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Recent developments in dynamic kinetic resolution

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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 2008 to the middle of 2010. This fast-moving field was most recently reviewed in 2008.[1] Prior to that, this area has been the subject of several excellent review articles.[2] Reviews concentrating on DKR based on chemoenzymatic methods have also been reported.[3] 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

Abbreviations: Ac, acetyl; AIBN, 2,2′-azobisisobutyronitrile; Ar, aryl; Atm, atmosphere; BARF, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; BIPHEP, 2,2′-bis(diphenylphosphino)-1,1′-biphenyl; Bn, benzyl; BTAH, benzyltrimethylammonium hydroxide; Bu, butyl; Bz, benzoyl; c, cyclo; Cod, cyclooctadiene; Cp, cyclopentadienyl; CPME, cyclopentyl methyl ether; Cy, cyclohexyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DACH, 1,2-diaminocyclohexane; dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DIEA, diisopropylethylamine; DIFLUORPHOS, 5,5′-bis(diphenylphosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole; DKR, dynamic kinetic resolution; DMAPEN, 2-dimethylamino-1-phenylethylamine; DMF, dimethylformamide; DMM, dimethylmethoxy; dmpe, 1,2-bis(dimethylphosphino)-ethane; DMSO, dimethylsulfoxide; DPEN, 1,2-diphenylethylenediamine; DYKAT, dynamic kinetic asymmetric transformation; ee, enantiomeric excess; Et, ethyl; Fu, furyl; GABA, γ-aminobutyric acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; Hex, hexyl; Hept, heptyl; L, ligand; LDA, lithium diisopropylamide; Me, methyl; MOM, methoxymethyl; Ms, mesyl; NADPH, nicotinamide adenine dinucleotide phosphate; Naph, naphthyl; Non, nonyl; Nu, nucleophile; Pa, pascal; Pent, pentyl; Ph, phenyl; PHOX, phosphinooxazoline; PMB, *p*-methoxybenzoyl; Pr, propyl; py, pyridyl; PYBOX, 2,6-bis(2-oxazolyl)pyridine; SDP, spiro diphosphine; SEM, 2-(trimethylsilyl)ethoxymethyl; TBAI, tetra-*n*-butylammonium iodide; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TFA, trifluoroacetic acid; TFE, trifluoroethanol; THF, tetrahydrofuran; Thio, thiophene; Tf, trifluoromethanesulphonyl; TMS, trimethylsilyl; Tol, tolyl; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, 4-toluenesulfonyl (tosyl).

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DKRs, and enzymatic or non-enzymatic transition-metal-catalysed DKRs have considerably expanded the synthetic scope of the process. In addition, novel enzymatic DKRs have been developed.

The importance of chirality is well recognised, mainly in connection with the fact that nearly all natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. Indeed, the use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. Indeed, the preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry.[4] The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals,[5] in electronic and optical devices, as components in polymers with novel properties and as probes of biological function, has made asymmetric synthesis a prominent area of investigation.[6] 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.[7] 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.[8] 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).

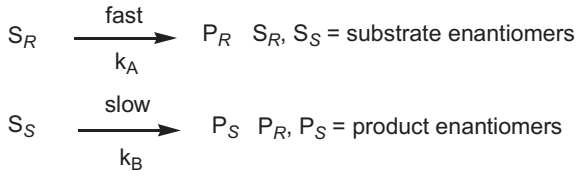


Fig. 1. Classical kinetic resolution.

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 is possible

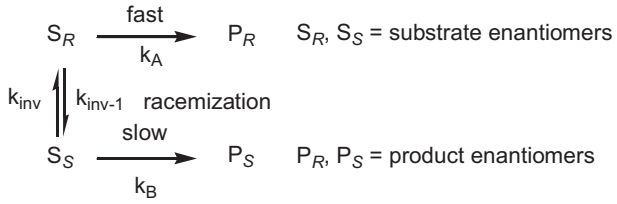


Fig. 2. Dynamic kinetic resolution.

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 Fig. 3.

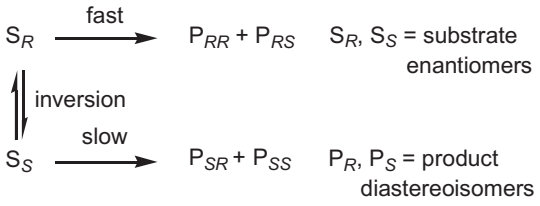


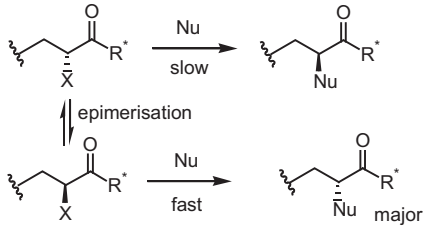
Fig. 3. Enantioselective synthesis of diastereoisomer via DKR.

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

2. Non-enzymatic methods

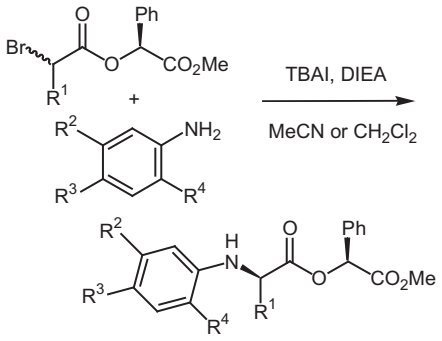
2.1. Chiral auxiliaries

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. 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.[9] 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 carboxylated function.

Extensive studies have been carried out on the 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 reached. This methodology has been recently recognised as a powerful synthetic method for asymmetric syntheses of α-heteroatom-substituted carboxylic acid derivatives. As an example, Park and Lee have applied this methodology to the nucleophilic substitution reaction of α-bromo esters containing methyl (*S*)-mandelate as chiral auxiliaries.[10] Hence, the displacement of the bromine with various aryl amine nucleophiles was found to proceed with high diastereoselectivities of up to 92% de combined with high yields to give the corresponding chiral amines, as shown in Scheme 2. The DKR was performed in the presence of tetra-*n*-butylammonium iodide (TBAI) combined with diisopropylethylamine (DIEA) in dichloromethane or acetonitrile as the solvent at room temperature.

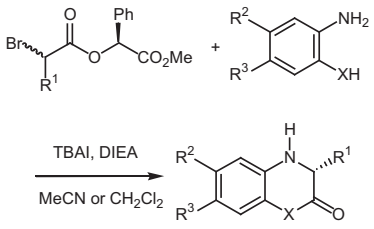


R^1 = Ph, R^2 = R^4 = H, R^3 = MeO: 93% de = 92%
R^1 = Me, R^2 = R^4 = H, R^3 = MeO: 88% de = 80%
R^1 = Et, R^2 = R^4 = H, R^3 = MeO: 95% de = 82%
R^1 = *n*-Bu, R^2 = R^4 = H, R^3 = MeO: 82% de = 80%
R^1 = Ph, R^2 = R^3 = H, R^4 = MeO: 93% de = 92%
R^1 = Me, R^2 = R^3 = H, R^4 = MeO: 70% de = 72%
R^1 = Ph, R^3 = R^4 = H, R^2 = MeO: 80% de = 88%
R^1 = Et, R^3 = R^4 = H, R^2 = MeO: 878% de = 80%

Scheme 2. Nucleophilic substitution of α-bromo esters containing methyl (*S*)-mandelate with aryl amines.

The scope of this methodology was extended to the reaction of these α-bromo esters with 1,2-diaminobenzene and 2-aminohydroxybenzene nucleophiles, allowing the asymmetric syntheses of the corresponding (*R*)-dihydroquinoxalinones and (*R*)-dihydrobenzoxazinones, respectively, the structural cores of which are of high interest as important pharmacophores in many biologically active compounds.[10] As shown in Scheme 3, the substitution reaction of methyl (*S*)-mandelate-derived α-bromo esters with variously substituted 1,2-phenylenediamines was spontaneously followed by cyclisation, yielding the corresponding chiral substituted dihydroquinoxalinones in both high yields of up to 92% and diastereoselectivities of up to 94% de. Similarly, the reaction between the α-bromo-α-phenyl ester and variously substituted 2-aminophenols afforded the corresponding chiral dihydrobenzoxazinones in good yields and high diastereoselectivities of up to 82% de (Scheme 3). Since both enantiomers of mandelic acid are readily available, this simple and easy methodology enables the preparation of the corresponding (*S*)-dihydroquinoxalinones and (*S*)-dihydrobenzoxazinones.

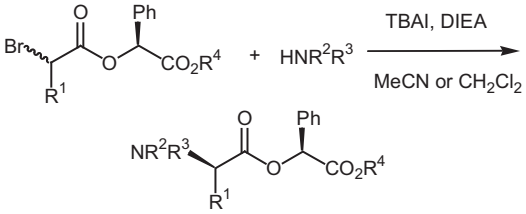
In 2010, these authors also applied this methodology to various alkyl amine nucleophiles, which provided in the same conditions the corresponding α-amino esters with up to 81% yield and 94% de, as shown in Scheme 4.[11] Moreover, the substitution of (*S*)-



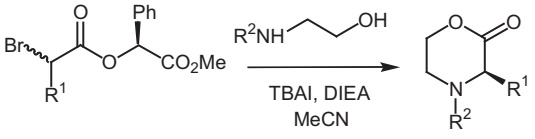
R^1 = Ph, R^2 = R^3 = H, X = NH: 92% de = 92%
R^1 = Ph, R^2 = R^3 = Cl, X = NH: 87% de = 94%
R^1 = Ph, R^2 = R^3 = Me, X = NH: 90% de = 88%
R^1 = Me, R^2 = R^3 = H, X = NH: 79% de = 78%
R^1 = Et, R^2 = R^3 = Me, X = NH: 81% de = 84%
R^1 = *n*-Bu, R^2 = R^3 = H, X = NH: 71% de = 80%
R^1 = Ph, R^2 = R^3 = H, X = O: 71% de = 82%
R^1 = Ph, R^2 = Me, R^3 = H, X = O: 79% de = 80%
R^1 = Ph, R^2 = H, R^3 = Me, X = O: 68% de = 80%
R^1 = Ph, R^2 = *t*-Bu, R^3 = H, X = O: 80% de = 82%

Scheme 3. Synthesis of (*R*)-dihydroquinoxalinones and (*R*)-dihydrobenzoxazinones.

mandelate-derived α-bromo esters with *N*-substituted 2-aminoethanol nucleophiles, which was followed by spontaneous cyclisation, provided a practical protocol for the asymmetric synthesis of 3-substituted morpholin-2-ones with enantioselectivities of up to 90% de, as shown in Scheme 4.



R^1 = Ph, R^2 = R^3 = Bn, R^4 = Me: 86% de = 94%
R^1 = R^4 = Me, R^2 = R^3 = Bn: 70% de = 80%
R^1 = Ph, R^2 = R^3 = Bn, R^4 = *i*-Pr: 84% de = 94%
R^1 = Ph, R^2 = R^3 = *n*-Bu, R^4 = Me: 92% de = 82%

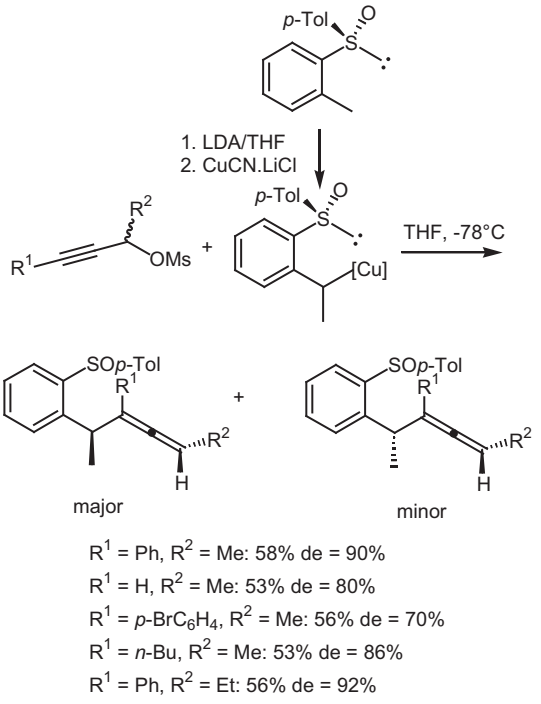


R^1 = Ph, R^2 = Bn: 81% de = 80%
R^1 = Ph, R^2 = *p*-MeOC$_6$H$_4$CH$_2$: 58% de = 82%
R^1 = Ph, R^2 = 2-Naph: 55% de = 82%
R^1 = Ph, R^2 = *p*-MeOC$_6$H$_4$: 66% de = 90%

Scheme 4. Nucleophilic substitution of α-bromo esters containing methyl (*S*)-mandelate with alkyl amines and synthesis of 3-substituted morpholin-2-ones.

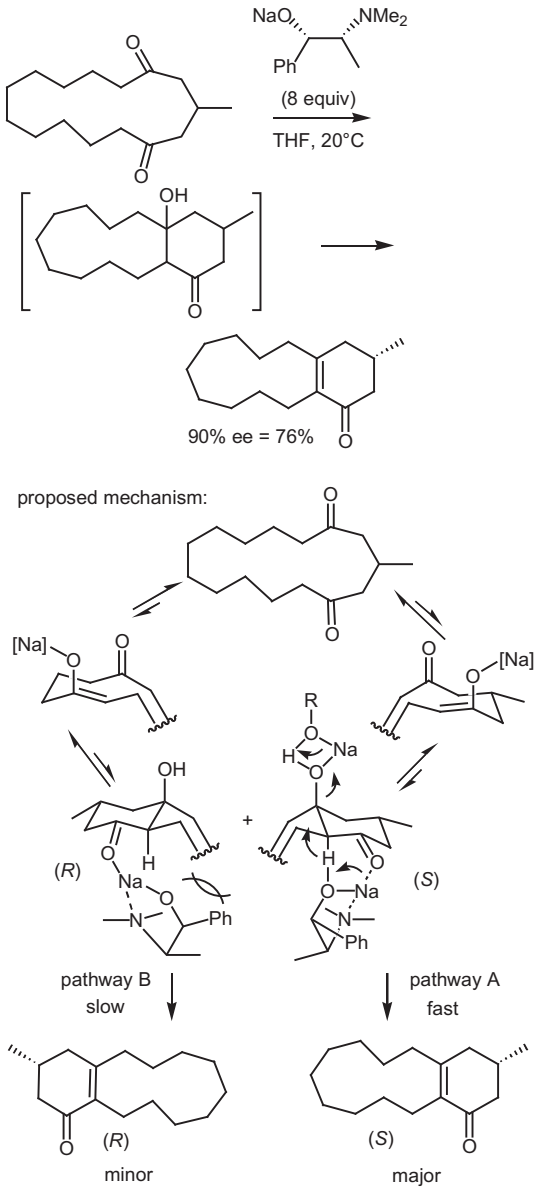
On the other hand, Garcia Ruano et al. have demonstrated that enantiomerically pure 2-(*p*-tolysulfinyl)benzylcopper reagents reacted with racemic propargylic mesylates, affording the corresponding chiral allenes with central and axial chirality.[12] These reactions took place in a completely regioselective S_N2' manner and followed a totally *anti* stereoselective pathway entirely controlled by the sulfinyl group. Moreover, the stereoselectivity at the benzylic position was very high with diastereoselectivities of up to 92% de. A complete kinetic resolution combined with a partial DKR of the racemic propargylic mesylates was proposed by the authors.

Indeed, the results indicated that no reaction of the chiral copper benzyl carbanion, derived from 1-ethyl-2-(*p*-tolylsulfinyl)benzene, with the (*S*)-enantiomer of the propargyl derivatives took place and suggested racemisation of this mesylate under the reaction conditions. Therefore, a complete kinetic resolution of the racemic propargyl mesylate and a partial DKR were reached with this process. As shown in Scheme 5, in all cases, the organocopper reagent only reacted with the (*R*)-enantiomer of the propargylic mesylates, yielding the corresponding chiral allenes, exhibiting the *R*-configuration at the chiral axis.



Scheme 5. Reaction of 2-(*p*-tolylsulfinyl)benzylcopper reagent with propargyl mesylates.

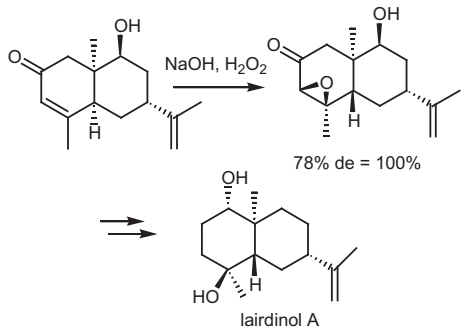
Due to their unique olfactive characteristics, the macrocyclic ketones, (*R*)-muscone and (*R*,*Z*)-5-muscenone, are highly prestigious musk odorants. A short and practical synthesis of these exceptional musk odorants has been recently developed by Knopff and Kuhne, starting from a readily available achiral macrocyclic diketone.[13] The key step of this synthesis was the first sodium *N*-methylephedrate-mediated asymmetric aldol condensation reaction, which proceeded through the DKR of an aldol intermediate. As shown in Scheme 6, when the aldol condensation of a macrocyclic diketone was performed in the presence of the chiral Na-alkoxide of (+)-*N*-methylephedrine, it produced the corresponding chiral cyclohexenone (*S*)-product in high yield and good enantioselectivity of up to 76% ee. In order to explain the formation of this (*S*)-product, the authors have suggested a DKR of the aldol intermediate (Scheme 6). The conformational analysis of the product showed that the sterically very demanding 11-membered ring of the bicyclic aldol was blocking an attack of the Na-alkoxide of (+)-*N*-methylephedrine on one side of the bridged proton. Chelation of the sodium cation of the latter to oxygen and nitrogen should give a rigid conformer with a sterically demanding face (methyl and phenyl groups). The authors have proposed that, in the faster deprotonation (pathway A) of the product, the methyl and the phenyl groups of the Na-alkoxide of (+)-*N*-methylephedrine were pointing away from the 11-membered ring. The retro-aldol reaction was faster than pathway B and converted the undesired (*R*)-enantiomer of the product into the starting diketone.



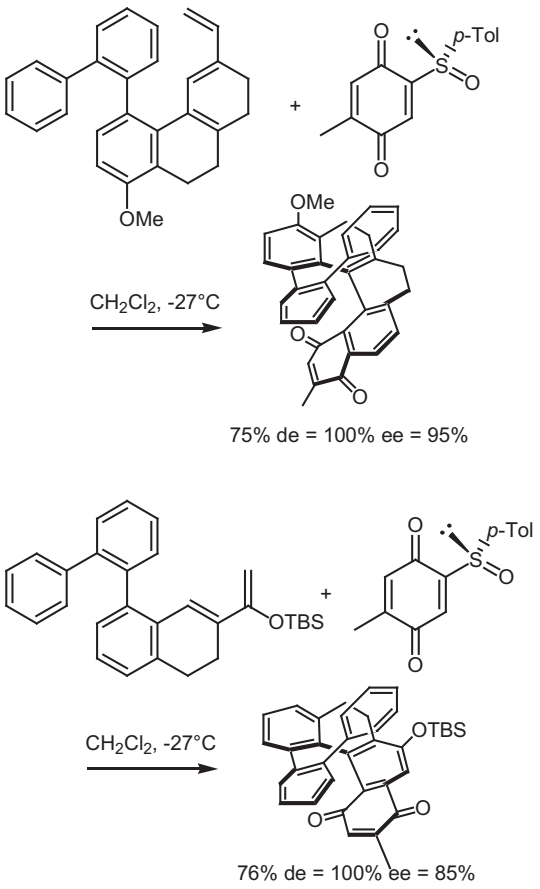
Scheme 6. Sodium *N*-methylephedrate-mediated aldol condensation reaction.

Ward et al. have reported the synthesis of lairdinol A, a component of the host-selective phytotoxin, depsilairdin, on the basis of the Diels–Alder reaction of (*R*)-carvone with 3-trimethylsilyloxy-1,3-pentadiene.[14] The key step of this synthesis established the trans ring fusion by the preferential epoxidation of a *trans*-fused enone into the corresponding epoxide through an equilibrating mixture of the *cis*- and *trans*-fused diastereomers. This DKR is depicted in Scheme 7. The formed chiral epoxide was further converted into the expected lairdinol A in six steps with 18% overall yield from (*R*)-carvone.

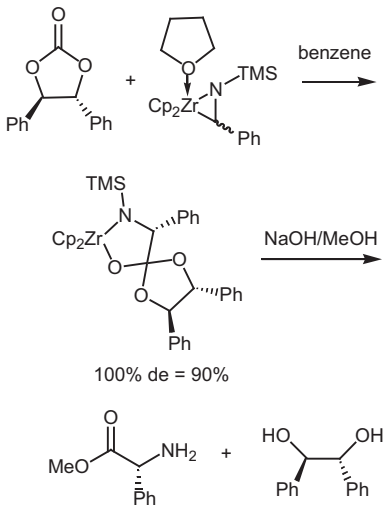
A DKR was reported by Carreno et al. in the asymmetric synthesis of atropisomeric biaryl[4] and [5]helicene quinones.[15] Hence, the asymmetric Diels–Alder reaction of a racemic biaryl diene with a chiral sulfinyl benzoquinone occurred with total control of axial and helical chirality. A DKR of the initial racemic biaryl-containing diene was achieved from a configurationally labile chiral axis, leading to a unique helical biaryl atropisomer. As shown in Scheme 8, the syntheses of (2-biphenyl)-substituted [5]helicene quinone and the configurationally stable (2-biphenyl)-substituted [4]helicene quinone were achieved in a very short, convergent and highly enantioselective manner.



Scheme 7. Synthesis of lairdinol A.

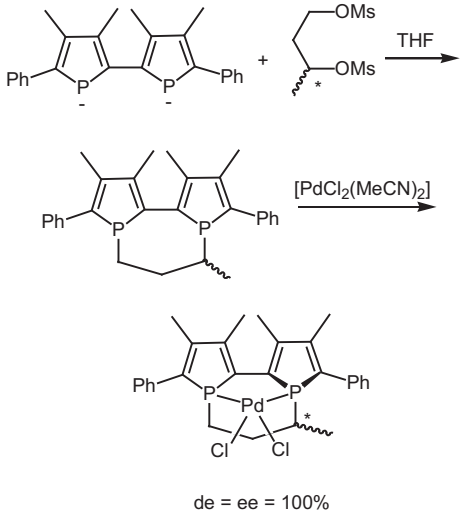


Scheme 8. Syntheses of biaryl[4] and [5]helicene quinones.



Scheme 9. Synthesis of amino acid methyl ester.

equilibrium mixture of the corresponding diastereomeric diphosphines.[17] The reaction of this equilibrium mixture with a transition metal, such as palladium, resulted through a DKR process in the corresponding diastereo- and enantiopure palladium complex, as shown in Scheme 10.



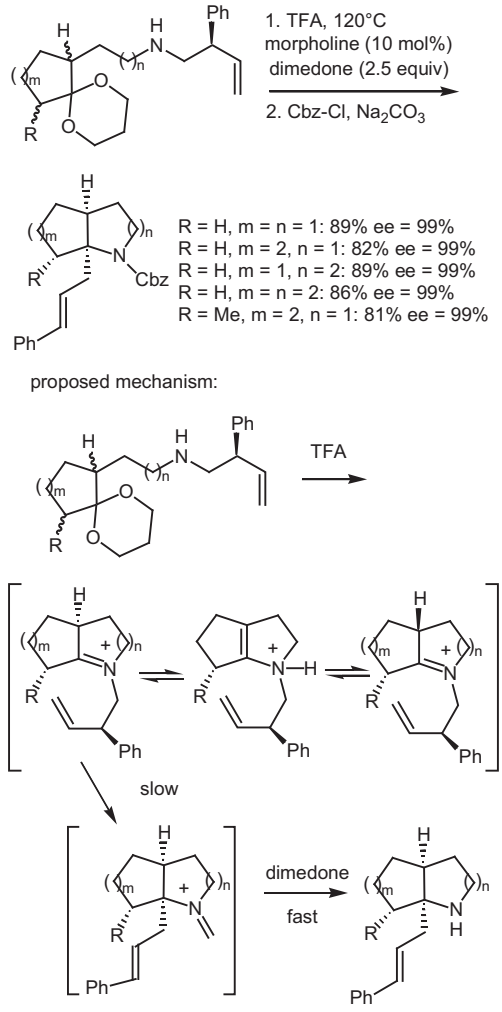
Scheme 10. Synthesis of palladium complex.

