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Dynamic kinetic resolution

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1. Introduction

Dynamic kinetic resolution (DKR) has recently been the subject of several excellent review articles.[1] The aim of this review is to highlight examples of DKRs which have not previously been covered by these preceding articles. Moreover, unlike its predecessors, this review includes the atroposelective reactions recently reported by Bringmann et al.[2] and their application in the synthesis of natural products and chiral auxiliaries.

The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis.[3] 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 to products at different rates. If the kinetic resolution is efficient, one of the enantiomers of the

Keywords: dynamic kinetic resolution; enzymatic or non-enzymatic methods; atroposelective reactions; synthesis of natural products.

Abbreviations: DKR, dynamic kinetic resolution; ee, enantiomeric excess; de, diastereoisomeric excess; HMPA, hexamethylphosphoramide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMAP, 4-(dimethylamino) pyridine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; THFA, tetrahydrofurfuryl alcohol; DABCO, 1,4-diazabicyclo[2.2.2]octane.

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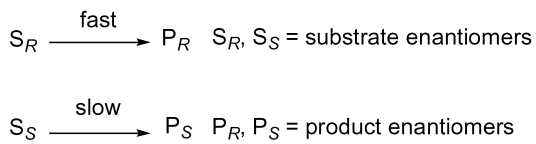


Figure 1. Classical kinetic resolution.

racemic mixture is transformed to the desired product while the other is recovered unchanged (Fig. 1).

This procedure has the limitation of having 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 the 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).

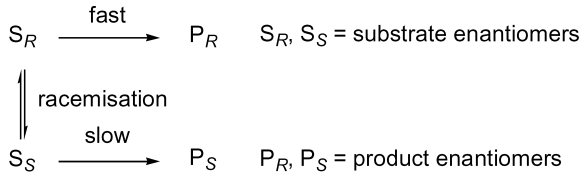


Figure 2. Dynamic kinetic resolution.

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 either chemically, biocatalytically or even spontaneously; conditions must be chosen to avoid the racemisation of the product. 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 center, an enantioselective synthesis of a diastereoisomer is also possible, as outlined in Figure 3.

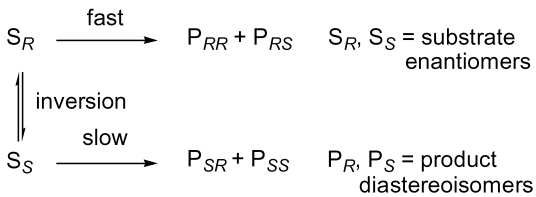


Figure 3. Enantioselective synthesis of a diastereoisomer via DKR.

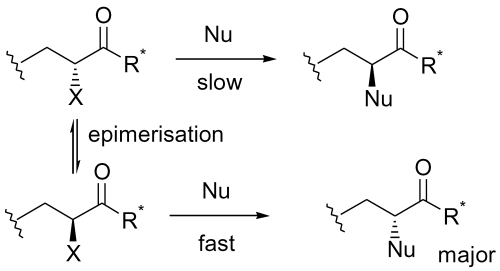
This review highlights and updates the principal techniques used to obtain DKR by either enzymatic or non-enzymatic methods.

2. Non-enzymatic methods

Besides metal complexes bearing chiral ligands, such as ruthenium catalysts together with a chiral ligand such as BINAP, there is also the possibility of using chiral auxiliaries for the asymmetric induction through a dynamic kinetic process.

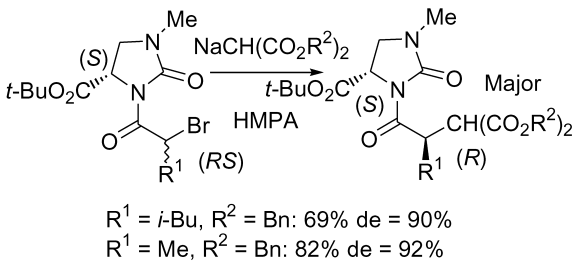
2.1. Chiral auxiliaries

2.1.1. Configurationally labile alkyl halides. Nucleophilic substitution on configurationally labile halides has been involved in compounds with a bromo or iodo atom in the α-position with respect to a carboxylic acid derivative, where the S_N2 reaction is governed by a chiral auxiliary placed in the carboxylic moiety.[1,4] Racemisation takes place by consecutive inversions at the labile centre induced by additives such as polar solvents, base or halide salts (Scheme 1).



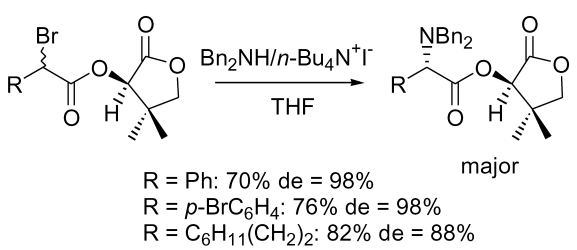
Scheme 1. S_N2 reactions on configurationally labile halides bearing a carboxylated function.

