meijer, E. W. *Chem. Commun.* **2006**, 3169–3171.

Biographical sketch

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