Norton et al. have demonstrated that the insertion of chiral C_2-symmetric diphenylethylene carbonate into the Zr–C bond of zirconaaziridine led to the asymmetric synthesis of the corresponding amino acid methyl ester after a subsequent treatment with NaOH in methanol.[16] Since the zirconaaziridine enantiomers interconverted, the reaction was a DKR. It was shown that the efficiency of this process was determined by the balance between the rate of enantiomer interconversion and the rate of insertion. A slow addition of the inserting enantiopure carbonate was often required to maximise the stereoselectivity of the reaction, allowing a diastereoselectivity of up to 90% de combined with a quantitative yield to be obtained, as shown in Scheme 9.

Daran et al. have shown that the asymmetric alkylation of a 2,2′-biphospholyl dianion with the enantiopure dimesylate of 1,3-butanediol performed under highly dilute conditions afforded an

In addition, Leigh et al. have reported a DKR of a rotaxane via an information ratchet mechanism.[18] The position of the macrocycle in a rotaxane-based molecular shuttle was used to affect the rate at which a bulky ester was introduced between two stations on the thread. Once in place, the ester provided a steric barrier trapping the ring on one side or the other. In this case, the rotaxane having two identical stations, the macrocycle distribution changed from 50:50 to 33:67, which corresponded to a DKR of a rotaxane with a moderate enantioselectivity of 34% ee. Therefore, the authors have demonstrated a functioning molecular information ratchet mechanism fuelled by the energy that came from a benzoylation reaction, which was sensitive to the position of a dynamically exchanging substrate. The ratchet was exemplified by driving the macrocycle distribution away from its equilibrium position in a symmetrical rotaxane-based molecular shuttle. Finally, Sobkowski et al. have demonstrated that the stereoselectivity of the condensation of chiral ribonucleoside

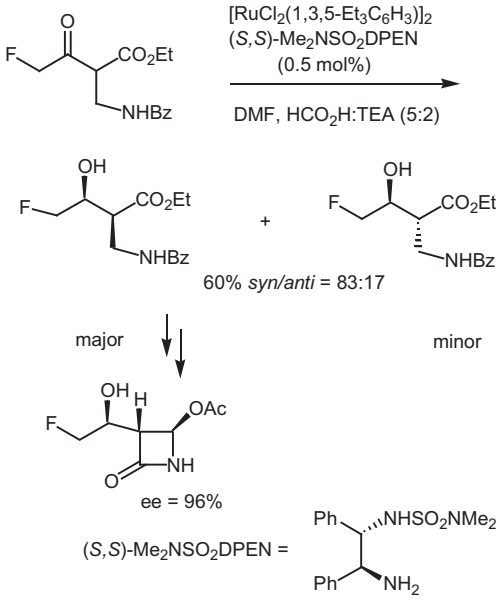
3′-*H*-phosphonates with alcohols was originated from a DYKAT (dynamic kinetic asymmetric transformation) process, involving the equilibrium of intermediates generated during the reaction.[19] This methodology allowed the stereoselective synthesis of ribonucleoside 3′-*H*-phosphonate diesters with moderate-to-good diastereoselectivity of up to 75% de. Very recently, Overman et al. have introduced a new strategy for DKR on the basis of aza-Cope rearrangements.[20] Thus, the heating of an aminoketal, derived from (*R*)-2-phenyl-3-butenamine, in the presence of dimedone and TFA combined with a catalytic amount of morpholine, provided the corresponding azabicyclic amine, which was subsequently converted into its Cbz derivative to facilitate purification. The latter product was obtained with an enantioselectivity of 99% ee, indicating a complete transfer of chirality from the allylic stereocentre (Scheme 11). The authors have explained the results by suggesting a rapid tautomeric equilibration of diastereomeric iminium cations combined with a diastereoselective sigmatropic rearrangement. Therefore, the reaction of the aminoketal with TFA established a rapid pre-equilibration between the two corresponding iminium ion diastereomers and the corresponding enammonium ion (Scheme 11). The cationic 2-aza-Cope rearrangement occurred more slowly and preferentially from one of the iminium ion diastereomers by the favoured chair transition structure, furnishing the corresponding thermodynamically less stable iminium ion product. Then, dimedone irreversibly trapped the latter, giving the 1-azabicyclic product in excellent enantioselectivity, more rapidly than it reverted to the equilibrium mixture of iminium and enammonium ions.



Scheme 11. DKR using aza-Cope rearrangements.

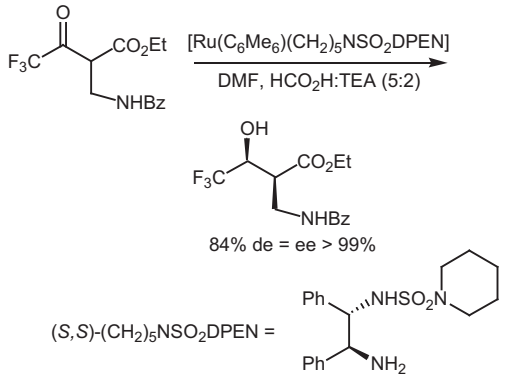
2.2. Chiral catalysts

2.2.1. Ruthenium-catalysed DKR. Besides chiral auxiliaries, there is also the possibility of using metal complexes bearing chiral ligands for generating 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.[21] 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 chiral catalysts are now available, which afford excellent levels of stereocontrol that could only previously be achieved using biocatalysts. Whilst the use of enzymes for the DKR of racemic substrates to afford enantiopure compounds in high enantioselectivities and good yields has emerged as a popular strategy in synthesis,[22] it is only relatively recently that the widespread application of non-enzymatic chiral catalysts for DKR has gained popularity within the synthetic community.[8d] In particular, ruthenium-catalysed hydrogenation has been widely used in the DKR of β-ketoesters.[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 the Takasago company for the production of acetoxyazetidinone (150 tons/year), a key intermediate in the synthesis of antibiotics.[23] More recently, Mohar et al. have developed an asymmetric synthesis of (1′*S*,3*R*,4*R*)-4-acetoxy-3-(2′-fluoro-1′-trimethylsilyloxyethyl)-2-azetidinone as a new fluorine-containing intermediate towards β-lactams.[24] The synthetic key step relied upon the DKR of ethyl 2-benzamidomethyl-4-fluoro-3-oxo-butanoate via asymmetric transfer hydrogenation catalysed by a ruthenium catalyst generated from $[RuCl_2(1,3,5\text{-}Et_3C_6H_3)]_2$ and (*S*,*S*)-Me_2NSO_2DPEN. This reaction was performed in the presence of a 5:2 mixture of HCO_2H/TEA as the hydrogen source at room temperature, using 0.5 mol % of the ruthenium catalyst, which led to the formation of the corresponding alcohol in an 83:17 diastereomeric ratio (*syn*/*anti*) and in quantitative yield. After a subsequent chromatographic separation, the chiral *syn* alcohol was isolated in excellent enantioselectivity of 96% ee, as shown in Scheme 12. This alcohol was further converted into the expected chiral fluorinated 2-azetidinone in three steps and 21% yield.



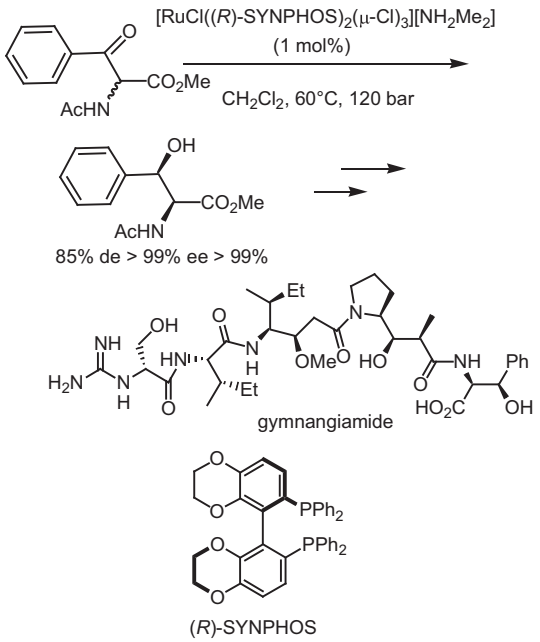
Scheme 12. Synthesis of fluorinated 2-azetidinone.

In 2010, closely related conditions were applied to ethyl 2-benzamidomethyl-3-oxo-4,4,4-trifluorobutanoate, leading to the corresponding *syn* fluorine-containing alcohol as a single stereoisomer, as shown in Scheme 13.[25] This product was further converted into fluorine-containing trinems, analogues of antibacterial sanfetrinem and LK-157.



Scheme 13. Synthesis of fluorine-containing alcohol.

The DKR methodology was also applied by Ratovelomanana-Vidal et al. to the development of an asymmetric total synthesis of gymnangiamide, a cytotoxic pentapeptide isolated from the marine hydroid *Gymnangium regae Jaderholm*.[26] The key step of this synthesis was based on the asymmetric hydrogenation of an α-substituted β-ketoester through DKR for the preparation of non-proteinogenic chiral amino acids. Therefore, the hydrogenation of the α-substituted β-ketoester depicted in Scheme 14, using 1 mol % of [RuCl((*R*)-SYNPHOS)$_2$(μ-Cl)$_3$][NH$_2$Me$_2$] catalyst at 60 °C in dichloromethane under 120 bar, yielded the corresponding chiral *syn* alcohol in high yield and almost complete diastereo- and enantioselectivity, as shown in Scheme 14. This alcohol was further converted into the valuable (2*S*,3*R*)-phenylserine fragment, which was subsequently transformed into the expected natural product, gymnangiamide.



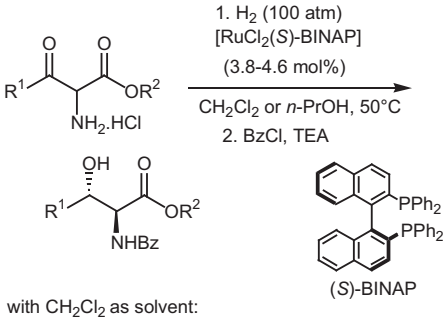
Scheme 14. Synthesis of gymnangiamide.

Very recently, Johnson and Steward have developed the DKR of β-silyloxy-α-ketoesters, previously prepared through a cyanide-catalysed, benzoin-type reaction between silyl glyoxylates and aldehydes.[27] The asymmetric transfer hydrogenation was performed in the presence of TEA as the base, formic acid as the hydride source and a ruthenium catalyst bearing a chiral 1,2-diamine, providing the corresponding enantioenriched monoprotected diols with moderate diastereo- and enantioselectivities of up to 66% de and 52% ee, respectively.

On the other hand, chiral β-hydroxy-α-amino acids with an *anti* configuration constitute important building blocks for the synthesis of a number of biologically active and natural products.[28] In this context, Hamada et al. have reported the *anti* selective asymmetric hydrogenation of α-amino-β-ketoester hydrochlorides through DKR using a ruthenium catalyst bearing a chiral diphosphine ligand, such as [RuCl$_2$((*S*)−BINAP)].[29] Hence, when the substrate bore a free amino function, the hydrogenation took place *anti* selectively through a five-membered cyclic transition state by chelation between the amino group and the keto carbonyl function to afford the corresponding *anti* β-hydroxy-α-amino ester after a subsequent benzoylation, whereas the hydrogenation of a protected α-amino-β-ketoester hydrochloride took place through a more common six-membered cyclic transition state by the chelation between the two carbonyl groups of the keto and ester functions to provide the corresponding *syn* β-hydroxy-α-amino ester. The *anti* selective asymmetric hydrogenation allowed a series of chiral β-hydroxy-α-amino esters to be produced in generally high yields and excellent *anti* diastereoselectivities of up to >98% de combined with excellent enantioselectivities of up to 97% ee, as shown in Scheme 14. It was demonstrated that the polarity of the solvent influenced the enantioselectivity. The best results were generally reached by using dichloromethane as the solvent, but *n*-propanol also gave satisfactory results. In order to explain the stereoselectivity of the process, the authors have proposed the mechanism depicted in Scheme 15, which revealed that the Ru-catalysed hydrogenation took place via the hydrogenation of the double bond in the enol tautomer of the substrate. Therefore, the [RuCl$_2$((*S*)−BINAP)] complex was hydrogenated to form the corresponding monohydride complex, which underwent a ligand-exchange reaction with the corresponding enol tautomer of the substrate to produce the corresponding coordinated complex. The insertion of the enol double bond into the Ru−H bond afforded a novel complex, which was subjected to σ-bond metathesis with hydrogen to generate the β-hydroxy-α-amino ester and the real catalyst.

The scope of the ruthenium-catalysed asymmetric transfer hydrogenation methodology was very recently extended to α-alkyl-substituted β-ketoamides by Limanto et al.[30] Indeed, the first enantio- and diastereoselective synthesis of various *syn* α-alkyl-substituted β-hydroxyamides via highly efficient Ru-catalysed hydrogenation through DKR of the corresponding β-ketoamides has been successfully demonstrated. As shown in Scheme 16, excellent diastereo- and enantioselectivities of up to 98% de and >99% ee, respectively, were observed when the process was performed in CH_2Cl_2 or toluene as the solvent, using a ruthenium catalyst bearing an electron-deficient sulfonyl diamine chiral ligand in the presence of HCO_2H and TEA. Various types of substrates, including aromatic and aliphatic α-substituted β-ketoamides, were shown to selectively yield the corresponding *syn* β-hydroxyamides in 75−90% yield. The potential utility of this class of compounds was demonstrated by the preparation of chiral highly functionalised *trans*-β-lactams.

With the aim of synthesising chiral pseudoephedrine derivatives, Itsuno has focused on employing a DKR based on a green, sustainable synthetic method, such as the use of polymer-immobilised catalysts, since they can easily be separated from the



with CH_2Cl_2 as solvent:

R^1 = *i*-Pr, R^2 = Me: 38% de = 98% ee = 95%

R^1 = *i*-Pr, R^2 = Et: 73% de = 92% ee = 93%

R^1 = R^2 = *i*-Pr: 96% de = 96% ee = 92%

R^1 = *i*-Pr, R^2 = Bn: 87% de > 98% ee = 96%

R^1 = Cy, R^2 = Bn: 85% de > 98% ee = 97%

R^1 = Et, R^2 = Bn: 89% de = 78% ee = 76%

with *n*-PrOH as solvent:

R^1 = *c*-Bu, R^2 = Bn: 92% de = 66% ee = 81%

R^1 = *c*-Pent, R^2 = Bn: 85% de = 96% ee = 95%

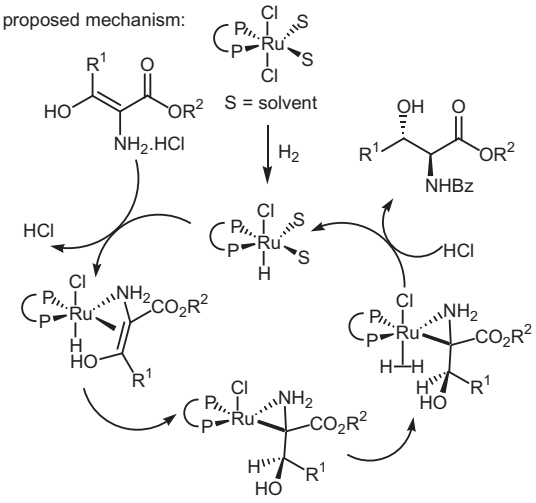
R^1 = *c*-Hept, R^2 = Bn: 86% de = 94% ee = 97%

R^1 = *t*-Bu, R^2 = Bn: 89% de = 92% ee = 79%

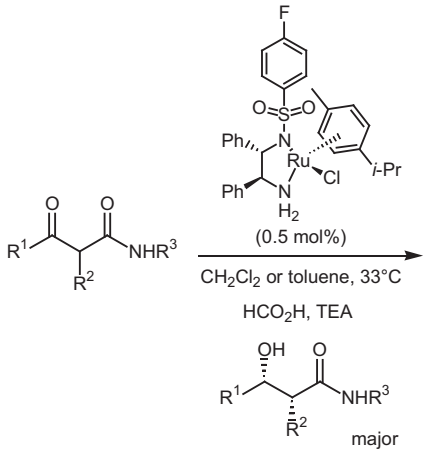
with CH_2Cl_2/*n*-PrOH as solvent:

R^1 = *n*-Pr, R^2 = Bn: 88% de = 64% ee = 78%

proposed mechanism:



Scheme 15. Synthesis of *anti* β-hydroxy-α-amino esters.



R^1 = *p*-BrC_6H_4, R^2 = *p*-FC_6H_4CH(*S*)-OTBS-$(CH_2)_2$, R^3 = *p*-IC_6H_4:
90% de = 96% ee > 99%

R^1 = R^3 = Ph, R^2 = Et: 80% de = 98% ee > 99%

R^1 = Ph, R^2 = Et, R^3 = *p*-$MeOC_6H_4$: 85% de = 96% ee = 99%

R^1 = R^3 = Ph, R^2 = Bn: 70% de = 98% ee = 99%

R^1 = R^3 = Ph, R^2 = CH_2-CH=CH_2: 74% de = 84% ee = 98%

R^1 = R^3 = Ph, R^2 = Ph-CH=CH: 77% de = 94% ee = 95%

R^1 = *p*-BrC_6H_4, R^2 = CH_2-CH=CH_2, R^3 = *p*-IC_6H_4:
90% de = 88% ee = 98%

R^1 = Cy, R^2 = Ph-CH=CH, R^3 = Ph: 80% de = 98% ee = 95%

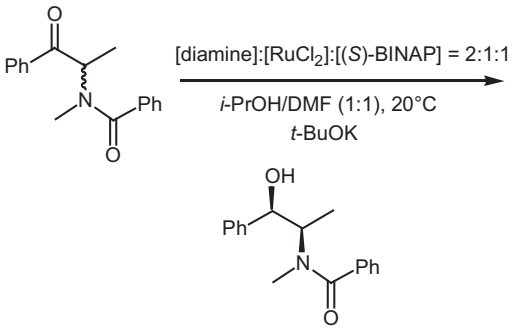
R^1 = Ph, R^2 = Ph-$(CH_2)_3$, R^3 = Bn: 75% de = 98% ee > 99%

Scheme 16. Synthesis of *syn* β-hydroxyamides.

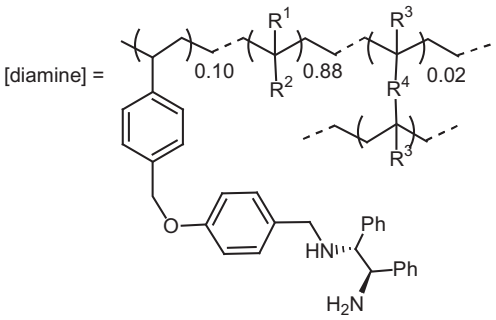
reaction mixture and be recycled.[31] In this context, these authors have developed the first DKR of α-amido ketones by using a polymer-immobilised chiral ruthenium catalyst.[32] As shown in Scheme 17, the asymmetric transfer hydrogenation of α-(*N*-benzoyl-*N*-methylamino)propiophenone through DKR was performed by employing a polymer-immobilised chiral 1,2-diamine-ruthenium catalyst combined with (*S*)-BINAP as a chiral ligand, yielding the corresponding chiral *syn* β-amido alcohol exclusively with near-perfect enantioselectivity. The polymeric precatalyst, generated from a hydrophilic polymer support, such as poly(hydroxyethyl methacrylate), could be reused several times without loss of catalytic activity. It was shown that no reaction occurred by using polystyrene-based polymeric chiral ligands, whereas poly(acrylamide) and poly(4-hydroxymethylstyrene) allowed quantitative conversions combined with excellent enantioselectivities to be obtained.

Asymmetric transfer hydrogenation conditions based on DKR methodology have been applied to other variously functionalised ketones. As an example, Zhang et al. have achieved the DKR of β-keto sulfones via asymmetric hydrogenation using [RuCl(*p*-cymene)](*S*,*S*)-TsDPEN as the chiral catalyst in the presence of HCO_2H and TEA as the hydrogen source.[33] The corresponding highly useful chiral
β-hydroxy sulfones were produced in good yields and high diastereoselectivities of up to >98% de combined with enantioselectivities of up to >99% ee, as shown in Scheme 18. It must be noted that remarkable results concerning the diastereo- and enantioselectivities with >98% de and >99% ee, respectively, were achieved for rigid α-tetralone and α-indanone derivatives (Scheme 18).

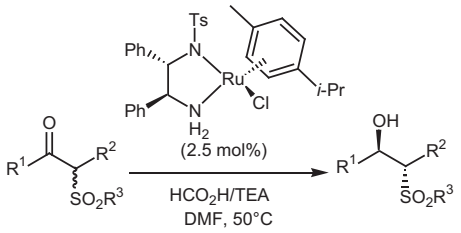
Another example of asymmetric hydrogenation of functionalised ketones through DKR was reported by Zhou et al. who involved α-amino ketones as the substrates.[34] This methodology represents one of the most elegant approaches to chiral 1,2-amino alcohols, one of the prevailing structural motifs found in a vast array of biologically active molecules.[35] Therefore, these authors have developed the highly enantio- and diastereoselective synthesis of a series of chiral β-*N*,*N*-dialkylamino alcohols on the basis of the asymmetric hydrogenation of the corresponding α-amino aliphatic ketones catalysed by [$RuCl_2$((*S*)-SDP)((*R*,*R*)-DPEN)]. The high efficiency of this catalyst allowed a low catalyst loading of only 0.01 mol %. As shown in Scheme 19, a variety of acyclic α-*N*,*N*-dialkylamino aliphatic ketones could be hydrogenated in these conditions, providing the corresponding *syn* amino alcohols with complete conversions and excellent diastereo- and enantioselectivities in all the reactions. It was noted, however, that the α-dialkylamino group of the substrates imposed a significant influence on the diastereoselectivity of the reaction. Generally, the ketones bearing a small dialkylamino group, such as dimethylamino or pyrrolidinyl, provided high diastereoselectivities, while ketones having a bulkier diethylamino group produced a low diastereoselectivity (42% de). In addition, the scope of this methodology could be successfully extended to α-*N*-monoalkylamino



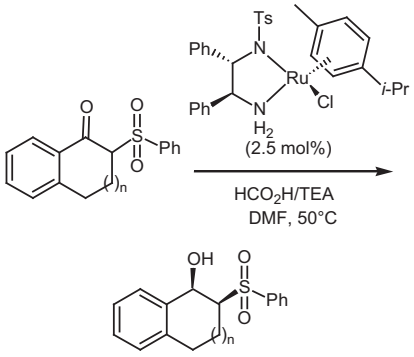
$R^1 = R^3 = Me$, $R^2 = CO_2(CH_2)_2OH$, $R^4 = CO_2(CH_2)_2OCO$:
100% de > 99% ee = 90%
$R^1 = Me$, $R^2 = CO_2(CH_2)_2OH$, $R^3 = H$, $R^4 = Ph$:
100% de > 99% ee > 99%
$R^1 = R^3 = Me$, $R^2 = CO_2Me$, $R^4 = CO_2(CH_2)_2OCO$:
82% de > 99% ee = 90%
$R^1 = H$, $R^2 = CONHi\text{-}Pr$, $R^3 = Me$, $R^4 = Ph$:
100% de > 99% ee = 92%
$R^1 = H$, $R^2 = Bn$, $R^3 = Me$, $R^4 = Ph$:
100% de > 99% ee = 95%



Scheme 17. Synthesis of *syn* β-amido alcohol with polymer-immobilised Ru catalyst.



$R^1 = R^3 = Ph$, $R^2 = Me$: 95% de = 86% ee = 98%
$R^1 = p\text{-}(i\text{-}Pr)C_6H_4$, $R^2 = Me$, $R^3 = Ph$: 85% de = 72% ee = 99%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = Me$, $R^3 = Ph$: 96% de = 80% ee = 97%
$R^1 = R^2 = Ph$, $R^3 = Br$: 96% ee = 99%
$R^1 = 2\text{-Naph}$, $R^2 = Me$, $R^3 = Ph$: 95% de = 74% ee = 98%



n = 0: 90% de > 98% ee > 99%
n = 1: 92% de > 98% ee > 99%

Scheme 18. Synthesis of β-hydroxy sulfones.

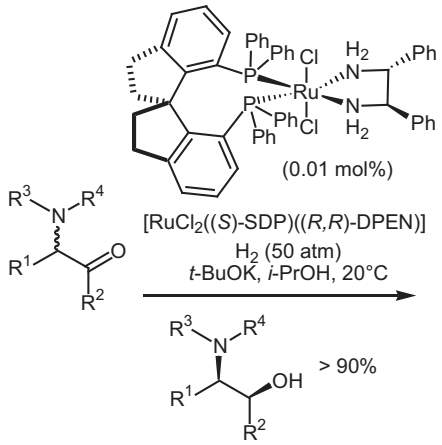
aliphatic ketones, in spite of the difficulty for this reaction, presumably arising from the unprotected amino group, which coordinated to the ruthenium centre of the catalyst, which results in a low catalytic activity. As shown in Scheme 19, the corresponding *syn* amino alcohols could be formed, however, in excellent yields (>90%) combined with both high enantio- (>90% ee) and diastereoselectivities (>82% de).

Moreover, these authors have demonstrated that these conditions could be applied to the asymmetric hydrogenation of α-aryloxydialkyl ketones via DKR.[36] As shown in Scheme 20, a series of chiral β-aryloxy alcohols were highly efficiently produced in 89–99% yields and good-to-excellent diastereo- and enantioselectivities of up to >98% de and 99% ee, respectively. High cis/trans selectivities were obtained with α-aryloxy cyclic ketones, whereas high *anti* selectivities were observed for conformationally flexible substrates, such as α-aryloxy acyclic dialkyl ketones. This methodology was applied to the enantioselective synthesis of the key chiral intermediate of a non-steroidal glucocorticoid modulator (Scheme 20).

In addition, Ohkuma et al. have investigated the efficiency of other ruthenium catalysts, such as *trans*-$RuCl_2$[(*S*)-TolBINAP][(*R*)-DMAPEN], for the asymmetric hydrogenation via DKR of α-monohetero-substituted ketones, such as α-alkoxy and α-amido ketones.[37] It was demonstrated that benzoin methyl ether was hydrogenated to give the corresponding *anti* alcohol in 98% ee predominantly, while the reaction of α-amidopropiophenones afforded the corresponding *syn* alcohols in enantioselectivities of >98% ee exclusively. The stereoselective outcome of the reaction was explained by using Felkin–Anh-type models, in which the bulkiest α-substituent located the *anti* periplanar position to the hydridic Ru–H. The results are shown in Scheme 21.

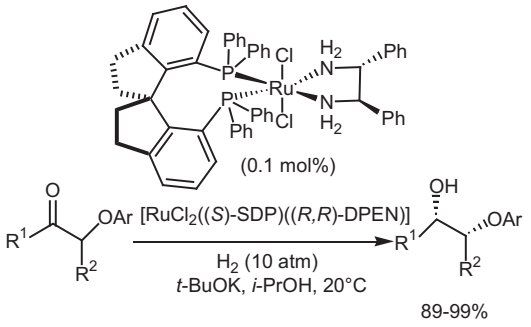
In the catalytic asymmetric hydrogenation of prochiral ketones, at least one new stereogenic centre is generated, whereas no new stereogenic centre is generated in the hydrogenation of α-branched aldehydes, which makes enantiocontrol of the reaction extremely difficult. Thus, the asymmetric hydrogenation of α-branched aldehydes still remains a challenge to chemists. In this context, Zhang et al. have recently demonstrated that using [RuCl(*p*-cymene)](*S*,*S*)-TsDPEN as the catalyst, and HCO_2H/TEA as the hydrogen source, a variety of 2-sulfonylaldehydes could be reduced to the corresponding optically active primary alcohols on the basis of a DKR process.[38] As shown in Scheme 22, high enantioselectivities of up to 90% ee combined with high yields were obtained for all *meta*- or *para*-(un)substituted 2-phenyl-2-sulfonylacetaldehydes, including 2-naphthylacetaldehyde. The reaction seemed to be insensitive to the electronic nature of the substituents. However, the steric feature of the substrates played an important role. Thus, *ortho*-substitution including electron-donating and -withdrawing substitution resulted in lower yields and dramatically decreased the enantioselectivity.

Chiral β-aryloxy primary alcohols constitute a very important class of building blocks for the synthesis of a wide variety of biologically active compounds, such as sorbinil homologues, juvenile hormones and glucokinase activating agents. However, the methods for the preparation of chiral β-aryloxy primary alcohols are limited to the ring opening of chiral epoxides, the resolution of racemic compounds with lipases and the conversions of lactic acid derivatives. In order to overcome these limitations, Zhou et al. have developed a novel catalytic enantioselective hydrogenation of α-aryloxyaldehydes via DKR by using a chiral (diamine)(spirodiphosphine)ruthenium(II) chloride catalyst.[39] Comparison of

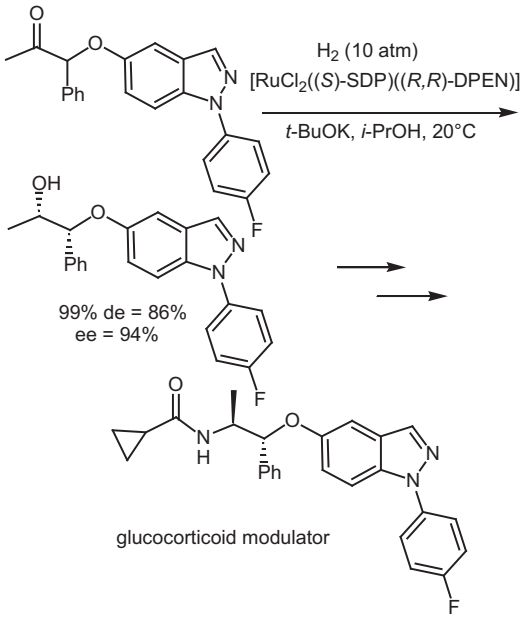


R^1 = Ph, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de > 98% ee > 99%
R^1 = Ph, R^2 = Me, R^3,R^4 = $(CH_2)_2O(CH_2)_2$:
de = 92% ee > 99%
R^1 = Ph, R^2 = Me, R^3,R^4 = $(CH_2)_2NMe(CH_2)_2$:
de > 98% ee = 99%
R^1 = Ph, R^2 = R^3 = R^4 = Me: de > 98% ee > 99%
R^1 = Ph, R^2 = Me, R^3 = R^4 = Et: de = 42% ee > 99%
R^1 = Ph, R^2 = Et, R^3,R^4 = $(CH_2)_4$: de = 92% ee = 99%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de = 90% ee > 99%
R^1 = *p*-ClC_6H_4, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de > 98% ee = 99%
R^1 = *p*-BrC_6H_4, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de > 98% ee = 99%
R^1 = *m*-$MeOC_6H_4$, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de = 90% ee = 98%
R^1 = *m*-Tol, R^2 = Me, R^3,R^4 = $(CH_2)_4$: de > 98% ee = 99%
R^1 = *o*-$MeOC_6H_4$, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de = 98% ee > 99%
R^1 = *o*-BrC_6H_4, R^2 = Me, R^3,R^4 = $(CH_2)_4$:
de = 88% ee > 99%
R^1 = R^3 = Ph, R^2 = Me, R^4 = H: de = 94% ee = 96%
R^1 = Ph, R^2 = Me, R^3 = *i*-Pr, R^4 = H: de > 98% ee = 99%
R^1 = R^2 = Me, R^3 = Ph, R^4 = H: de > 98% ee = 96%
R^1 = R^2 = Me, R^3 = Cy, R^4 = H: de = 98% ee = 96%
R^1 = Et, R^2 = Me, R^3 = Ph, R^4 = H: de = 90% ee = 95%
R^1 = R^2 = Me, R^3 = Bn, R^4 = H: de = 90% ee = 97%

Scheme 19. Synthesis of β-*N*,*N*-dialkylamino- and β-alkylamino alcohols.



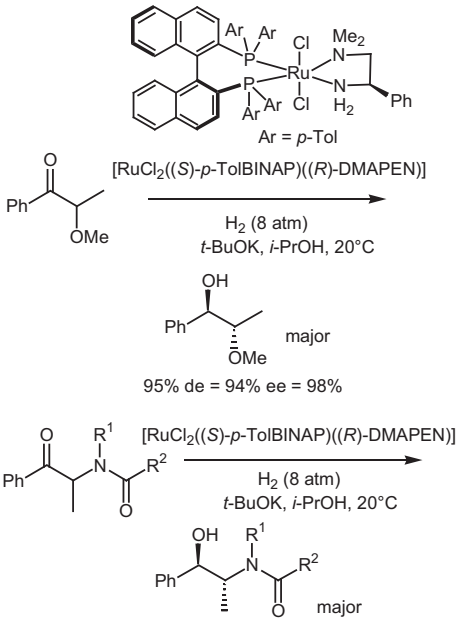
Ar = Ph, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 99%
Ar = *p*-Tol, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 99%
Ar = *p*-$MeOC_6H_4$, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 99%
Ar = *p*-ClC_6H_4, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 98%
Ar = *p*-BrC_6H_4, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 99%
Ar = *m*-Tol, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 99%
Ar = *o*-Tol, R^1,R^2 = $(CH_2)_4$: de > 98% ee = 98%
Ar = Ph, R^1 = R^2 = Me: de = 78% ee = 96%
Ar = *p*-$MeOC_6H_4$, R^1 = Me, R^2 = Ph: de = 96% ee = 95%
Ar = *p*-BrC_6H_4, R^1 = Me, R^2 = Ph: de = 92% ee = 95%
Ar = R^2 = Ph, R^1 = Et: de = 94% ee = 84%



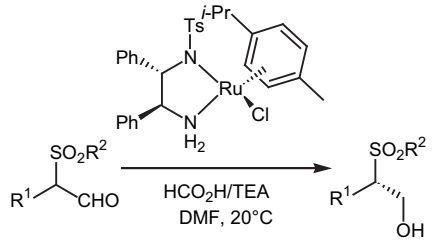
Scheme 20. Synthesis of β-aryloxy alcohols.

various chiral spirodiphosphine and diamine ligands revealed that the combination of the ligand (*S*)-DMM–SDP bearing 4-methoxy-3,5-dimethylphenyl groups and the chiral diamine (*R*,*R*)-DACH gave the highest enantioselectivities of up to 81% ee for the formed corresponding chiral β-aryloxy alcohols. As shown in Scheme 23, the best results were obtained for the hydrogenation of α-aryloxyaldehydes bearing a bulky alkyl substituent, such as an isopropyl group, at the α-position.

While the formation of a variety of carbon stereocentres has been effectively achieved, stereoselective approaches for the preparation of *P*-stereogenic phosphines have, until recently, been non-existent. In this context, Bergman et al. have developed several chiral ruthenium catalysts that were investigated for the enantioselective Ru-catalysed alkylation of secondary phosphines into the corresponding chiral air- and moisture-tolerant tertiary phosphine-borane products after a subsequent treatment with $BH_3 \cdot THF$.[40] These reactions proceeded through the intermediacy of nucleophilic phosphido species, which had low barriers to pyramidal inversion, allowing a DKR process. The initially discovered ruthenium catalyst, $[((R)\text{-}i\text{-Pr-PHOX})_2Ru(H)][BPh_4]$, was found to be effective in the reaction of methylphenylphosphine with benzylic chlorides, providing the corresponding tertiary phosphine–borane products with high yields and moderate-to-high enantioselectivities, as shown in Scheme 24. The scope of this catalyst was shown, however, to be limited to the alkylation of benzylic chlorides, suggesting the need for improved catalysts. Efforts aimed at developing more

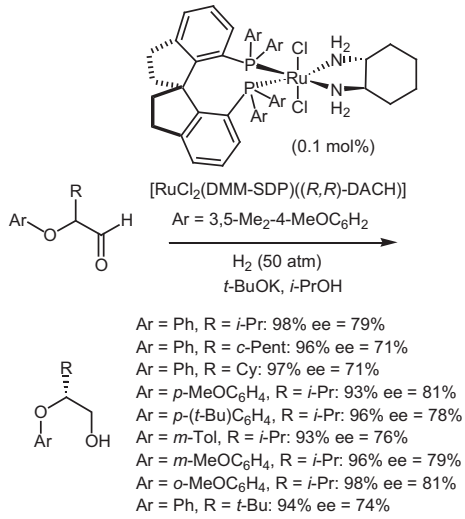


Scheme 21. Hydrogenations of α-alkoxy and α-amido ketones.



Scheme 22. Synthesis of 2-sulfonyl primary alcohols.

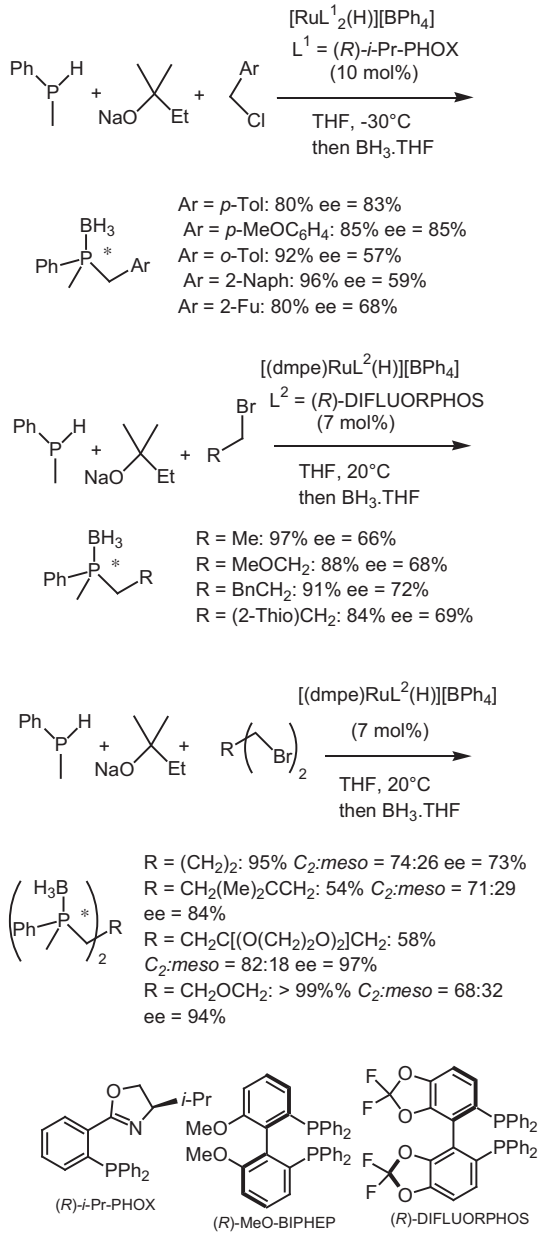
reactive and selective catalysts for this alkylation reaction led to the discovery of tetraphosphine mixed ligand catalysts, such as the MeO–BIPHEP/dmpe ruthenium catalyst, which was effective for the alkylation of benzylic chlorides and performed comparably to the *i*-Pr-PHOX catalyst, but under ambient conditions (instead of −30 °C with *i*-Pr-PHOX catalyst). Moreover, the discovery of the DIFLUORPHOS/dmpe catalyst allowed the asymmetric phosphine alkylation of methylphenylphosphine to be performed with aliphatic bromides, providing the corresponding tertiary phosphine–borane products to be obtained in moderate-to-good enantioselectivities, as shown in Scheme 24. In addition, the scope of this methodology was also extended to the preparation of alkyl-tethered *P*-stereogenic diphosphines through the reaction between methylphenylphosphine and dibromides with high enantioselectivities, as shown in Scheme 24.



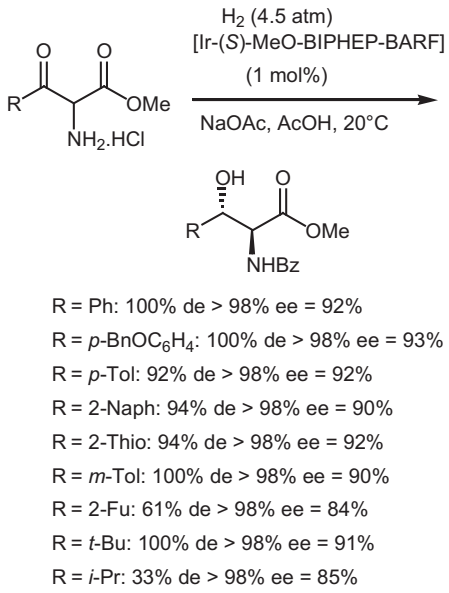
Scheme 23. Synthesis of β-aryloxy alcohols.

2.2.2. DKR catalysed by metals other than ruthenium. Chiral complexes of metals other than ruthenium have also been used in the context of DKR. As an example, Hamada and Makino have demonstrated that, in addition to ruthenium, iridium proved to be an excellent catalyst for highly *anti* selective hydrogenation of α-amino-β-ketoester hydrochlorides into the corresponding *anti* β-hydroxy-α-amino esters through DKR.[41] The best results were obtained by using the iridium catalyst, [Ir–(*S*)-MeO–BIPHEP–BARF], under low hydrogen pressure (4.5 atm) in the presence of sodium acetate in acetic acid at room temperature. In these conditions, a series of *anti* β-hydroxy-α-amino esters could be produced in moderate-to-quantitative yields with a complete *anti* diastereoselectivity in all cases of substrates and with good-to high enantioselectivities of up to 93% ee, as shown in Scheme 25. Surprisingly, the hydrogenation of the hindered substrate bearing a *tert*-butyl group efficiently proceeded to provide the corresponding *anti* β-hydroxy-α-amino ester with >98% de in quantitative yield and 91% ee, which represented the highest value for the *tert*-butyl substrate and was superior to that obtained by the same authors for the [$RuCl_2$–(*S*)-BINAP]-catalysed *anti* selective hydrogenation performed at a much higher pressure of 100 atm (79% ee, Scheme 15).[29] These results constituted the first example of hydrogenation via DKR catalysed by an iridium catalyst.

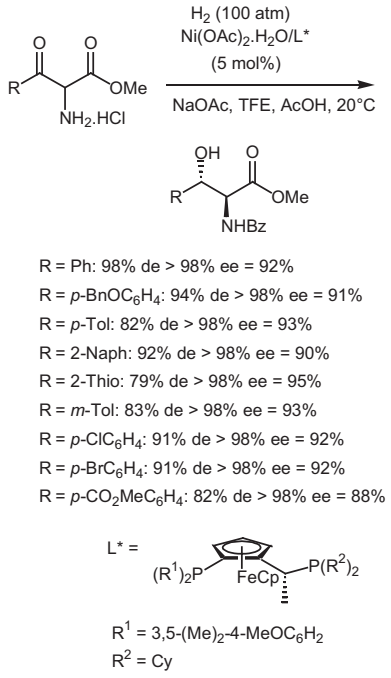
Nickel, one of the abundant and cheap base transition metals, has attracted a great deal of attention in catalytic organic synthesis.[42] In this area, these authors have also demonstrated that these reactions could be successfully performed using homogeneous chiral nickel-bisphosphine catalysts.[43] Indeed, the hydrogenations through DKR of a series of α-amino-β-ketoester hydrochlorides into the corresponding *anti* β-hydroxy-α-amino esters were achieved by using a combination of nickel acetate and a chiral ferrocenylphosphine in the presence of sodium acetate in a mixture of acetic acid and trifluoroethanol as the solvent at room temperature under 100 atm of hydrogen. In these conditions, the expected *anti* β-hydroxy-α-amino esters were produced in generally high yields, with almost complete diastereoselectivity and good-to-high enantioselectivities, which were the highest for the aromatic substrates, as shown in Scheme 26. It must be noted that this hydrogenation was even superior to the corresponding iridium-catalysed hydrogenation regarding the substrate generality and enantioselectivity. It was noteworthy that such a complicated asymmetric reaction proceeded smoothly with a combination of a cheap metal, nickel, and a commercially available phosphine ligand without using any precious transition-metal catalyst.



Scheme 24. Alkylations of secondary phosphines.



Scheme 25. Ir-catalysed synthesis of *anti* β-hydroxy-α-amino esters.

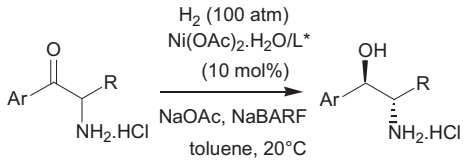


Scheme 26. Ni-catalysed synthesis of *anti* β-hydroxy-α-amino esters.

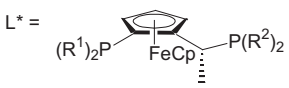
As an extension of this study, these authors have applied these conditions to the asymmetric hydrogenation of aromatic α-aminoketone hydrochlorides.[44] Surprisingly, no reaction took place under similar conditions. However, it was discovered that the presence of a catalytic amount of NaBARF in addition to sodium acetate in toluene was essential for this hydrogenation catalysed by the same homogeneous nickel catalyst. In these adapted conditions, the synthesis of a series of *anti* β-amino alcohol hydrochlorides was achieved with moderate-to-high yields, almost complete *anti* diastereoselectivity in all cases of substrates and high enantioselectivities of up to 96% ee, as shown in Scheme 27.

On the other hand, Johnson and Parsons have developed the synthesis of chiral tetrahydrofurans on the basis of asymmetric Mg-catalysed [3+2] cycloadditions of cyclopropanes with aldehydes occurring through DKR.[45] Therefore, a catalyst generated from a Lewis acid, such as MgI_2 and a chiral PYBOX ligand was found to promote the cycloaddition of aldehydes with one enantiomer of methyl malonato cyclopropanes and promote the interconversion of the cyclopropane enantiomers, providing the corresponding cycloadducts in good yields and high enantioselectivities of up to 93% ee. As shown in Scheme 28, aryl, cinnamyl as well as aliphatic aldehydes underwent cycloadditions with a variety of cyclopropanes bearing electron-rich donor groups.

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 stereoinformation. The fundamental concept is summarised in Scheme 29. A bromoarenecarboxylic 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

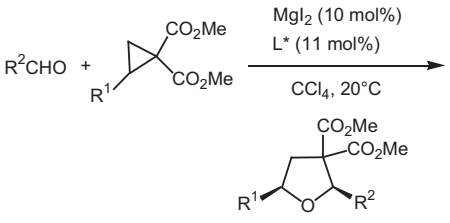


Ar = *p*-Tol, R = Me: 92% de > 98% ee = 86%
Ar = *p*-MeOC$_6$H$_4$, R = Me: 22% de > 98% ee = 85%
Ar = *p*-Tol, R = *i*-Pr: 21% de > 98% ee = 96%
Ar = *p*-Tol, R = Bn: 92% de > 98% ee = 84%
Ar = Ph, R = Et: 94% de > 98% ee = 85%
Ar = Ph, R = *n*-Pr: 91% de > 98% ee = 82%



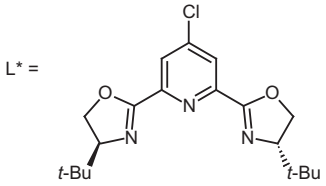
R^1 = 3,5-(Me)$_2$-4-MeOC$_6$H$_2$
R^2 = Cy

Scheme 27. Ni-catalysed synthesis of *anti* β-amino alcohol hydrochlorides.



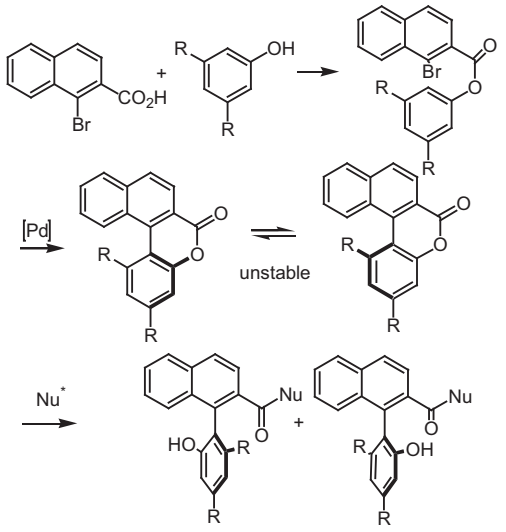
de > 96%

R^1 = R^2 = *p*-MeOC$_6$H$_4$: 88% ee = 90%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = *p*-ClC$_6$H$_4$: 65% ee = 88%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = *o*-Tol: 81% ee = 93%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = (*E*)-CH=CHPh: 92% ee = 88%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = *n*-Pent: 64% ee = 85%
R^1 = 2-Thio, R^2 = *p*-MeOC$_6$H$_4$: 91% ee = 94%
R^1 = 2-Thio, R^2 = (*E*)-CH=CHPh: 91% ee = 94%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = 2-Thio: 84% ee = 91%
R^1 = *p*-MeOC$_6$H$_4$, R^2 = *i*-Pr: 55% ee = 82%
R^1 = 2-Thio, R^2 = Ph: 64% ee = 93%
R^1 = R^2 = 2-Thio: 78% ee = 93%
R^1 = (*E*)-CH=CHPh, R^2 = *p*-MeOC$_6$H$_4$: 75% ee = 90%



Scheme 28. Mg-catalysed synthesis of tetrahydrofurans.

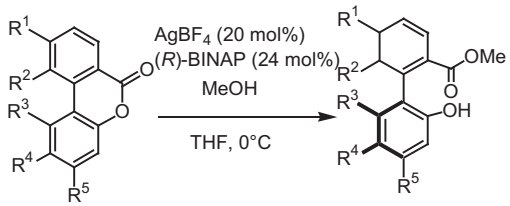
corresponding lactones, which are configurationally unstable. These lactones are the key intermediates in the concept, since they can be ring opened with chiral nucleophiles according to the principle of DKR, yielding the now configurationally stable biaryls.[46] The cleavage of the bridge can be achieved 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



Scheme 29. 'Lactone concept'.

flexible and reliable access to a broad spectrum of structurally diverse biaryl species with any desired configuration at the axis. The carboxy- and phenoxy-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 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 a number of chiral natural products,[47] along with several useful catalysts.[48] In this context, Yamada and Ashizawa have developed asymmetric atroposelective ring opening of biaryl lactones with methanol catalysed by $AgBF_4$ combined with a chiral ligand, such as (*R*)-BINAP, in THF as the solvent.[49] As shown in Scheme 30, a series of chiral axially biaryl products could be prepared through this methodology with generally high yields and moderate-to-high enantioselectivities of up to 84% ee. One drawback of this process was the reaction time, which was longer than 24 h. In 2010, the same authors demonstrated that these reactions could be highly accelerated by microwave irradiation without any loss of enantioselectivity at almost the same internal temperature (10–20 °C).[50] In

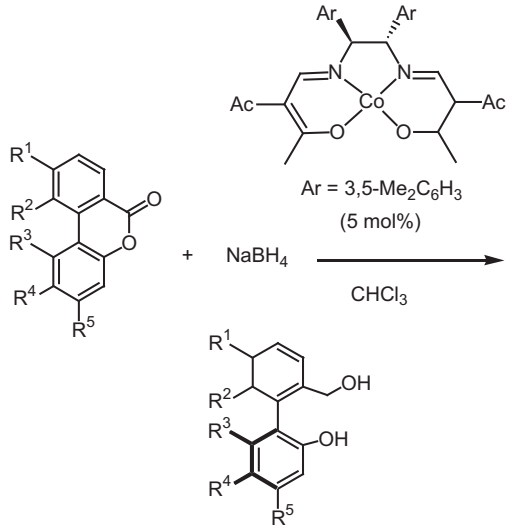


R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = H: 92% ee = 82%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = Cl: 84% ee = 70%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^4 = R^5 = Me: 97% ee = 64%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = OMe: 79% ee = 84%
R^1 = R^4 = H, R^2 = R^3 = R^5 = Me: 89% ee = 84%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = OTBS: 82% ee = 80%

Scheme 30. Ag-catalysed atroposelective ring-opening reaction of biaryl lactones with methanol.

these conditions, the reaction time could be reduced to 23 min in some cases. The authors assumed that this remarkable effect would not be a simple thermal effect, but an activation of the nucleophile, methanol, by microwave irradiation.

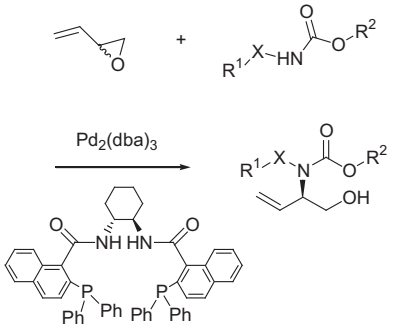
In addition, these authors have successfully developed a versatile atropo-enantioselective borohydride reduction with DKR of various types of biaryl lactones catalysed by an optically active β-ketoiminatocobalt(II) complex.[51] The corresponding chiral biaryl products were produced by using $NaBH_4$ as the reducing agent in generally high yields and excellent enantioselectivities of up to 93% ee, as shown in Scheme 31.



R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = H:
87% ee = 89%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = Cl:
74% ee = 85%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^4 = R^5 = Me:
85% ee = 84%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = OMe:
88% ee = 91%
R^1 = R^4 = H, R^2 = R^3 = R^5 = Me: 64% ee = 89%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = OTBS:
90% ee = 93%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = OAc:
85% ee = 89%
R^1,R^2 = CH=CH-CH=CH, R^3 = R^5 = Me, R^4 = $OSiMe_2$*i*-Pr:
89% ee = 93%
R^1,R^2 = R^3,R^4 = CH=CH-CH=CH, R^5 = H: 87% ee = 80%

Scheme 31. Co-catalysed atroposelective reduction of biaryl lactones with $NaBH_4$.

In 1999, Trost and Toste introduced the concept of dynamic kinetic asymmetric transformation (DYKAT),[52] frequently referred to as DKR, since it involves the equilibration of diastereomeric intermediates generated from the racemic substrates. A number of examples of this type of reactions have recently been developed. As an example, Takahata et al. have applied this methodology to the total asymmetric synthesis of the antiepileptic drug, levetiracetam.[53] A more recent example was reported by Alexakis and Langlois, dealing with the Cu-catalysed asymmetric allylic alkylation of racemic cyclic substrates.[54] Of particular interest was the addition of primary alkyl Grignard reagents to racemic cyclic substrates, such as 3-bromocyclopent-1-ene, 3-bromocyclohept-1-ene and 3-bromocyclohept-1-ene, which afforded the corresponding alkylated products with excellent enantioselectivities of up to 99% ee, in the presence of a chiral copper catalyst. These results constituted the first example of DYKAT in Cu-catalysed asymmetric allylic alkylation. Another highly efficient DYKAT has been reported by Shibasaki et al. based on a Ba-catalysed aldol/retro-aldol reaction.[55] Thus, α-alkylidene-β-hydroxy esters were obtained by the reaction of aryl, heteroaryl, alkenyl and alkyl aldehydes with β,γ-unsaturated esters in both excellent enantio- and diastereoselectivities of 87–99% ee and 90–94% de, respectively. These reactions were performed in the presence of $Ba(O\text{-}i\text{-}Pr)_2$ combined with (*S*)-BINOL. The authors have proposed that the dienolates generated in situ from the β,γ-unsaturated esters by the chiral catalyst reacted with the aldehyde at the α- and/or γ-position. If the chiral catalyst promoted a rapid retro-aldol reaction of an α-adduct, the isomerisation of the latter to the more thermodynamically stable α-alkylidene-β-hydroxy ester could be a DYKAT. On the other hand, Cordova et al. have reported the first examples of one-pot highly chemo- and enantioselective DYKATs, based on the reactions between α,β-unsaturated aldehydes and propargylated carbon acids, providing the corresponding chiral cyclopentenes.[56] Therefore, catalytic iminium activation, enamine activation and transition-metal-catalysed enyne cycloisomerisation could all be efficiently merged for the development of these DYKATs and the formation of all-carbon quaternary stereocentres with high enantioselectivity of up to 99% ee. The reactions were performed in the presence of $Pd(PPh_3)_4$ combined with a chiral L-proline derivative. In 2008, Trost and O'Boyle reported the synthesis of 7-*epi* (+)-FR900482, a potent antitumour therapeutic, which included a Pd-catalysed DYKAT reaction, providing a chiral amino alcohol as a single stereoisomer.[57] Finally, Mangion et al. have found that hydrazines and hydroxylamines could be excellent nucleophiles for the Pd-catalysed allylic amination of butadiene monoepoxide in the presence of a chiral biphosphine ligand.[58] The DYKATs afforded the corresponding amino alcohols in good yields and enantioselectivities, as shown in Scheme 32. The method was applicable to acyclic and heterocyclic amines and applied towards a five-step synthesis of (*R*)-piperazic acid.

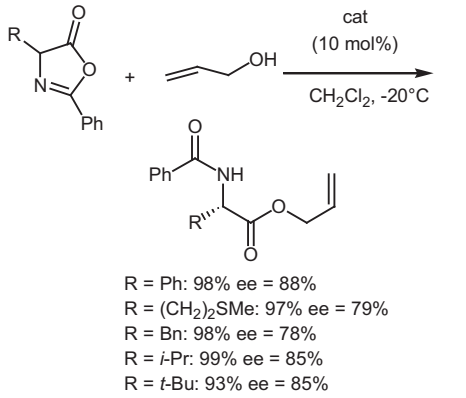


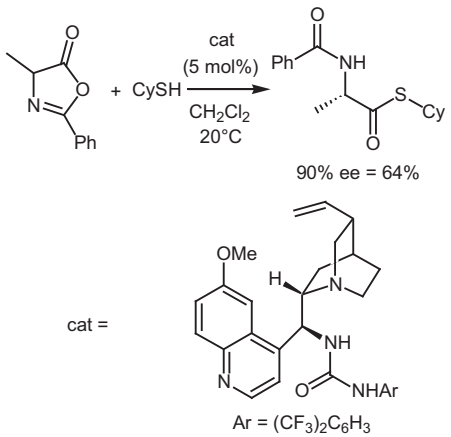
XR^1 = NCbz, R^2 = Bn: 79% ee = 94%
XR^1 = NBn, R^2 = Et: 88% ee = 83%
XR^1 = OCH_2-3,4-$Cl_2C_6H_3$, R^2 = Bn: 83% ee = 88%
XR^1 = $O(CH_2)_2$-NHCbz, R^2 = Bn: 72% ee = 87%

Scheme 32. DYKAT of hydrazines and hydroxylamines.

2.2.3. Organocatalysed DKR. While the end of the last century has been dominated by the use of metal catalysts,[59] a change in perception has occurred during the last few years when several reports confirmed that relatively simple organic molecules could be highly effective and remarkably enantioselective catalysts of a variety of fundamentally important transformations. Enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications

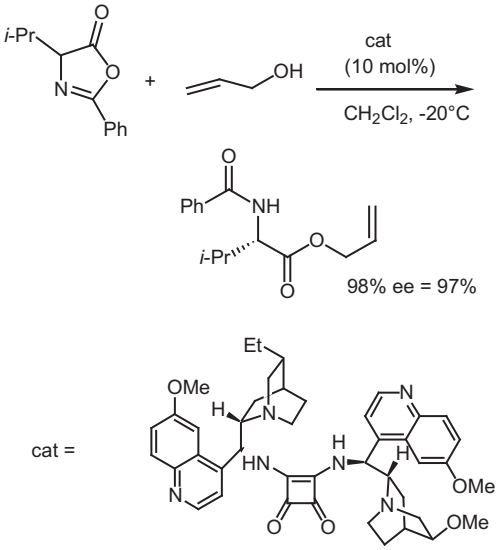
regarding the applications of this type of reactions, which paint a comprehensive picture for their real possibilities in organic synthesis.[60] This rediscovery has initiated an explosive growth of research activities in organocatalysis, both in industry and in academia. Organocatalysts have several important advantages, since they are usually robust, inexpensive, readily available and non-toxic. 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 the last seven years, the first examples of organocatalysed DKR processes have been reported, such as that developed by Connon et al., which involved dihydroquinine-derived urea derivatives as highly efficient organocatalysts.[61] These bifunctional cinchona alkaloid-derived catalysts were employed to promote the highly efficient DKR of azalactones with allyl alcohol, providing the corresponding chiral amino esters in excellent yields and high enantioselectivities of up to 88% ee, as shown in Scheme 33. It was demonstrated that the organocatalyst was relatively insensitive to the steric bulk of the azalactone alkyl substituent, since both unhindered azalactones and the more bulky analogues underwent enantioselective DKR to furnish orthogonally protected amino acids with very good enantioselectivity, allowing alanine-, methionine- and phenylalanine-derived azalactones to undergo the DKR process. In order to extend the broad applicability of these catalysts, these authors have investigated the use of thiol nucleophiles in these processes, furnishing the corresponding enantioenriched α-amino acid thioesters of potential use in chemical biology,[62] albeit in moderate enantioselectivity (≤64% ee) (Scheme 33).





Scheme 33. Cinchona alkaloid-catalysed DKRs of azalactones.

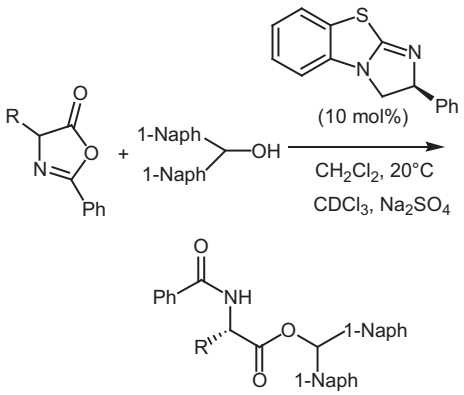
It is well known, however, that urea-based organocatalysts can form H-bonded aggregates, due to their bifunctional nature, resulting in a strong dependency of the reactivity and enantioselectivity on the concentration and temperature. Due to the self-association phenomena of this type of catalysts, the enantioselectivity generally decreases with increasing concentration or decreasing temperature, which can hamper their practical use. In order to overcome these limitations, Song et al. have developed a new class of highly active and enantioselective bifunctional organocatalysts, which did not self aggregate in the solution state.[63] The self-association-free, bifunctional squaramide-based dimeric cinchona alkaloid depicted in Scheme 34 showed an excellent catalytic activity combined with the highest level of enantioselectivity (97% ee) reported to date for the DKR of the azalactone depicted in Scheme 30 with allyl alcohol. Furthermore, the poor solubility of this type of catalyst in organic solvents enabled an easy recovery through a simple precipitation method, allowing repeated recycling without any loss of turnover time or enantioselectivity.



Scheme 34. Dimeric cinchona alkaloid-catalysed DKR of azalactone.

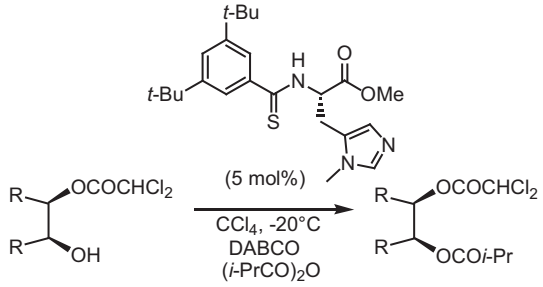
In the same context, Birman et al. have recently reported the organocatalysed reactions of azalactones with di(1-naphthyl) methanol as the nucleophile.[64] A series of chiral amidine-based catalysts were investigated for these reactions, resulting in the selection of a chiral benzotetramizole as the most efficient, which provided the corresponding di(1-naphthyl)methyl esters of α-amino acids in excellent yields and enantioselectivities of up to 96% ee, as shown in Scheme 35. The best results were obtained with C4-aryl-substituted azalactones, which is remarkable, given the fact that the highest enantiomeric excess previously reported for either enzymatic or non-enzymatic DKR of these substrates has been 75% ee.

Very recently, Qu and Cao have shown that an enantioselective acylation catalysed by a thioamide-modified 1-methylhistidine methyl ester (Scheme 36) in combination with DABCO-mediated racemisation of the substrate led to the efficient DKR of *meso*-1,2-diol monodichloroacetates.[65] As shown in Scheme 36, both cyclic and acyclic *meso*-1,2-diol monodichloroacetates could be transformed into the corresponding enantiomerically enriched (1*S*,2*R*)-hetero-substituted diol esters in good yields and moderate enantioselectivities of up to 74% ee.



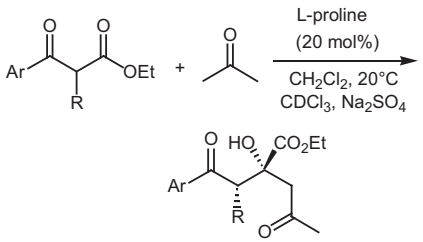
R = Ph: 89% ee = 94%
R = $(CH_2)_2$SMe: 92% ee = 90%
R = Bn: 94% ee = 83%
R = *p*-$MeOC_6H_4$: 86% ee = 92%
R = *p*-BrC_6H_4: 90% ee = 95%
R = 2-Naph: 88% ee = 91%
R = 1-Naph: 46% ee = 76%
R = *p*-FC_6H_4: 90% ee = 95%
R = Me: 90% ee = 83%
R = *i*-Bu: 97% ee = 80%
R = *p*-$ClOC_6H_4$: 88% ee = 96%

Scheme 35. Benzotetramizole-catalysed DKR of azalactones.

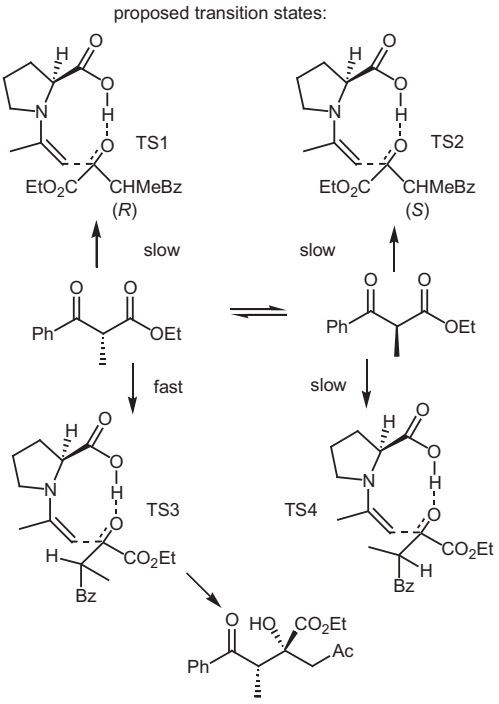


R,R = $(CH_2)_4$: 90% ee = 74%
R,R = $(CH_2)_5$: 91% ee = 74%
R,R = $(CH_2)_6$: 91% ee = 70%
R = Me: 83% ee = 68%
R = *n*-Pr: 90% ee = 62%

Scheme 36. Thioamide-catalysed DKR of *meso*-1,2-diol monodichloroacetates.



Ar = Ph, R = Me: 81% de = 96% ee = 96%
Ar = Ph, R = Et: 61% de = 74% ee = 96%
Ar = Ph, R = *n*-Pr: 51% de = 60% ee = 96%
Ar = *p*-ClC_6H_4, R = Me: 72% de > 98% ee = 92%
Ar = *p*-BrC_6H_4, R = Me: 76% de > 98% ee = 98%
Ar = *p*-*i*-PrC_6H_4, R = Me: 72% de > 98% ee = 94%
Ar = 2,5-$Me_2C_6H_3$, R = Me: 75% de = 88% ee = 96%
Ar = 2-Naph, R = Me: 74% de > 98% ee = 94%
Ar = 2-Fu, R = Me: 77% de = 94% ee = 97%
Ar = 2-Thio, R = Me: 81% de = 90% ee = 97%

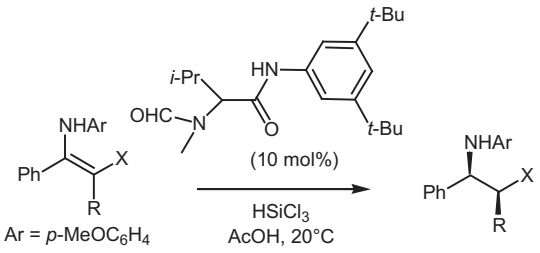


Scheme 37. L-Proline-catalysed DKR aldol reaction of acetone with β-substituted α-ketoesters.

While a number of DKR processes based on an intermolecular aldol reaction between aldehydes and ketones have been reported, those induced by an organocatalyst have often involved aldehydes. The first highly efficient diastereo- and enantioselective organocatalytic addition of acetone to an activated ketone, such as a β-substituted α-ketoester, was developed by Zhang et al. through a DKR process.[66] Hence, the proline-catalysed asymmetric aldol reaction of acetone with various 2,4-dioxo-3-methyl-4-aryl-butanoates offered an elegant way to create two adjacent stereogenic centres simultaneously in a single chemical operation with excellent diastereoselectivity of up to >98% de and enantioselectivity of up to 98% ee, providing a truly useful tool for preparing the corresponding important chiral products. The stereochemical outcome of the reaction could be explained by examination of the four plausible transition states shown in Scheme 37. In transition states TS1 and TS2, the α-carbonyl oxygen atom is hydrogen bonded, so that an *S*-stereogenic centre would be created by the addition of an acetone molecule, where the large CH(Me)Bz group is close to the enamine moiety, and hence energetically less favoured. In transition states TS3 and TS4, the substrate molecule creates an *R*-stereogenic centre, where the small CO_2Et group is close to the enamine. In transition state TS3, the configurationally labile *R*-configured substrate molecule is hydrogen bonded by the proline OH. As the carbonyl group is crowded, the large group on the β-carbon, Bz, lies *anti* to the oxygen atom, and thus the attacking CH_2 experiences less hindrance, compared to that in transition state TS4, where the Me group in the (*S*)-form must be considered. This arrangement results in a preferential reaction via TS3, providing (*R*)-ethyl-2-hydroxy-4-oxo-2-((*S*)-1-oxo-1-phenylpropan-2-yl) pentanoate as the major isomer.

In another context, an L-valine-derived formamide was applied by Kocovsky et al. as an organocatalyst to the asymmetric hydrosilylation of enamines, allowing a direct access to a range of β-amino acid derivatives.[67] This method relied on the fast equilibration between the enamine and the imine forms, which was promoted by acetic acid employed as an additive. In these conditions, a series of enamines could be reduced into the corresponding

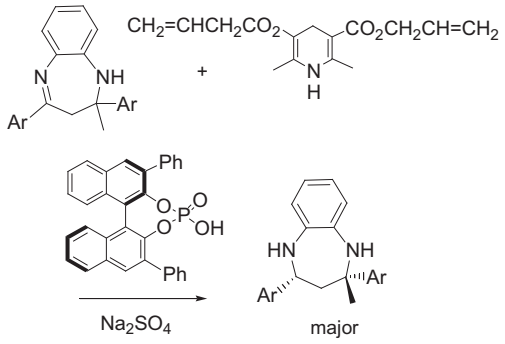
amino esters and aminonitriles in high yields and with good enantioselectivities, as shown in Scheme 38. In almost all cases of substrates, the *syn* diastereoselectivity of the reaction was excellent (90–99% de).



R = Ph, X = CO_2Et: 84% de > 98% ee = 76%
R = *p*-$MeOC_6H_4$, X = CO_2Et: 80% de > 98% ee = 77%
R = *p*-FC_6H_4, X = CO_2Et: 77% de > 98% ee = 73%
R = Me, X = CO_2Et: 85% de = 96% ee = 77%
R = Et, X = CO_2Et: 86% de = 90% ee = 82%
R = *n*-Bu, X = CO_2Et: 84% de = 90% ee = 76%
R = Ph, X = CN: 46% de > 98% ee = 83%
R = *p*-$MeOC_6H_4$, X = CN: 43% de > 98% ee = 83%
R = *p*-FC_6H_4, X = CN: 72% de > 98% ee = 79%

Scheme 38. DKR hydrosilylation of enamines catalysed by L-valine-derived formamide.

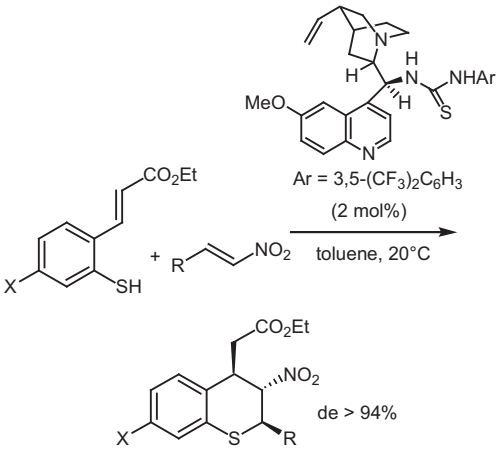
In 2009, Gong et al. reported the dynamic kinetic transfer hydrogenation reaction of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines, using chiral phosphoric acids as organocatalysts and Hantzsch ester as the hydride source.[68] A 3,3′-H8-BINOL-derived phosphoric acid was identified as the optimal chiral catalyst for this process, affording the corresponding 1,3-diamine derivatives with moderate diastereoselectivities of up to 78% de and enantioselectivities of up to 94% ee, as shown in Scheme 39.



Ar = *p*-$CF_3C_6H_4$: 92% de = 78% ee = 85%
Ar = *p*-BrC_6H_4: 81% de = 66% ee = 87%
Ar = *p*-ClC_6H_4: 83% de = 66% ee = 86%
Ar = *p*-PhC_6H_4: 95% de = 60% ee = 94%
Ar = *m*-BrC_6H_4: 87% de = 72% ee = 89%

Scheme 39. Transfer hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines.

In the last few years, a number of highly efficient enantioselective organocatalytic domino Michael reactions have been developed, among which are reactions predominantly catalysed by L-proline derivatives.[69] On the other hand, Wang et al. have recently developed a novel asymmetric domino Michael reaction catalysed by a cinchona alkaloid amine thiourea, affording a one-pot access to enantioenriched thiochromanes with the creation of three new stereogenic centres in remarkably high efficiency and stereoselectivity.[70] As shown in Scheme 40, the domino Michael reaction of *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester with a series nitroalkenes performed in the presence of the organocatalyst depicted in the scheme yielded the corresponding thiochromanes in excellent yields and enantioselectivities of up to 99% ee combined with an excellent diastereoselectivity of >94% de in all cases. The system seemed inert to any electronic changes to the aromatic ring of the *trans*-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester, since the presence of methyl and methoxy groups on the aromatic ring of these substrates led to the corresponding domino Michael products in comparable yields and enantioselectivities (Scheme 40).

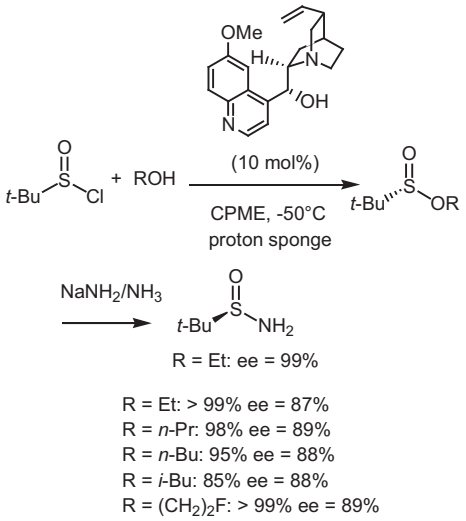


R = Ph, X = H: 90% ee = 97%
R = *p*-FC_6H_4, X = H: 92% ee = 97%
R = *p*-ClC_6H_4, X = H: 99% ee = 97%
R = *p*-BrC_6H_4, X = H: 91% ee = 94%
R = *m*-BrC_6H_4, X = H: 83% ee = 97%
R = *p*-$MeOC_6H_4$, X = H: 88% ee = 97%
R = *p*-BnC_6H_4, X = H: 95% ee = 97%
R = *o*-$MeOC_6H_4$, X = H: 90% ee = 99%
R = *m*-$BnOC_6H_4$, X = H: 87% ee = 92%
R = 2-Thio, X = H: 97% ee = 98%
R = *n*-Bu, X = H: 32% ee = 93%
R = Me, X = Me: 93% ee = 99%
R = X = OMe: 42% ee = 97%

Scheme 40. Cinchona alkaloid-catalysed domino Michael reaction.

In another context, Ellman and Wakayama have employed quinidine as an organocatalyst to promote the reaction of *tert*-butanesulfinyl chloride with various alcohols to provide via DKR the corresponding chiral alkyl *tert*-butanesulfinates in high yields and good-to-high enantioselectivities of up to 89% ee, as shown in Scheme 41.[71] The best results were obtained when the reaction was performed at −50 °C in cyclopentyl methyl ether (CPME) as the solvent and in the presence of a proton sponge as the base. Subsequent treatment of the formed alkyl *tert*-butanesulfinates with $NaNH_2$ in ammonia followed by simple trituration of the products with octane furnished the corresponding *tert*-butanesulfinamides with up to 99% ee.

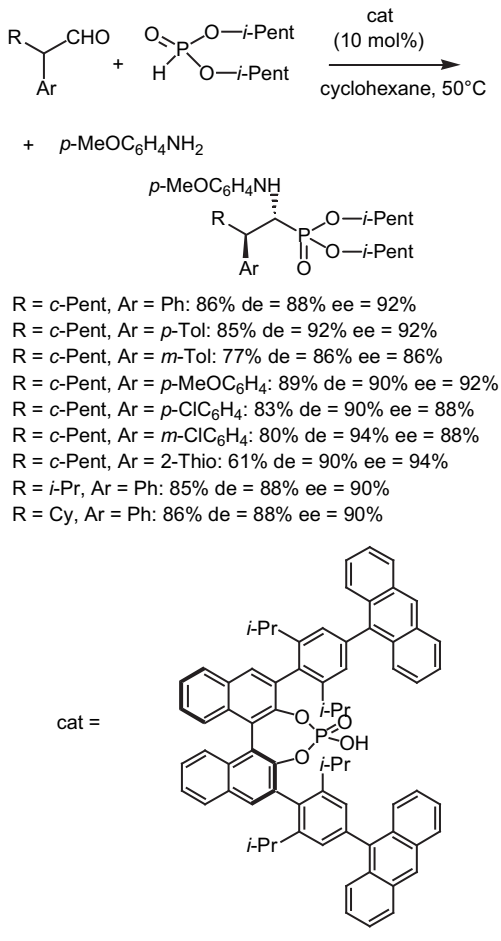
The reaction of a carbonyl compound, an amine, and a phosphite by in situ imine hydrophosphonylation, often called the Kabachnik–Fields reaction, is an attractive approach to α-amino phosphonates, which have great promise as antibacterial and anti-HIV agents as well as protease inhibitors. Consequently, their enantioselective synthesis has attracted considerable interest.[72] In this context, List et al. have developed an enantioselective organocatalytic version of this three-component reaction, providing, in one step, a series of chiral β-branched α-amino carboxylic acids.[73] Therefore, the reaction between an α-branched aldehyde,



Scheme 41. Quinidine-catalysed DKR of *tert*-butanesulfinyl chloride.

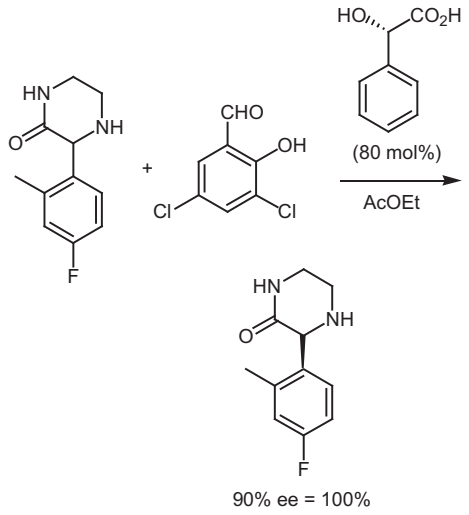
p-anisidine and di(3-pentyl)phosphite in the presence of a new chiral phosphoric acid as organocatalyst yielded through DKR the corresponding Kabachnik–Fields products in high yields, diastereoselectivities of up to 94% de and enantioselectivities of up to 94% ee, as shown in Scheme 42.

GW597599 is a novel NK-1 antagonist for the treatment of central nervous system disorders and emesis. The initial synthetic route to this important product involved a classical resolution step



Scheme 42. Kabachnik–Fields reaction catalysed with phosphoric acid.

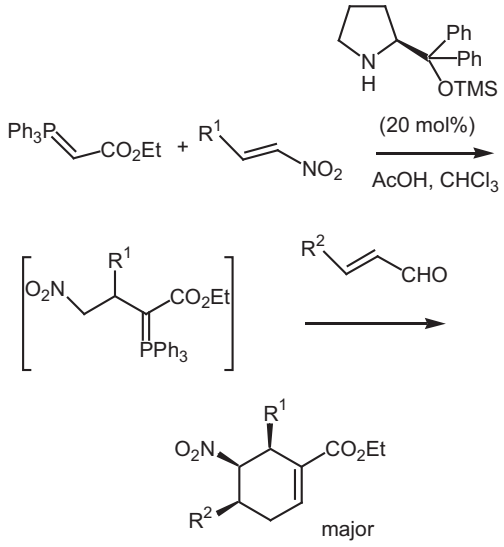
of a ketopiperazine obtained in 38% yield through a classical fractional crystallisation using (+)-mandelic acid (0.8 equiv) in ethyl acetate.[74] In order to avoid wasting the unwanted enantiomer, these authors have introduced a DKR process. Thus, the ketopiperazine secondary amine could form an iminium derivative with an appropriate aldehyde, such as dichlorosalicylaldehyde, increasing the acidity of the benzylic proton. The resulting derivative could easily racemise, allowing the unwanted enantiomer to precipitate out as its mandelate salt, leaving the unwanted enantiomer in solution ready to be further racemised. Using this methodology, the enantiopure (*S*)-ketopiperazine was isolated in 90% yield, as shown in Scheme 43.



Scheme 43. DKR of ketopiperazine.

In addition, several works dealing with asymmetric organocatalytic DYKAT processes[75] have been recently reported, involving the equilibration of intermediates generated during the reactions. As an example, Hong et al. have developed organocatalytic enantioselective one-pot cascade Michael–Michael Wittig reactions between three components, phosphorus ylide, nitroolefins and α,β-unsaturated aldehydes, providing the corresponding chiral trisubstituted cyclohexenecarboxylates via [1+2+3] annulation with excellent enantioselectivities of up to 99% ee, as shown in Scheme 44.[76] In this reaction, catalysed by an L-proline derivative, the conjugate addition of the stabilised Wittig reagent to the nitroolefin generated another racemic stabilised Wittig reagent, which could decompose back, providing a vehicle for their interconversion. Consequently, since the racemisation process was fast relative to the subsequent nitro-Michael and Wittig reactions, an effective DKR resulted, followed by the organocatalytic enantioselective conjugate addition of the in situ-generated nitroalkane to the α,β-unsaturated aldehyde, with the subsequent Wittig reaction, leading to the [1+2+3] annulation product.

Another example of a reaction including a DKR and based on the racemisation of an intermediate was described by Moberg et al. dealing with the organocatalytic enantioselective acetylcyanation of α-oxo esters into the corresponding *O*-acetylated cyanohydrins.[77] The reaction catalysed with a cinchona alkaloid derivative proceeded by a non-selective addition of cyanide ion to give the non-protected cyanohydrin, followed by a DKR to provide the enantioenriched acetylated product in moderate-to-good enantioselectivities of up to 82% ee. The authors have proposed the mechanism depicted in Scheme 45. The reaction was supposed to be initiated by HCN, produced from acetyl cyanide and methanol, or by cyanide present as an impurity in the acylating agent. Racemic non-protected cyanohydrin, resulting from the reaction of the



$R^1 = R^2 = H$: 83% ee = 95%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = H$: 82% ee = 99%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = H$: 90% ee = 99%
$R^1 = p\text{-}FC_6H_4$, $R^2 = H$: 91% ee = 96%
$R^1 = 3,4\text{-}OCH_2OC_6H_3$, $R^2 = H$: 71% ee = 99%
$R^1 = Ph$, $R^2 = p\text{-}BrC_6H_4$: 82% ee = 97%
$R^1 = Ph$, $R^2 = p\text{-}NO_2C_6H_4$: 85% ee = 99%
$R^1 = Ph$, $R^2 = p\text{-}ClC_6H_4$: 77% ee = 95%

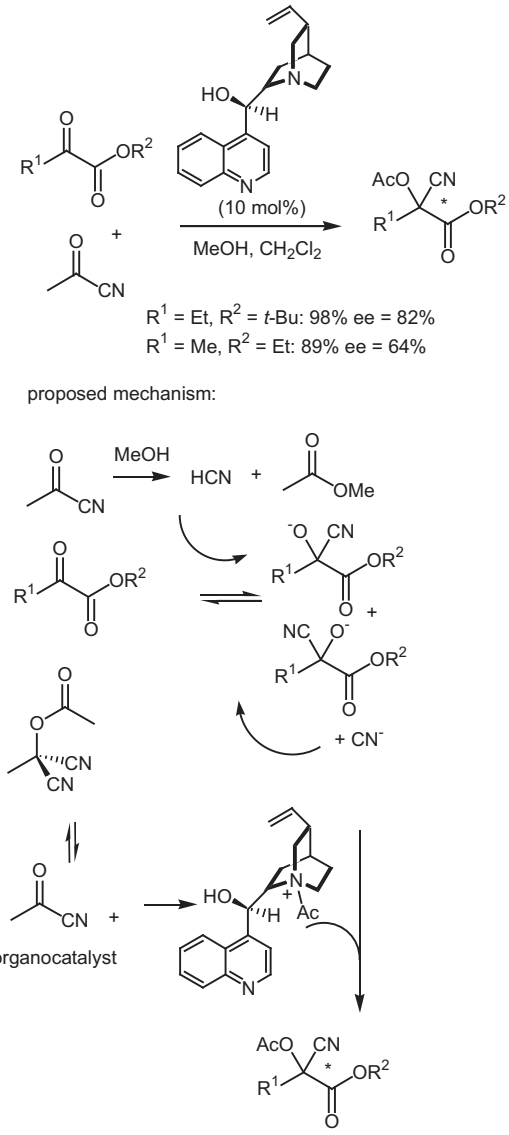
Scheme 44. Cascade Michael–Michael Wittig reaction.

α-oxo ester with cyanide, was acylated by the acetylated amine, obtained from the chiral organocatalyst and acetyl cyanide. This process is a DKR, which required a rapid equilibrium between the α-oxo ester and cyanohydrin. The acetylated amine derived from the organocatalyst was expected to be a more efficient acyl-transfer reagent than acetyl cyanide. The acylation liberated cyanide, which enabled the catalytic turnover. Finally, Shibata et al. have achieved the first highly enantioselective direct α-hydroxylation of racemic malonates with oxaziridines through DYKAT catalysed by a chiral nickel catalyst to provide the corresponding chiral α-hydroxy malonates in high yields and enantioselectivities of up to 98% ee.[78]

Despite the prevalence and importance of atropisomerism in organic structures, the field of asymmetric catalysis has not yet recorded extensive success in the development of catalysts, that control this stereochemical feature. Indeed, catalytic reactions of this nature are presently rare, and only modest atropisomer selectivity has been observed. In this context, Miller et al. have very recently developed the DKR of biaryl atropisomers via peptide-catalysed asymmetric bromination.[79] The reaction proceeded via an atropisomer-selective electrophilic aromatic substitution reaction using a simple bromination reagent, such as *N*-bromophthalimide. As shown in Scheme 46, a series of chiral brominated biaryl compounds could be prepared with excellent enantioselectivities of >90% ee in most cases and combined with good-to-high yields (65–87%). The best results were obtained when using the tripeptide depicted in Scheme 46 as the organocatalyst.

3. Enzymatic methods

In recent years, the use of biocatalysts for organic transformations has become an increasingly attractive alternative to conventional chemical methods.[22,80] The use of an enzyme, rather



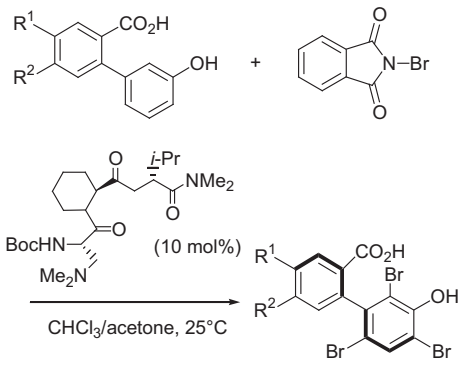
$R^1 = Et$, $R^2 = t\text{-}Bu$: 98% ee = 82%
$R^1 = Me$, $R^2 = Et$: 89% ee = 64%

Scheme 45. Acetylcyanation of α-oxo esters.

than a transition-metal catalyst, represents an attractive option for DKR, in view of the likely mild conditions associated with enzyme-catalysed racemisation processes. These reactions can be carried out at ambient temperature and atmospheric pressure, avoiding the use of more extreme conditions, which could cause problems, such as isomerisation, racemisation, epimerisation and rearrangement. Moreover, biocatalysis often offers advantages over chemical synthesis, since the reactions are often highly enantio- and regioselective. In recent years, impressive examples using new enzymes have been discovered and major progress in DKR has taken place, demonstrating that biocatalysis is rapidly developing and is still a growing field, allowing a number of key intermediates for pharmaceutical synthesis to be reached.[81]

3.1. Enzymatic hydrolysis and esterification reactions

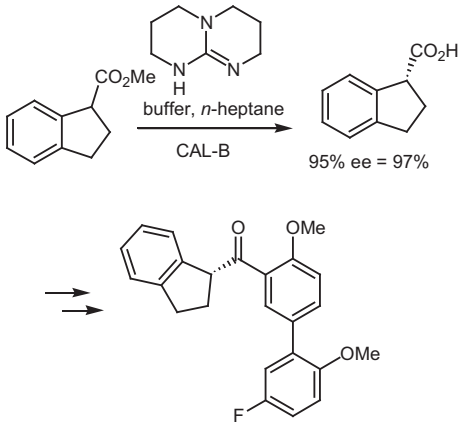
2,3-Dihydro-1-*H*-indene-1-carboxylic acid is an important precursor for a series of aryl indan-1-yl ketones, which constitute new lead compounds for human peptidyl-prolyl-*cis*/*trans*-isomerase inhibitors. In this context, Pietruszka et al. have developed the DKR of methyl 2,3-dihydro-1-*H*-indene-1-carboxylate performed in the



$R^1 = R^2 = H$: 80% ee = 94%
$R^1 = NO_2$, $R^2 = H$: 85% ee = 94%
$R^1 = H$, $R^2 = NO_2$: 75% ee = 93%
$R^1 = H$, $R^2 = MeO$: 70% ee = 92%
$R^1 = H$, $R^2 = F$: 70% ee = 94%
$R^1 = F$, $R^2 = H$: 65% ee = 93%
R^1,$R^2 = CH_2OCH_2$: 70% ee = 90%

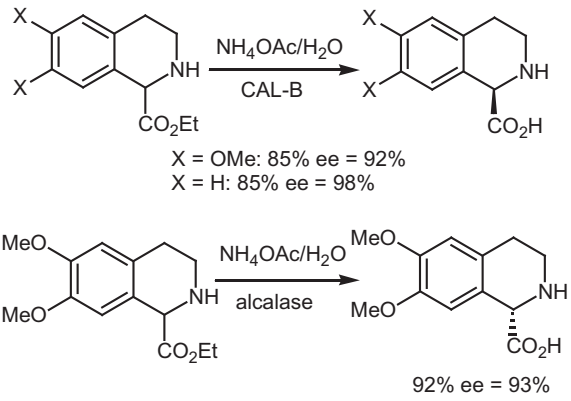
Scheme 46. Organocatalysed bromination.

presence of *Candida antarctica* lipase B (CAL-B) combined with a base, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene, as the racemisation agent.[82] Indeed, this system provided the synthesis of the expected highly enantiomerically enriched indanecarboxylic acid (97% ee) in an excellent yield of 95%, as shown in Scheme 47. This product proved to be a valuable starting material from which to obtain the biaryl indan-1-yl ketone, a potential biologically active product.



Scheme 47. DKR of methyl 2,3-dihydro-1-*H*-indene-1-carboxylate.

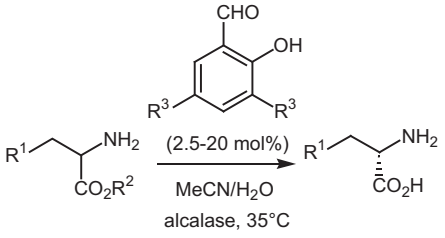
The first synthesis of both enantiomers of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid was accomplished by Fülöp et al. through highly efficient DKR processes, which represented the first procedure for the preparation of both enantiomers of an amino acid through enzyme-catalysed DKR.[83] These methods were based on the CAL-B- or subtilisin Carlsberg-catalysed enantioselective hydrolysis of ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate in aqueous NH_4OAc. The corresponding (*R*)- and (*S*)-products, respectively, were produced with high enantiopurity (92–93% ee) in good yields (85–92%), as shown in Scheme 48. Moreover, this methodology was applied to the DKR of unsubstituted ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate, which yielded the corresponding carboxylic acid in 85% yield and



Scheme 48. DKRs of ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.

98% ee when submitted to the CAL-B catalysis conditions, as shown in Scheme 48.

In another context, Beller et al. have found a convenient procedure for the racemisation of α-amino acid esters in the presence of catalytic amounts of salicylaldehydes, such as 3,5-dinitrosalicylaldehyde or 3,5-dichlorosalicylaldehyde.[84] Hence, after the condensation reaction of the α-amino acid ester with the aldehyde, the acidity of the α-hydrogen atom at the chiral centre was remarkably increased. Consequently, a rapid protonation–deprotonation at the α-carbon atom took place, which caused the racemisation. Notably, the stabilisation of the imine through hydrogen bonding enhanced the opportunity for the protonation–deprotonation sequence. After hydrolysis of the intermediate Schiff base, the racemised amino acid ester and the aldehyde were liberated. The combination of this racemisation protocol with alcalase-catalysed ester hydrolysis allowed the successful DKR of various α-amino acid esters to be achieved in high yields and enantioselectivities of up to 99% ee. As shown in Scheme 49, a broad range of chiral α-amino acids of tyrosine and phenylalanine were prepared by this methodology. Moreover, the established method was applied to a range of aliphatic amino acid esters of alanine, leucine, norleucine, norvaline and methionine, providing the corresponding α-amino acids, albeit in lower enantioselectivities.

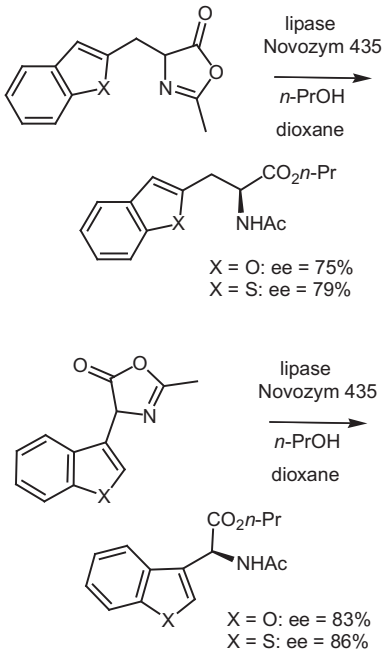


R^1 = Ph, R^2 = Bn, R^3 = Cl: 87% ee = 88%
R^1 = Ph, R^2 = Et, $R^3 = NO_2$: 95% ee = 99%
R^1 = Ph, R^2 = *n*-Bu, R^3 = Cl: 63% ee = 92%
$R^1 = p$-HOC_6H_4, R^2 = Bn, R^3 = Cl: 95% ee = 99%
$R^1 = p$-HOC_6H_4, R^2 = Et, R^3 = Cl: 92% ee = 98%
$R^1 = p$-HOC_6H_4, R^2 = *i*-Pr, R^3 = Cl: 92% ee = 99%
$R^1 = MeSCH_2$, R^2 = Et, $R^3 = NO_2$: 96% ee = 89%
$R^1 = R^2$ = Et, $R^3 = NO_2$: 98% ee = 64%
R^1 = *i*-Pr, R^2 = Et, $R^3 = NO_2$: 99% ee = 97%

Scheme 49. DKR of α-amino acid esters.

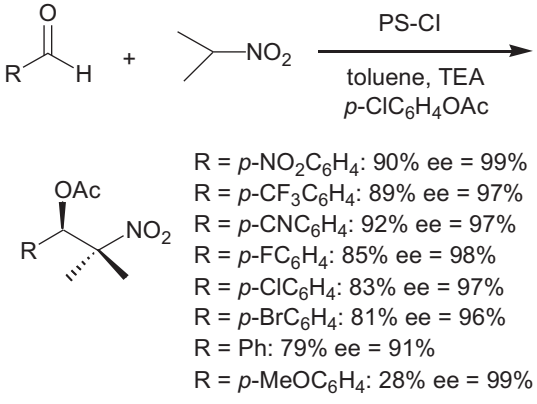
On the other hand, various biocatalytic esterification methods have been developed in the last two years on the basis of DKR. As an example, Irimie et al. have reported the DKR of various

functionalised oxazolones mediated by the lipase, Novozym 435, which furnished the corresponding 2-amino-3-(heteroaryl)propanoic esters with quantitative yields and high enantioselectivities of up to 86% ee.[85] As shown in Scheme 50, dioxane proved to be the most selective solvent for the biocatalytic ring-opening reaction, while *n*-propanol was found to be the most selective nucleophilic agent for all substrates.



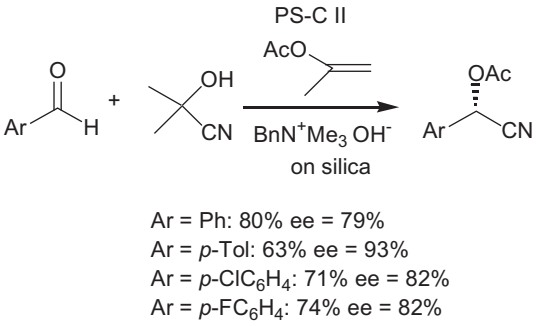
Scheme 50. Ring opening of oxazolones.

The nitroaldol or Henry reaction between a carbonyl group, such as an aldehyde, and a nitroalkane is thermodynamically controlled and provides the corresponding β-nitroalkanol derivative. This equilibrium reaction can be used as the racemisation step of the undesired enantiomer. In this context, Ramström et al. have developed the asymmetric synthesis of β-nitroalkanol derivatives through the combination of a nitroaldol reaction with a lipase-catalysed transesterification.[86] Indeed, the one-pot reaction of 2-nitropropane with a range of aldehydes provided through DKR the corresponding β-nitroalkanol derivatives in excellent yields and enantioselectivities of up to 99% ee, as shown in Scheme 51. The reaction was performed in toluene with *Pseudomonas cepacia* lipase I (PS-CI) as the lipase, TEA as the equilibrium-inducing agent and *p*-chlorophenyl acetate as the acyl donor.



Scheme 51. One-pot combined nitroaldol reaction and lipase-catalysed transesterification.

Silica-supported benzyltrimethylammonium hydroxide (BTAH), prepared very easily, was found by Sakai et al. to be quite effective as a racemising agent.[87] Moreover, it did produce an unpleasant odour as ion-exchange resins did, and was easy to handle. Using silica-supported BTAH together with a porous ceramic-immobilised lipase, efficient lipase-catalysed DKR of cyanohydrins, generated from aldehydes and acetone cyanohydrin in one pot, has been successfully achieved. This DKR provided synthetically useful cyanohydrin acetates with high enantioselectivities of up to 93% ee, as shown in Scheme 52. The best results were obtained by employing *P. cepacia* lipase II (PS-C II) combined with isopropenyl acetate as the acyl donor.



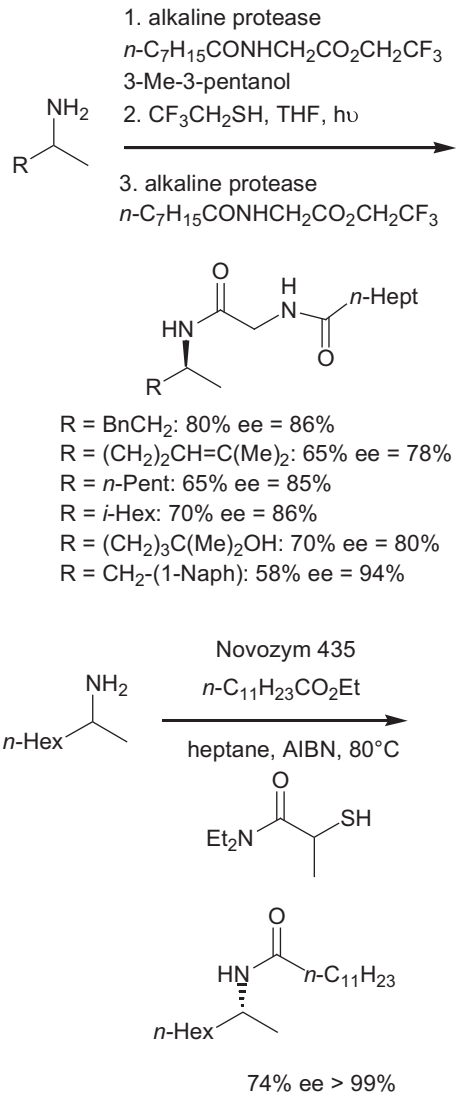
Scheme 52. Lipase-catalysed DKR of cyanohydrins using silica-supported BTAH as racemising agent.

The potential of zeolites in acid catalysis for fine chemical applications has been extensively explored, since these materials are versatile and economical heterogeneous catalysts with very specific selectivity properties. For example, they constitute powerful catalysts for the racemisation of benzylic alcohols. In this context, Masters et al. have investigated the use of catalytic nanoreactors, prepared by encapsulation of zeolite H-Beta using a layer-by-layer assembly of polyelectrolytes, in the DKR of secondary alcohols.[88] The encapsulation of the acidic zeolite racemisation catalyst allowed the pH-sensitive enzyme, *C. antarctica* lipase B, to be protected. These conditions were applied to the DKR of secondary alcohols, such as 1-phenylethanol and 1-indanol, performed in the presence of vinyl acetate as the acyl donor, which provided the corresponding (*R*)-acetates in good yields of 70 and 59%, respectively, along with good enantioselectivities of 86 and 92% ee, respectively. In the same area, Iborra et al. have described the first continuous DKR of 1-phenylethanol in ionic liquids and supercritical carbon dioxide by using a combination of immobilised lipase, Novozym 435, and acid zeolite catalysts packed as a heterogeneous particle mixture.[89] The reactor operated as a catalytic unit able to continuously transform, at 50 °C and 100 bar in the presence of vinyl acetate as the acyl donor, 1-phenylethanol into the corresponding (*R*)-acetate with both excellent enantioselectivity of 97% ee and yield of 98%, combining the advantages of ionic liquids to stabilise enzymes in supercritical fluids, as a non-aqueous green reaction/extraction system, with the advantages of a continuous-flow process (up to 14 days) for easy product separation and catalyst reuse. However, the use of acid zeolites as catalysts was found to generate several secondary products, namely via dehydration to styrene (eventually followed by polymerisation) and coking, that are responsible for both yield reductions and catalyst deactivation. In particular, zeolite H-Beta presents a three-dimensional network of large channels accessed through large pores, which promote the formation of heavy products. It has been demonstrated that intermediate-pore-size zeolites, such as H-ZSM-5, were more

efficient in preventing the formation of ethers and styrene oligomers. In this context, Lemos et al. have investigated this type of zeolite in the DKR of 1-phenylethanol into the corresponding (*R*)-acetate by using lipase, Novozym 435, combined with vinyl acetate as the acyl donor.[90] Unfortunately, the formation of heavy products related to the presence of vinyl acetate caused the yield to be limited to 17%, albeit with enantioselectivity of 100% ee.

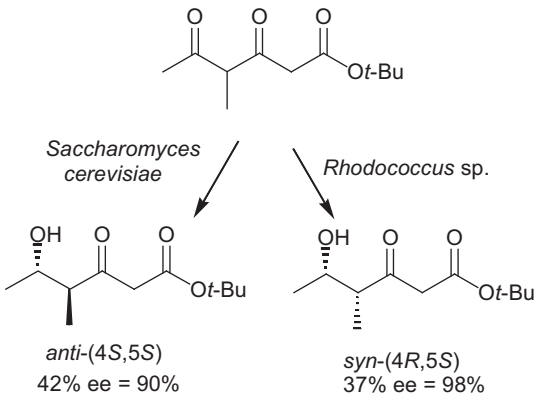
3.2. Miscellaneous enzymatic reactions

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.[91] However, in the last few years, some examples of DKR of amines have appeared in the literature. As an example, Gil et al. have reported the DKR of a series of aliphatic amines through a highly efficient one-pot sequential DKR process, involving an in situ free radical-mediated racemisation and an enzymatic resolution, which provided the corresponding (*S*)-amides in good yields and high enantioselectivities of up to 94% ee, as shown in Scheme 53.[92] Hence, these products were produced through a one-pot sequence of three reactions, beginning with an alkaline protease-catalysed kinetic resolution using *N*-octanoyl glycine trifluoroethyl ester as the acyl donor, followed by a light-induced radical racemisation mediated by trifluoroethanethiol in the presence of the enzyme and the residual acyl donor, and then a subsequent second kinetic resolution which occurred after adding a second portion of both the enzyme and the acyl donor. Moreover, these authors have demonstrated that this novel type of protocol could be applied with even better enantioselectivities to the synthesis of (*R*)-amides by using lipase, Novozym 435, instead of the alkaline protease.[93] Therefore, when 2-aminooctane was treated with this enzyme in the presence of ethyl laurate as the acyl donor, *N*,*N*-diethyl-2-mercapto-propionamide as the racemising agent, and AIBN in heptane at 80 °C, it yielded (*R*)-*N*-(octan-2-yl)dodecanamide in 74% yield and excellent enantioselectivity of >99% ee (Scheme 53).



Scheme 53. DKRs of amines.

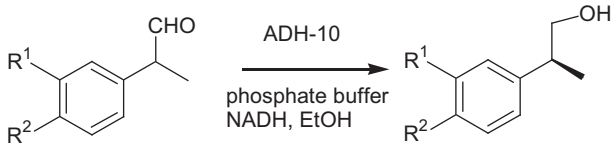
The reduction of β- and α-ketoesters[94] can be accomplished using baker's yeast or other microorganisms, and a wide range of applications of this methodology have been reported.[95] This technique was first applied in 1976 to the asymmetric reduction of α-monosubstituted β-oxoesters by baker's yeast, which is the most popular microorganism, due to its availability and ease of handling, since it does not require sterile conditions.[96] More recently, Müller et al. have investigated the alcohol dehydrogenase-catalysed DKR of *tert*-butyl 4-methyl-3,5-dioxohexanoate.[97] Indeed, since 5-hydroxy-3-oxohexanoates can serve as building blocks for the synthesis of polyketide analogues or polyketide-derived natural products, they serve as important model compounds for polyketide chemistry. These authors have shown that two out of the four possible enantiopure diastereomers of the corresponding alcohol could be selectively accessed through DKR of the same substrate by using two different alcohol dehydrogenases. Thus, the use of *Rhodococcus* sp. provided the corresponding *syn*-(4*R*,5*S*) product in 37% yield and 98% ee, while employing *Saccharomyces cerevisiae* reduced *tert*-butyl 4-methyl-3,5-dioxohexanoate into the corresponding *anti*-(4*S*,5*S*) product in 42% yield and 90% ee, as shown in Scheme 54.



Scheme 54. Reductions of *tert*-butyl 4-methyl-3,5-dioxohexanoate.

In the same area, Blum et al. disclosed a remarkably general dynamic reductive kinetic resolution entry into (*S*)-profens, in 2010.[98] As shown in Scheme 55, the reduction of a series of 2-arylpropionaldehydes with alcohol dehydrogenase (ADH)-10 afforded the corresponding (*S*)-alcohols in excellent yields and enantioselectivities of up to 99% ee.

Baeyer–Villiger monooxygenases are highly promiscuous enzymes, which enable stereoselective conversions of ketones into esters or lactones.[99] Currently, several enzymes have been identified and characterised for their potential use as biocatalysts capable of performing DKR. As an example, Gotor et al. have reported the



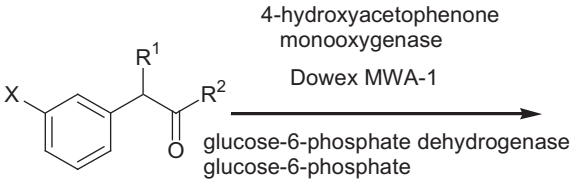
R^1,R^2 = CH=CH-CH=CH: 57% ee = 94%
R^1 = H, R^2 = *i*-Bu: 92% ee = 99%
R^1 = R^2 = H: 74% ee = 98%
R^1 = F, R^2 = Ph: 77% ee = 97%
R^1 = H, R^2 = CF_3: 55% ee = 98%
R^1 = Bz, R^2 = H: 85% ee = 95%
R^1 = OPh, R^2 = H: 85% ee = 95%

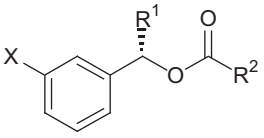
Scheme 55. Reduction of 2-arylpropionaldehydes.

use of 4-hydroxyacetophenone monooxygenase from *Pseudomonas fluorescens* ACB in combination with a weak anion exchange resin to perform DKR of benzyl ketones.[100] Indeed, this DKR could be achieved by combining an isolated Baeyer–Villiger monooxygenase-catalysed Baeyer–Villiger oxidation of benzyl ketones with a racemisation induced by Dowex MWA-1 as a weak anion resin, which provided the corresponding benzyl esters with good yields and good-to-high enantioselectivities of up to 83% ee, as shown in Scheme 56. It must be noted that the oxidations were coupled to a second enzymatic reaction catalysed by glucose-6-phosphate dehydrogenase in order to regenerate NADPH. Moreover, the same authors have developed the Baeyer–Villiger oxidation of α-acetylphenylacetonitrile into the corresponding enantiopure (*R*)-2-acetoxyphenylacetonitrile in 58% yield and an excellent enantioselectivity of 98% ee, as shown in Scheme 56.[101] This reaction was catalysed by phenylacetone monooxygenase in the presence of aqueous buffer and a mixture of *i*-Pr_2O and AcOEt as cosolvents. In addition, Baeyer–Villiger monooxygenases have been tested by the same authors in the oxidation of benzo-fused ketones, such as 2-alkyl-1-indanones.[102] Therefore, when employing a single mutant of phenylacetone monooxygenase (M446G PAMO) under the proper reaction conditions, it was possible to achieve the corresponding 3-alkyl 3,4-dihydroisocoumarins with high yields and enantioselectivities through regioselective DKR processes, as shown in Scheme 56.

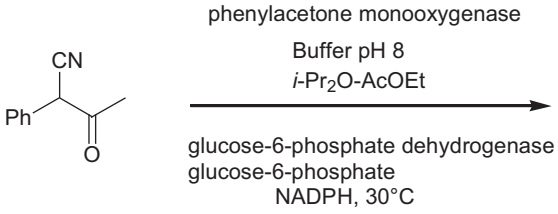
In order to prepare GABA analogues, Kroutil et al. have reported the synthesis of (*R*)-α-phenylpyrrolidin-2-one based on the DKR of 4-oxo-3-phenylbutyric acid ethyl ester, achieved by using ω-transaminase ATA-117 as the racemising agent combined with D-alanine as the amino donor.[103] As shown in Scheme 57, the reaction was performed in buffered solution at 30 °C, employing lactate dehydrogenase to remove the formed pyruvate, providing the expected product in high yield and enantioselectivity of 68% ee. This reaction constituted the first DKR involving an enantioselective amination reaction catalysed by a ω-transaminase.

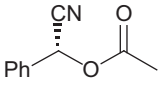
(+)-Scyphostatin is regarded as the most specific and potent inhibitor of neutral sphingomyelinase, a pharmacological target for treating inflammation and immunological and neurological disorders.[104] Since the biological activity of this product is believed to be associated with its epoxyenone headgroup, Hoye et al. have developed a new strategy for the synthesis of the epoxycyclohexene core of this biologically interesting product.[105] This concise and stereoselective synthesis was based on a DKR coupled to a reversible vinylogous Payne rearrangement of a mixture of the pseudoenantiomers depicted in Scheme 58, generated through the Wharton rearrangement of the corresponding diepoxide. The DKR was achieved by using lipase Amano PS as the chiral discriminator, generating the expected enantiopure epoxy-alkenol in moderate yield, as



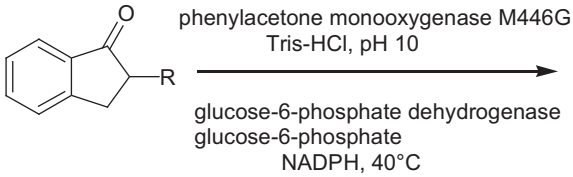


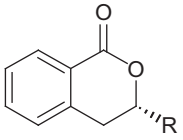
R^1 = R^2 = X = Me: 69% ee = 81%
R^1 = R^2 = Me, X = CF_3: 88% ee = 79%
R^1 = Me, R^2 = Et, X = H: 66% ee = 83%
R^1 = Et, R^2 = Me, X = H: 72% ee = 80%





58% ee > 98%



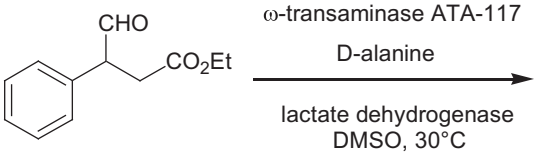


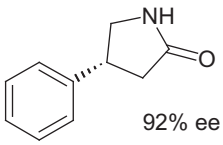
R = Et: 72% ee = 91%
R = *i*-Pr: 53% ee > 97%
R = *n*-Bu: 80% ee = 92%

Scheme 56. Baeyer–Villiger reactions of benzyl ketones.

shown in Scheme 58. It must be noted that this DKR is noteworthy, because it sets four stereogenic centres in a single event.

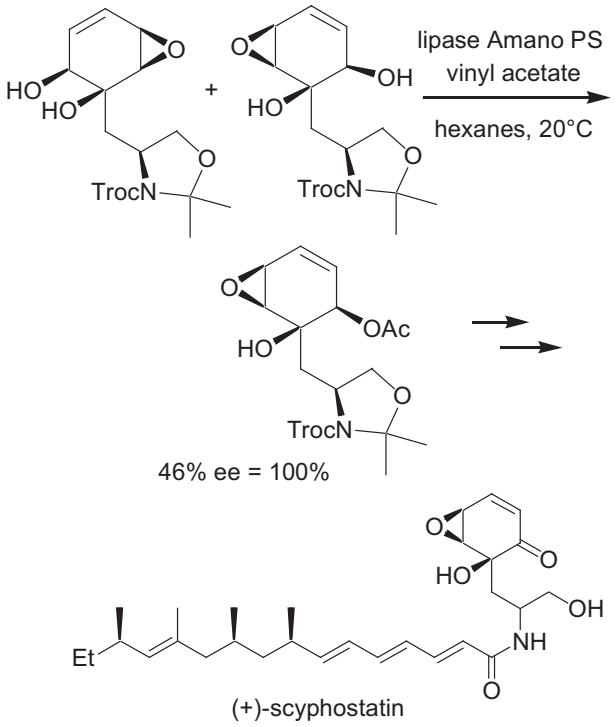
On the other hand, Lütz et al. have reported a new process concept of DKR via preferential crystallisation combined with enzymatic racemisation.[106] This methodology was successfully applied to





92% ee = 68%

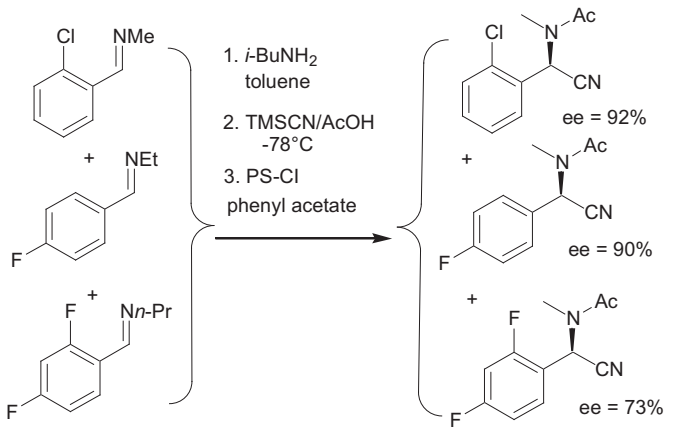
Scheme 57. Synthesis of (*R*)-α-phenylpyrrolidin-2-one.



Scheme 58. Synthesis of epoxycyclohexene core of (+)-scyphostatin.

the DKR of asparagine by using an enzyme lyophilisate WT amino acid racemase from *Pseudomonas putida* KT2440, yielding L-asparagine in >92% ee and quantitative yield through a continuous process. While L-asparagine was removed from the system by preferential crystallisation, the resulting D-asparagine excess was racemised enzymatically. Measurements of the racemase activity before and after the crystallisation process showed no significant differences, which would allow for enzyme recovery and recycling.

The Strecker reaction, occurring between an aldehyde, ammonia and a cyanide source, constitutes one of the most important multicomponent reactions developed, leading to α-aminonitriles, which are versatile substrates for many synthetic applications, such as the preparation of α-amino acids and their derivatives.[107] A popular version for asymmetric purposes is based on the use of preformed imines and a subsequent nucleophilic addition of HCN or TMSCN in the presence of a chiral catalyst.[108] Ramström and Vongvilai have developed a novel method to prepare chiral α-aminonitriles based on the Strecker reaction, where transamination with *iso*-butylamine was combined with imine cyanation performed with TMSCN in AcOH through a double dynamic covalent resolution protocol.[109] This multilevel system provided a vast range of substances from a small number of starting materials, yielding double dynamic covalent systems of *N*-substituted α-aminonitriles. Moreover, the resulting systems could be resolved through a coupled process in the form of a kinetically controlled lipase-mediated amidation reaction, using phenyl acetate as the acyl donor. In this context, three *N*-methyl α-aminonitriles, depicted in Scheme 59, could be produced with high enantioselectivities of up to 92% ee and excellent yields.



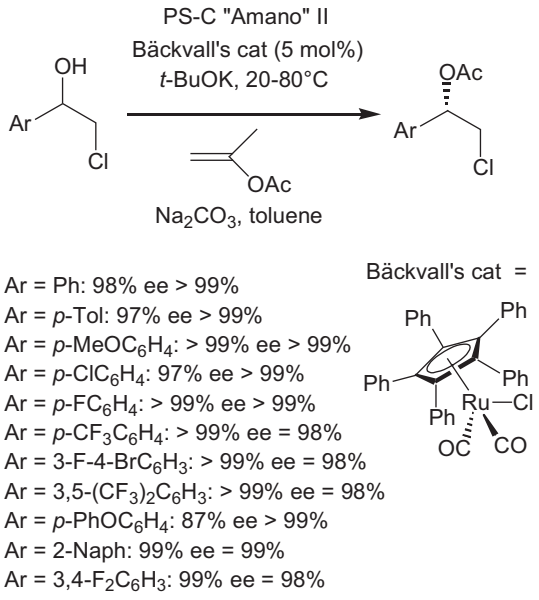
Scheme 59. Synthesis of *N*-methyl α-aminonitriles through double dynamic multicomponent resolution system.

4. Use of transition metals and enzymes in tandem

4.1. Ruthenium and enzyme-catalysed DKR

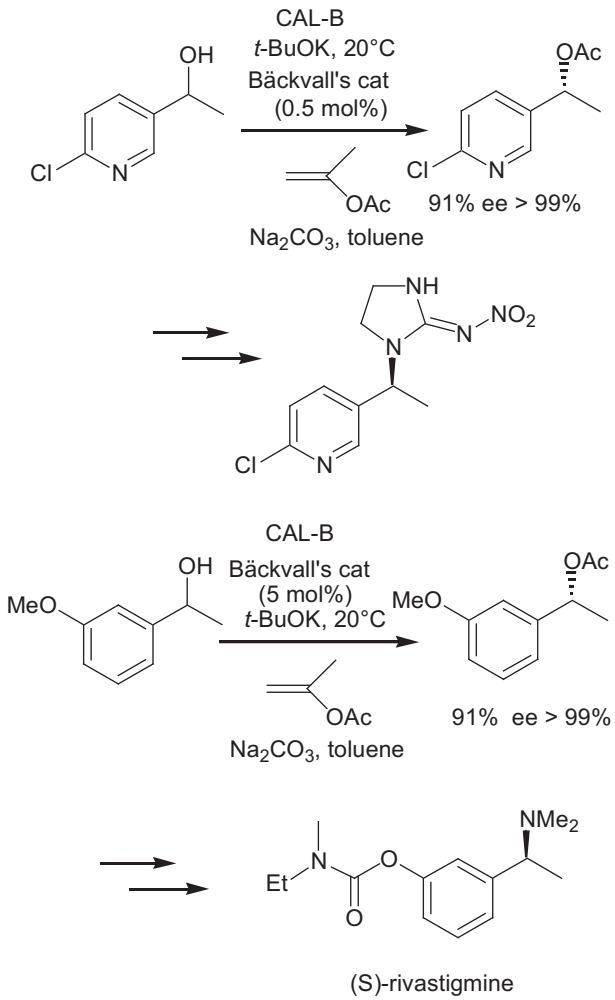
In 1996, Williams et al. demonstrated the compatibility of enzymes and transition metal complexes by reporting two examples illustrating this novel concept, such as a palladium-catalysed racemisation of an allylic acetate in the presence of a hydrolase,[110] and a racemisation of a secondary alcohol through Oppenhauer oxidation/Meerwein–Ponndorf–Verley reduction with concomitant acylation of one enantiomer with a lipase from *P. fluorescens*.[111] In order to achieve these reactions, a few conditions must be met. A selective enzyme is crucial and the organometallic catalyst must facilitate a fast racemisation of the substrate. Last, but not least, the catalyst should not influence the enzyme in terms of selectivity and reactivity. In the ideal case, the enzyme hydrolyses one enantiomer of the allylic acetate, giving rise to the allylic alcohol, which is not susceptible to Pd-catalysed racemisation. Indeed, the use of transition metal-enzyme combinations to effect tandem in situ racemisation and resolution, independently highlighted by Reetz,[112] Stürmer[113] and Bäckvall,[114] has widely extended the scope of DKRs.[3b,115] Since the demonstration of the compatibility of enzymes with metal complexes in one pot,[2e,3a,112] 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 for the DKRs of various secondary alcohols, but also for diols, amines and esters. Meanwhile, the lipase–ruthenium combination has been the most widely used method up to the present time. As an example, Bäckvall et al. have demonstrated that a pentaphenylcyclopentadienylruthenium complex, depicted in Scheme 60, and lipases in tandem were highly performing for the DKR of a wide variety of alcohols including aromatic chlorohydrins.[116] Therefore, the reaction of these substrates with *P. cepacia* lipase (PS-C 'Amano' II) combined with this catalyst in the presence of isopropenyl acetate as the acyl donor, and a base, such as *t*-BuOK in toluene provided the corresponding chiral β-chloroacetates in almost quantitative yields at room temperature for most of the cases. As can be seen in Scheme 60, the DKR worked very well for all the substrates, both with activating and deactivating groups, providing the corresponding acetates in enantioselectivities often exceeding 99% ee. For chlorohydrins bearing highly electron-withdrawing groups on the aromatic ring, an elevated temperature (60–80 °C) was required to make the racemisation faster, allowing the selectivity of the enzyme to be still high, since the corresponding products were produced in enantioselectivity of 98% ee. These chiral acetates constituted useful synthetic intermediates, since they can be transformed into a range of important chiral compounds, such as chiral epoxides.

Bäckvall's ruthenium catalyst was also employed at a lower loading (0.5 mol %) by these authors in combination with *C. Antarctica* lipase B (CAL-B) to perform the DKR of 1-(6-chloropyridin-3-yl)ethanol by using similar conditions.[117] The corresponding



Scheme 60. DKR of aromatic chlorohydrins in presence of Bäckvall's catalyst and lipases.

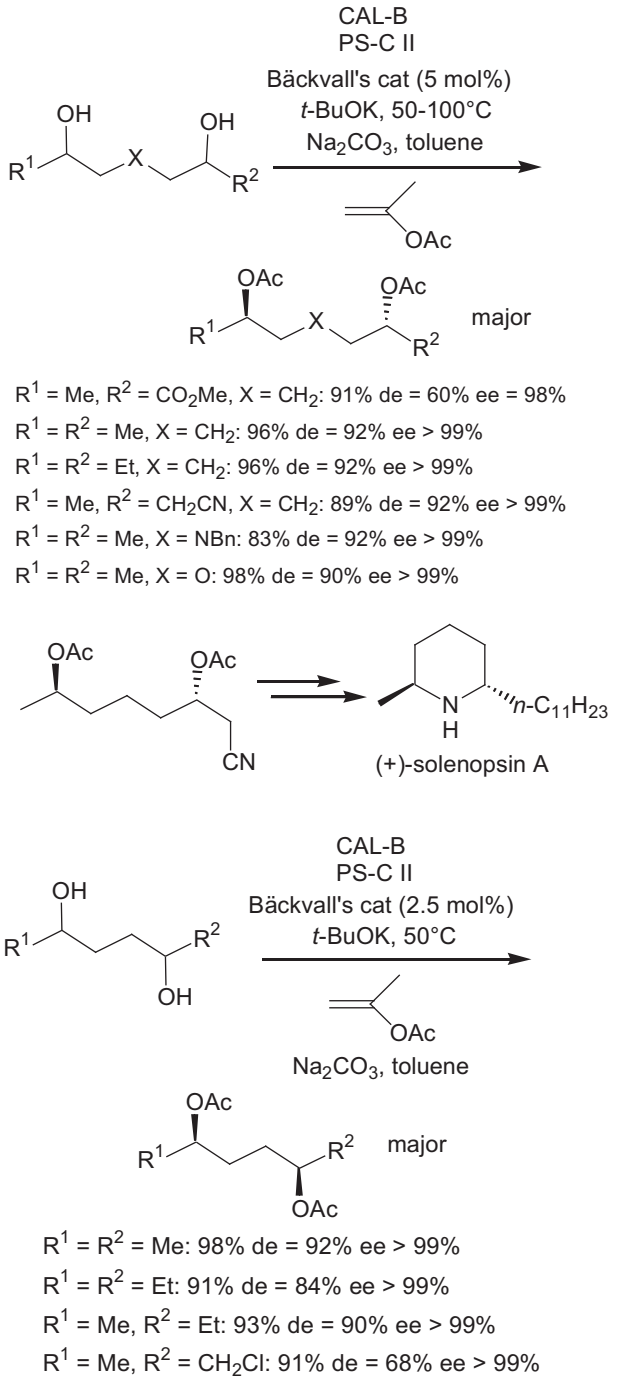
acetate was achieved in 91% yield and enantioselectivity of >99% ee, as shown in Scheme 61. This reaction constituted the key step of a synthesis of a neonicotinoid pesticide derivative. These conditions



Scheme 61. Syntheses of neonicotinoid pesticide derivative and (*S*)-rivastigmine.

were also applied by Gotor et al. to the total synthesis of (*S*)-rivastigmine, which is employed as a drug for the treatment of dementia of the Alzheimer's type.[118] As shown in Scheme 61, the key step of this synthesis was based on the DKR of 1-(3-methoxyphenyl)ethanol, providing the corresponding (*R*)-acetate in excellent yield and enantioselectivity of >99% ee, which was further converted into the expected (*S*)-rivastigmine.

In addition, Bäckvall's ruthenium catalyst was applied as a combination with *C. Antarctica* lipase B (CAL-B) and *P. cepacia* lipase II (PS-C II), in the presence of *t*-BuOK as the base and isopropenyl acetate as the acyl donor, to the highly efficient DKR of a series of 1,5-diols, resulting in the formation of the corresponding enantiomerically pure 1,5-diacetates in high yields and *anti* selectivity, as shown in Scheme 62.[119] These compounds constituted



Scheme 62. DKRs of 1,5- and 1,4-diols.

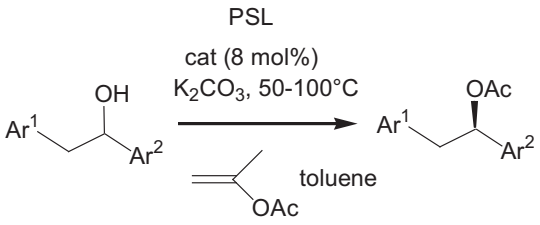
useful building blocks for the enantioselective synthesis of important 2,6- and 3,5-disubstituted six-membered heterocycles. As an example, one of these products was employed as an intermediate in the total synthesis of the natural product, (+)-solenopsin A (Scheme 62).[120] As an extension of this methodology, a series of 1,4-diols could be converted into the corresponding 1,4-diacetates with excellent yields, high *syn* selectivity and enantioselectivity of >99% ee in all cases of substrates, as shown in Scheme 62.[121] The usefulness of these enantiopure 1,4-diacetates was demonstrated by the synthesis of enantiopure 2,5-disubstituted pyrrolidines.

Generally, the most frequently employed enzymes, such as *C. Antarctica* lipase B, for the DKR of secondary alcohols accepted a limited range of substrates bearing a small (up to three carbon units) and one significantly larger substituent at the hydroxymethine centre. Accordingly, this type of enzyme was inapplicable to the DKR of 1,2-diarylethanols with two bulky substituents at the hydroxymethine centre. In order to overcome this limitation, Park et al. have found that *Pseudomonas stutzeri* lipase (PSL) was highly enantioselective towards 1,2-diarylethanols.[122] These enzymes were used in the presence of a ruthenium catalyst closely related to Bäckvall's catalyst, which was demonstrated to be more practical to synthesise by these authors. Therefore, the application of this lipase/ruthenium couple, in the presence of isoprenyl acetate as the acyl donor and K_2CO_3 in toluene at room temperature, to the DKR of a wide series of 1,2-diarylethanols provided the corresponding acetates in excellent yields and with enantioselectivities approaching 100% ee in all cases of substrates, as shown in Scheme 63.

Another analogue of Bäckvall's catalyst was used by Kanerva et al. for the DKR of secondary alcohols, such as 1-phenyl- and 1-(furan-2-yl)ethanols. The reaction was performed with *C. Antarctica* lipase B in the presence of isoprenyl acetate as the acyl donor in toluene.[123] This catalyst showed a higher stability combined with an improved performance as an alcohol racemisation catalyst, in comparison with Bäckvall's catalyst. The enhanced stability of this catalyst, as compared to Bäckvall's catalyst, could be related to the better shielding of the metal centre towards hydrolysis, hindering catalyst decomposition. As shown in Scheme 64, the corresponding acetates were obtained in high-to-excellent yields and excellent enantioselectivity of >97% ee.

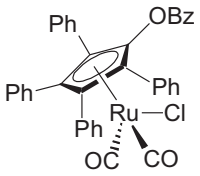
On the other hand, Nanda et al. have developed a total synthesis of the naturally occurring phytotoxic noneolide, stagonolide-C, in which two key intermediates were synthesised through the DKRs of alcohols.[124] Both these two highly efficient DKRs were performed by using *C. Antarctica* lipase B as the enzyme, isopropenyl acetate as the acyl donor, a mixture of K_2CO_3 and *t*-BuOK as the base, and a ruthenium catalyst analogue of Bäckvall's catalyst. In both reactions, the corresponding key acetates were produced in high yields combined with excellent enantioselectivities, as shown in Scheme 65. These acetates were respectively converted into the corresponding intermediates, which were further coupled to give an intermediate, which was finally cyclised into the expected stagonolide-C.

Bäckvall's catalyst and its analogues usually required a strong base, such as *t*-BuOK, to perform DKR of secondary alcohols and, moreover, these catalysts could not be reused. Additionally, for secondary alcohols bearing a sulfonyl or phosphonate moiety, which easily coordinates to ruthenium, none of these catalysts could operate smoothly and efficiently. For these reasons, Yuan and Chen have developed a novel cyclopentadienylbenzoylruthenium(II) catalyst, having a unique metallic spiro structure.[125] This novel ruthenium complex was successfully used as a powerful catalyst in combination with *C. Antarctica* lipase B in the DKR of a wide range of secondary alcohols under mild conditions. As shown in Scheme 66, the reaction provided the corresponding acetates when performed in the presence of K_3PO_4, and isoprenyl acetate as the acyl donor in toluene at 25 °C. Both excellent yields and

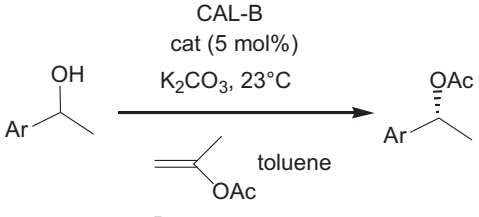


$Ar^1 = Ar^2$ = Ph: 98% ee = 98%
Ar^1 = *m*-Tol, Ar^2 = Ph: 96% ee = 98%
Ar^1 = *m*-$MeOC_6H_4$, Ar^2 = Ph: 97% ee = 97%
Ar^1 = *p*-FC_6H_4, Ar^2 = Ph: 98% ee = 97%
Ar^1 = *p*-Tol, Ar^2 = Ph: 97% ee = 97%
Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = Ph: 96% ee = 99%
Ar^1 = *p*-*i*-PrC_6H_4, Ar^2 = Ph: 95% ee = 99%
Ar^1 = Ph, Ar^2 = *m*-Tol: 95% ee = 98%
Ar^1 = Ph, Ar^2 = *m*-$MeOC_6H_4$: 96% ee = 98%
Ar^1 = Ph, Ar^2 = *m*-$PhOC_6H_4$: 99% ee = 99%
Ar^1 = Ph, Ar^2 = *p*-FC_6H_4: 96% ee = 98%
Ar^1 = Ph, Ar^2 = *p*-Tol: 98% ee = 98%
Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$: 95% ee = 96%
Ar^1 = Ph, Ar^2 = *p*-*i*-PrC_6H_4: 97% ee = 99%

cat =



Scheme 63. DKR of 1,2-diarylethanols.



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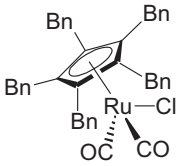
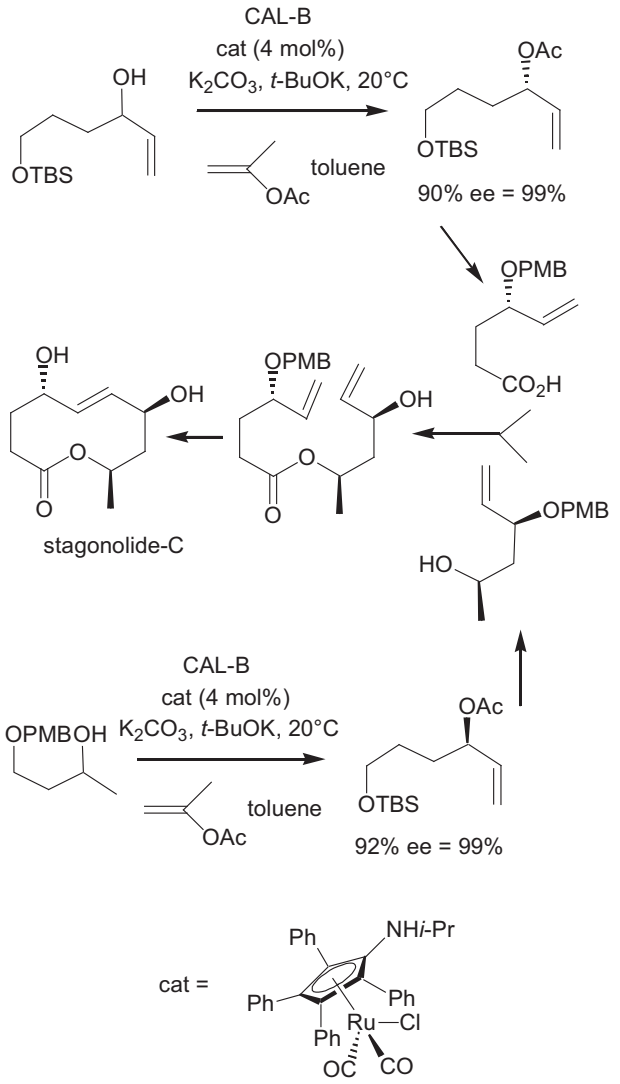


Ar = Ph: 90% ee > 97%
Ar = 1-Fu: 95% ee > 97%

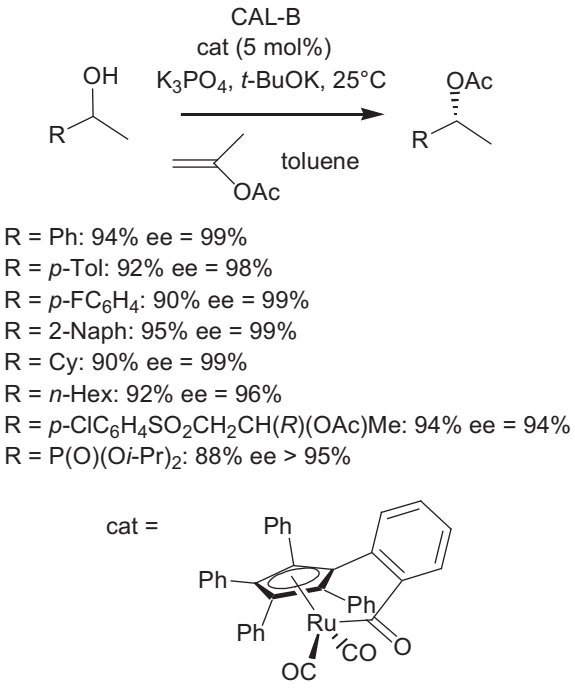
Scheme 64. DKR of secondary alcohols.

enantioselectivities of up to 99% ee were obtained, even with alcohols including sulfonyl or phosphonate functionalities. It must be noted that this catalyst could be recovered with 90% yield and reused with the same activity.

Shvo's diruthenium complex is an active catalyst in a considerable number of homogeneous reactions, such as DKRs.[126] Its catalytic activity is mainly due to the fact that it dissociates into two monomeric ruthenium species in solution under thermal



Scheme 65. Synthesis of stagonolide-C.



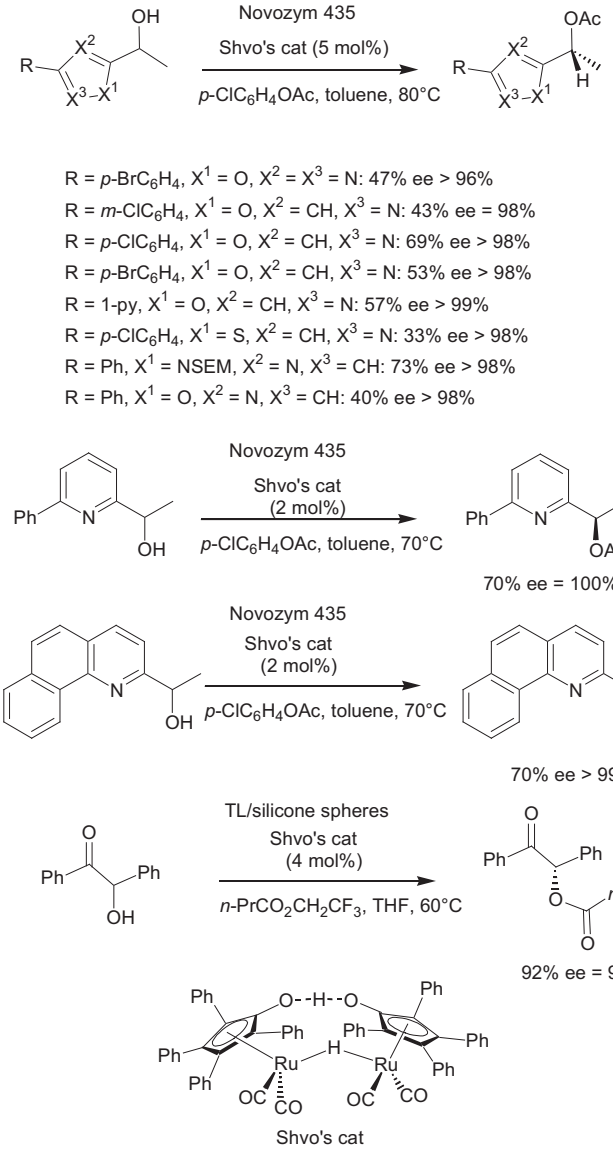
Scheme 66. DKR of secondary alcohols.

conditions and it can be readily combined with various lipases in DKRs. As an example, Minidis et al. have employed a combination of this catalyst with a lipase, Novozym 435, to achieve DKR of a series of 1-heteroaryl-substituted ethanols, such as those substituted with oxadiazoles, isoxazoles, 1*H*-pyrazole, or 1*H*-imidazole.[127] In the presence of 4-chlorophenyl acetate as the acyl donor, the corresponding acetates were produced in moderate-to-high yields and excellent enantioselectivities, as shown in Scheme 67. In order to prepare novel chiral pincer ligands based on the 6-phenyl-2-aminomethylpyridine and 2-aminomethylbenzo[*h*]quinoline scaffolds, Felluga et al. have applied similar conditions to the DKR of 2-pyridyl and 2-benzoquinolyl ethanols, which provided the corresponding enantiopure acetates in 70% yield and excellent enantioselectivity of >99% ee, as shown in Scheme 67.[128] In addition, Alcantara et al. have demonstrated that the immobilisation of *P. stutzeri* lipase (TL) in a hydrophobic material by silicon elastomer entrapment resulted in a considerable activation of this enzyme, possibly due to enhanced mass transfer of hydrophobic compounds like benzoin and stabilisation of the lipase in its active form, while commercial lipase suffers from deactivation when incubated at 50 °C.[129] After immobilisation, temperatures of up to 60 °C have been applied to the successful DKR of benzoin into the corresponding *n*-butyrate in the presence of trifluoroethyl acetate as the acyl donor in THF, as shown in Scheme 67. It must be noted that this catalytic system could be reused at least fourfold without significant loss of activity.

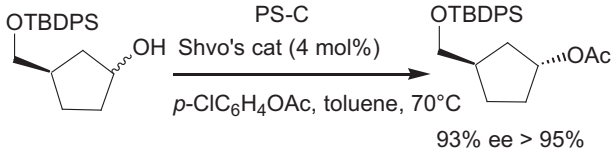
Carbocyclic nucleosides are structural analogues of natural and synthetic nucleosides, which often exhibit powerful antitumour and antiviral activities. In the course of synthesising chiral members of this family of compounds, Castillon et al. have developed the DKR of a 3-hydroxymethyl-cyclopentanol intermediate as the key step, providing the corresponding acetate, which constituted the key intermediate of this synthesis.[130] This DKR process was performed with a combination of Shvo's catalyst and *P. cepacia* lipase (PS-C) in the presence of 4-chlorophenyl acetate as the acyl donor in toluene, yielding the corresponding product in 93% yield and enantioselectivity of >95% ee, as shown in Scheme 68. This intermediate was further converted into the expected carbocyclic-ddA, opening a novel enantioselective approach to carbocyclic nucleosides.

In addition, Thomas et al. have investigated the DKR of 1-phenylethanol with *P. cepacia* lipase I immobilised on ceramic particles (lipase Amano PS-CI) in supercritical carbon dioxide, using [Ru(*p*-cymene)Cl_2]$_2$ as the racemising catalyst.[131] In the presence of acetophenone as a hydrogen acceptor and phenyl acetate as the acyl donor, the corresponding (*R*)-phenylethyl acetate was obtained in 70% yield and enantioselectivity of 96% ee after six days of reaction at 55 °C. It must be noted that this reaction could also be performed in hexane, albeit providing a lower enantioselectivity of 91% ee.

Enantiomerically pure chiral amines are particularly important for 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 harsh conditions, such as a high temperature combined with a long reaction time, because their racemisation is more difficult than that of alcohols and they can act as strong ligands for active metal intermediates.[132] In these harsh reaction conditions, most enzymes would be denatured, making them unsuitable for DKR. Efficient catalysts for the racemisation of amines are thus rarer than those for the racemisation of alcohols. Recently, milder conditions for amine racemisation have been developed through the use of ruthenium-, palladium-, and

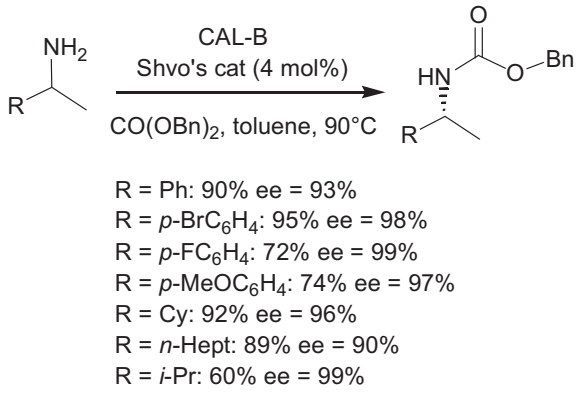


Scheme 67. DKRs of 1-heteroaryl ethanols and benzoin with Shvo's catalyst.



Scheme 68. Synthesis of carbocyclic nucleoside.

iridium-based catalysts. As an example, Bäckvall at al. have reported the use of Shvo's ruthenium catalyst in combination with *C. Antarctica* lipase B in the DKR of primary amines in which the products were benzyl carbamates, allowing further release of the free amines under very mild conditions.[133] Indeed, a drawback with other DKR procedures of amines is that the product is a chiral amide, from which the free amine can only be liberated under harsh reaction conditions. As shown in Scheme 69, a series of amines could be converted through DKR in the presence of dibenzyl carbonate as the acyl donor into the corresponding carbamates in both excellent yields and enantioselectivities.



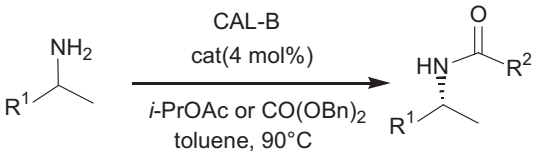
Scheme 69. DKR of amines with Shvo's catalyst.

In addition, another ruthenium catalyst of the Shvo type was employed by these authors in combination with *C. Antarctica* lipase B to perform the DKR of a number of functionalised primary amines to give the corresponding acetates when using isopropyl acetate as the acyl donor.[134] As shown in Scheme 70, these products were isolated as almost single enantiomers in all cases in high yields. This protocol could be extended to the use of dibenzyl carbonate as the acyl donor, allowing the easy release of the free amine from the corresponding carbamates under mild conditions. As shown in Scheme 70, these carbamates were produced in comparable yields and enantioselectivities as the acetates. This highly efficient methodology was applied to the synthesis of the selective serotonin reuptake inhibitor, norsertraline, employed for the treatment of depression. The first step of this synthesis was the DKR of the readily available 1,2,3,4-tetrahydro-1-naphthylamine, which yielded the corresponding enantiopure acetate in good yield by treatment with *C. Antarctica* lipase B in combination with the catalyst and isopropyl acetate (Scheme 70).

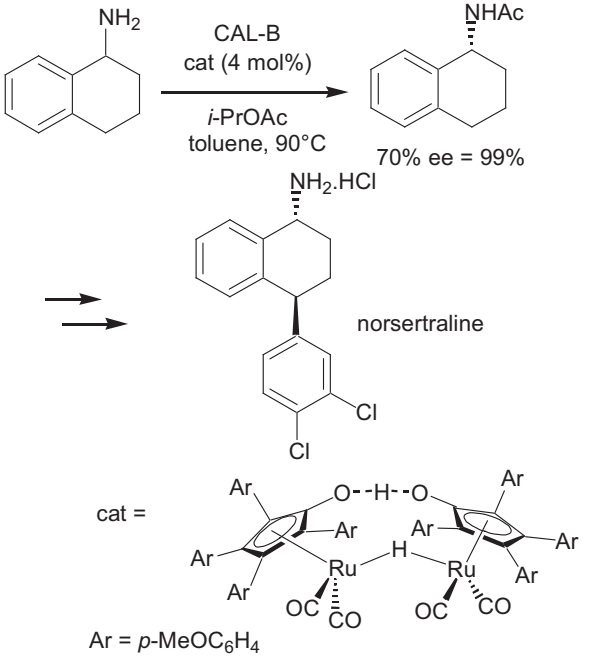
Very recently, the same authors have reported the DKR of the β-amino ester, ethyl 3-amino-3-phenylpropanoate, by using *C. Antarctica* lipase A (CAL-A) immobilised in mesocellular foam (GamP-MCF) in combination with the methoxy analogue of Shvo's catalyst at 90 °C.[135] It was shown that the use of 2,4-dimethyl-3-pentanol as a hydrogen donor allowed side product formation to be suppressed. Thus, the reaction performed in the presence of trifluoroethyl butyrate as the acyl donor provided the corresponding (*S*)-amide in 85% yield and 89% ee.

4.2. Enzymatic DKR using metals other than ruthenium

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. Moreover, 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. Feringa et al. have recently reported the synthesis of a cationic half-sandwich iridacycle complex, which was found to be the most active racemisation catalyst for β-haloalcohols upon activation with a base such as *t*-BuOK.[136] Furthermore, the combination of this water-compatible catalyst with haloalcohol dehalogenase Hhec C153S W249F, incorporating the double mutations, Cys 153Ser, which increased the enzyme stability towards oxidation, and Trp249Phe, which increased its enantioselectivity, especially for aromatic substrates, allowed the first direct DKR of a range of β-haloalcohols to provide the corresponding enantioenriched epoxides to be achieved. As



R^1 = *p*-$CF_3C_6H_4$, R^2 = Me: 91% ee = 99%
R^1 = 1-Thio, R^2 = Me: 85% 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 = *p*-FC_6H_4, R^2 = Me: 84% ee = 98%
R^1 = 2-Naph, R^2 = Me: 80% ee = 99%
R^1 = *p*-BrC_6H_4, R^2 = OBn: 95% ee = 98%
R^1 = *p*-$MeOC_6H_4$, R^2 = OBn: 74% ee = 97%
R^1 = *p*-FC_6H_4, R^2 = OBn: 72% ee = 99%
R^1 = *i*-Pr, R^2 = OBn: 60% ee = 99%

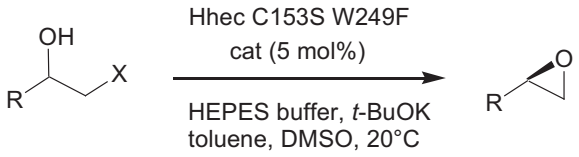


Scheme 70. DKRs of amines.

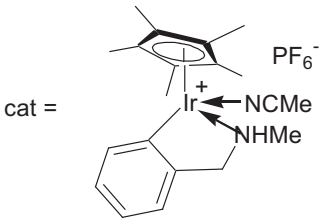
shown in Scheme 71, these epoxides were produced in a single step in good-to-high yields combined with excellent enantioselectivities.

In 2010, Bäckvall et al. reported for the first time the chemoenzymatic DKR of axially chiral allenes.[137] Thus, the DKR of allenic alcohols could be achieved by using a combination of a palladium catalyst, such as [{(IPr)$PdBr_2$}$_2$], with porcine pancreatic lipase (PPL) in the presence of vinyl butyrate as the acyl donor. The corresponding (*S*)-butyrates were produced in good yields and enantioselectivities of up to 89% ee, as shown in Scheme 72.

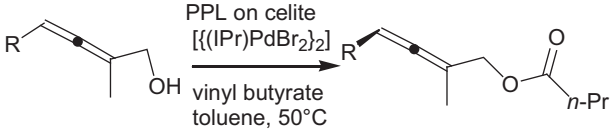
Cp^*Ir^{III}(NHC) complexes are known to be efficient catalysts in the transfer hydrogenation of carbonyl compounds. One of these catalysts has been used by Peris and Corberan in the one-pot enzymatic DKR of the β-branched aldehyde depicted in Scheme 73.[138] Therefore, the treatment of this aldehyde by Amano lipase PS-D I and the catalyst at 80 °C in the presence of chlorophenyl acetate as the acyl donor provided the corresponding acetate in good yield, albeit with moderate enantioselectivity of 61% ee, as shown in Scheme 73.



R = Ph, X = Cl: 90% ee = 98%
R = *p*-$NO_2C_6H_4$, X = Cl: 76% ee = 97%
R = *p*-$NO_2C_6H_4$, X = Br: 86% ee = 90%
R = *m*-$NO_2C_6H_4$, X = Cl: 65% ee = 94%
R = *p*-CNC_6H_4, X = Cl: 59% ee = 96%
R = *p*-CNC_6H_4, X = Br: 89% ee = 86%
R = *p*-$CF_3C_6H_4$, X = Cl: 51% ee = 99%

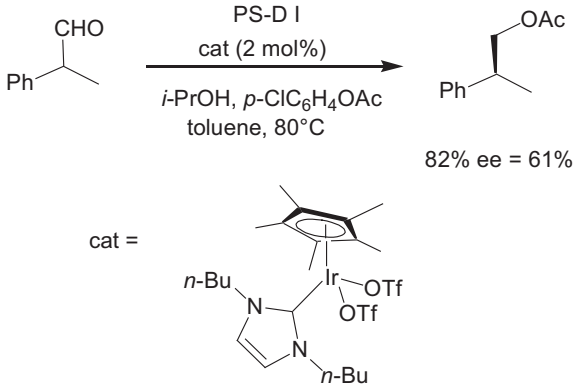


Scheme 71. DKR of β-haloalcohols.



R = Ph: 81% ee = 86%
R = *m*-Tol: 70% ee = 89%
R = 2-Naph: 83% ee = 89%
R = *p*-ClC_6H_4: 80% ee = 87%
R = *n*-Pent: 87% ee = 66%

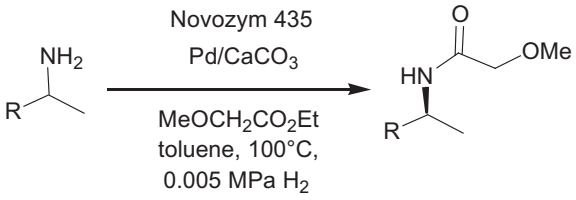
Scheme 72. Pd-catalysed DKR of allenic alcohols.



Scheme 73. DKR of β-branched aldehyde.

On the other hand, palladium on alkaline-earth supports have been successfully used by De Vos et al. as racemisation catalysts for benzylic amines.[139] Although these catalysts were highly active and selective for the racemisation of benzylic amines, the reaction times for DKR were still longer than 24 h in some cases, and small amounts of side products were formed. In order to improve the performance of these Pd catalysts, these authors have employed

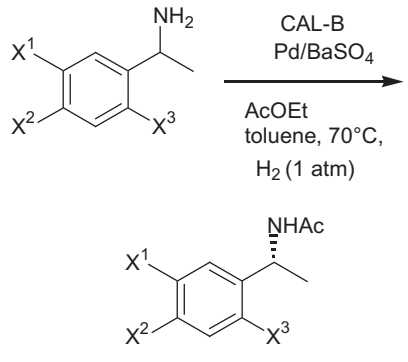
microwave irradiation as a heating source.[140] Therefore, it was demonstrated that racemisation reactions of benzylic amines under microwave irradiation catalysed by $Pd/CaCO_3$ were faster and more selective. Furthermore, it was checked that the microwave irradiation had no influence on the activity and enantioselectivity of the immobilised *C. Antarctica* lipase B (Novozym 435). Consequently, the microwave-promoted DKR of a range of these amines was achieved by using a combination of this enzyme with $Pd/CaCO_3$ in the presence of ethyl methoxyacetate as the acyl agent at 100 °C under a hydrogen atmosphere, furnishing the corresponding amides in high yields and excellent enantioselectivities of up to 98% ee, as shown in Scheme 74. In the same context, these authors have demonstrated that Pd on an amine-functionalised silica proved to be more selective for the racemisation of 1-phenylethylamine than Pd on alkaline-earth supports.[141] The difference in selectivity between various Pd catalysts was determined by the rates of formation of the side products. Therefore, the combination of a Pd catalyst with lipase, Novozym 435, for the DKR of 1-phenylethylamine gave the best results when Pd on 3-aminopropyl-functionalised silica or Pd on 3-(1-piperazino)propyl-functionalised silica were used as the racemisation catalysts, namely 93% yield of the corresponding (*R*)-amide with enantioselectivity of 99% ee.



R = Ph: 99% ee = 99%
R = *p*-Tol: 99% ee = 97%
R = 2-Naph: 98% ee = 95%

Scheme 74. Microwave-promoted DKR of benzylic amines with $Pd/CaCO_3$.

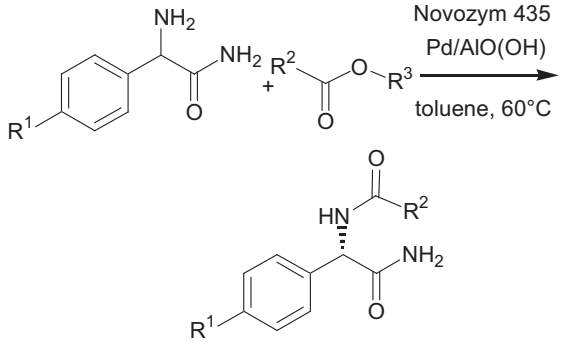
Andrade et al. have demonstrated that the DKR mediated by palladium and lipase could be efficiently applied to selenium-containing amines.[142] As shown in Scheme 75, a series of organoselenium-1-phenylethanamines were submitted to DKR catalysed by a combination of $Pd/BaSO_4$ and *C. antarctica* lipase B in the presence of ethyl acetate as the acyl donor in toluene at 70 °C under a hydrogen atmosphere (1 atm), providing the corresponding selenium-containing amides in generally high yields and enantioselectivity of >99% ee in all cases of substrates.



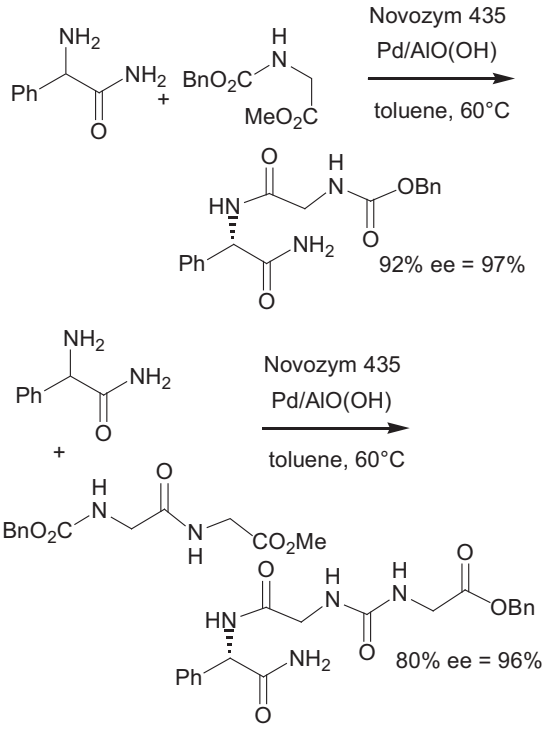
$X^1 = X^3 = H$, X^2 = SeEt: 74% ee > 99%
$X^1 = X^3 = H$, X^2 = SeMe: 76% ee > 99%
$X^1 = X^3 = H$, X^2 = Se*n*-Bu: 77% ee > 99%
$X^1 = X^3 = H$, X^2 = SeBn: 72% ee > 99%
X^1 = SeEt, $X^2 = X^3 = H$: 87% ee > 99%
$X^1 = X^2 = H$, X^3 = SeEt: 30% ee > 99%

Scheme 75. Pd-catalysed DKR of organoselenium-1-phenylethanamines.

On the other hand, Kim et al. have chosen palladium nanoparticles entrapped in an AlO(OH) matrix as the racemisation catalyst combined with lipase, Novozym 435, to achieve the DKR of phenylglycine amide.[143] With this combination of catalysts with various acyl donors, such as ethyl methoxyacetate, ethyl acetate, ethyl phenyl acetate, or methyl *p*-hydroxyphenylacetate in toluene at 60 °C, the corresponding acylated amides were obtained in excellent yields and enantioselectivities, as shown in Scheme 76.



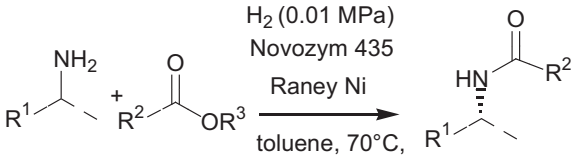
R^1 = H, R^2 = CH_2OMe, R^3 = Et: 98% ee = 97%
R^1 = H, R^2 = Me, R^3 = Et: 96% ee = 98%
R^1 = H, R^2 = Bn, R^3 = Et: 93% ee = 95%
R^1 = H, R^2 = CH_2*p*-(HO)C_6H_4, R^3 = Me: 90% ee = 98%
R^1 = F, R^2 = CH_2OMe, R^3 = Et: 91% ee = 97%
R^1 = Cl, R^2 = CH_2OMe, R^3 = Et: 88% ee = 97%
R^1 = OMe, R^2 = CH_2OMe, R^3 = Et: 91% ee = 97%
R^1 = CF_3, R^2 = CH_2OMe, R^3 = Et: 90% ee = 97%



Scheme 76. Pd-catalysed DKRs of phenylglycine amide derivatives.

The most efficient acyl donor, ethyl methoxyacetate, was selected to extend this methodology to a range of phenylglycine amide derivatives to achieve the corresponding additional products in comparable excellent yields and enantioselectivities (Scheme 76). Interestingly, the DKR reactions of phenylglycine amide performed in the presence of *N*-benzyloxycarbonylglycine methyl ester or *N*-benzyloxycarbonylglycylglycine methyl ester as the acyl donor, provided the corresponding di- and tripeptides, respectively, in high yields and excellent enantioselectivities of >96% ee, as shown in Scheme 76. Therefore, this highly efficient methodology constituted a new route to enantiopure amino acid derivatives.

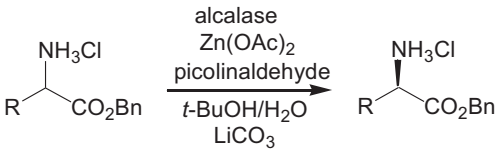
Since palladium on C or on alkaline-earth supports are generally not effective for the DKR of aliphatic amines and, in the search for less expensive heterogeneous racemisation catalysts, De Vos et al. have shown that heterogeneous Raney nickel could be applied to the racemisation of aliphatic amines in addition to the more usually employed benzylic amines.[144] Moreover, when combined with lipase, Novozym 435, Raney nickel allowed the DKR of a range of amines to be efficiently achieved, as shown in Scheme 77. For aliphatic amines, racemisation and enzymatic resolution could be combined in one pot, resulting in an efficient DKR process. When ethyl methoxyacetate was used as the acyl donor, the reaction allowed the corresponding amides to be obtained in good yields and excellent enantioselectivities, as shown in Scheme 77. For benzylic amines, which reacted less rapidly with the enzyme, it could be demonstrated that the slow enzymatic conversion of the amine in the presence of the Ni catalyst was the main effect impeding efficient one-pot DKR. Consequently, a two-pot process was proposed in which the liquid was alternately shuttled between two vessels containing the solid racemisation catalyst and the biocatalyst. After four such cycles, the corresponding amides were isolated in good yields and high enantioselectivities (Scheme 77).



R^1 = *n*-Bu, R^2 = CH_2OMe, R^3 = Et: 99% ee = 98%
R^1 = *n*-Pent, R^2 = CH_2OMe, R^3 = Et: 74% ee = 98%
R^1 = *n*-Hex, R^2 = CH_2OMe, R^3 = Et: 75% ee = 82%
R^1 = Cy, R^2 = CH_2OMe, R^3 = Et: 70% ee = 96%
R^1 = CH_2Bn, R^2 = CH_2OMe, R^3 = Et: 79% ee = 98%
R^1 = Ph, R^2 = *n*-Non, R^3 = Me: 62% ee = 94%
R^1 = *p*-Tol, R^2 = CH_2OMe, R^3 = Et: 72% ee = 80%

Scheme 77. Ni-catalysed DKR of amines.

On the other hand, Aron et al. have very recently identified zinc complexes of picolinaldehyde as low-cost and environmentally benign catalysts for the racemisation of amino acids.[145] When this type of catalyst was combined with alcalase, it allowed the DKR of a series of amino acid esters to be achieved with enantioselectivities of up to >98% ee, as shown in Scheme 78. Aromatic as well as straight- and γ-branched-chain amino acids were resolved in good yields with high enantiopurity, whereas β-branched amino acids were poorly resolved.



R = Bn: 79% ee > 98%
R = CH_2*p*-HOC_6H_4: 63% ee > 98%
R = *i*-Bu: 77% ee > 98%
R = *n*-Pr: 89% ee = 64%
R = *n*-Bu: 75% ee > 98%

Scheme 78. Zn-catalysed DKR of amino acids.

5. Conclusions

This review updates the principal methods employed to obtain DKR that have been reported in the literature from the beginning of 2008 and until the middle of 2010 by either enzymatic or non-enzymatic methods and illustrates the diversity of useful products that can be obtained through this powerful concept. The last two years have witnessed significant developments in the efficiency and scope of the application of DKRs. Therefore, 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 and metal catalysis has also been the subject of spectacular development. Moreover, the use of organocatalysts to promote DKRs 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 the 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 perspective over the past few years.

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Biographical sketch

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