In one example, *tert*-butyl (4*S*)-1-methyl-2-oxoimidazolidine-4-carboxylate was used as a chiral auxiliary for DKR of α-bromocarboxylic acids. In this case, the nucleophile was a malonic ester enolate and the role of the polarity of the solvent (HMPA) was demonstrated (Scheme 2).[5] The alkylated products were further easily converted to chiral α-alkylsuccinic acid derivatives and chiral β-amino acid derivatives.



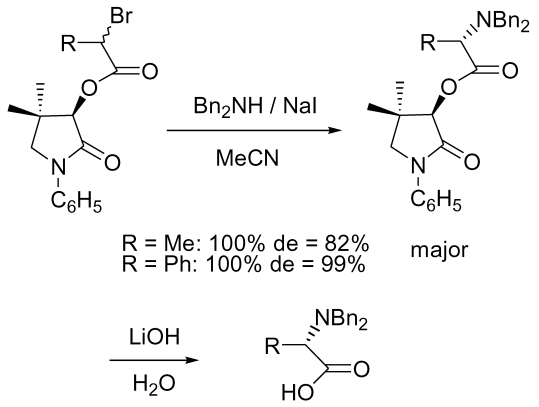
Scheme 2. S_N2 reactions with malonic ester enolates in HMPA.

The same reaction was applied to benzylamine as the nucleophile and yielded the expected aminoimides in good chemical yield and excellent enantiomeric purity (R^1=Et: 92%, de=98%).[6] In the same article, dibenzylamine was successfully condensed on racemic α-bromoesters of (*R*)-pantolactone (Scheme 3).



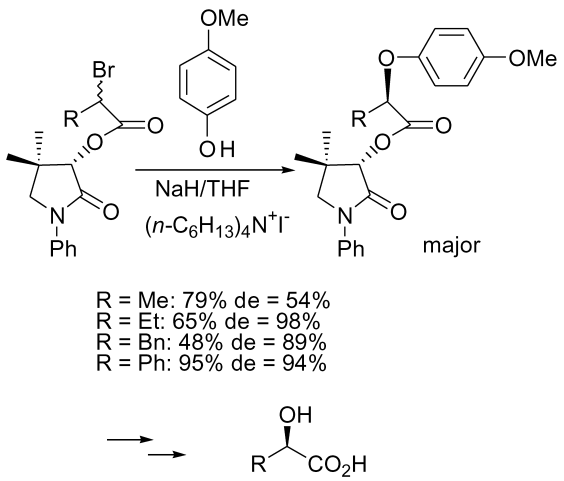
Scheme 3. Condensation of dibenzylamine on (*R*)-pantolactone derivatives.

In the course of preparing α-amino acids and their *N*,*N*-dibenzyl derivatives, Camps et al. always involved (*R*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone as the chiral auxiliary[7] (Scheme 4). In this way, α-dibenzylamino acids were obtained through a DKR followed by a non-epimerisable hydrolysis.



Scheme 4. DKR of α-bromoesters on reaction with dibenzylamine.

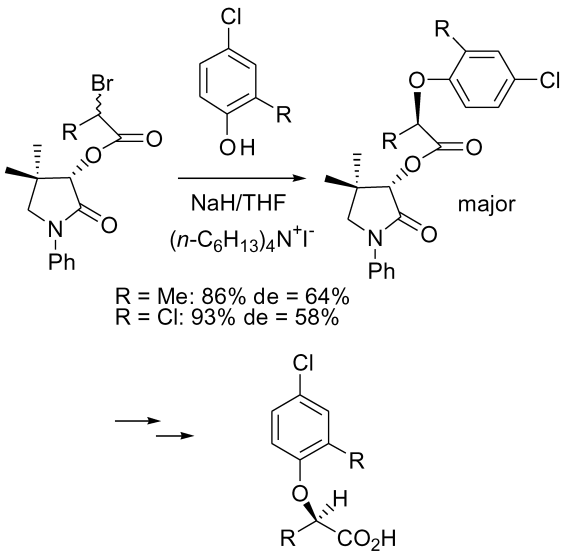
The use of alkoxides as nucleophiles is not common in the area of DKR. In 1997, however, Camps et al. reported the asymmetric synthesis of α-hydroxyacids based on the DKR of a diastereomeric mixture of α-bromoesters, derived from (*R*)- or (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, with *p*-methoxyphenoxide in the presence of tetra-*n*-hexylammonium iodide (Scheme 5).[8]



Scheme 5. Diastereoselective synthesis of esters with *p*-methoxyphenoxide via DKR.

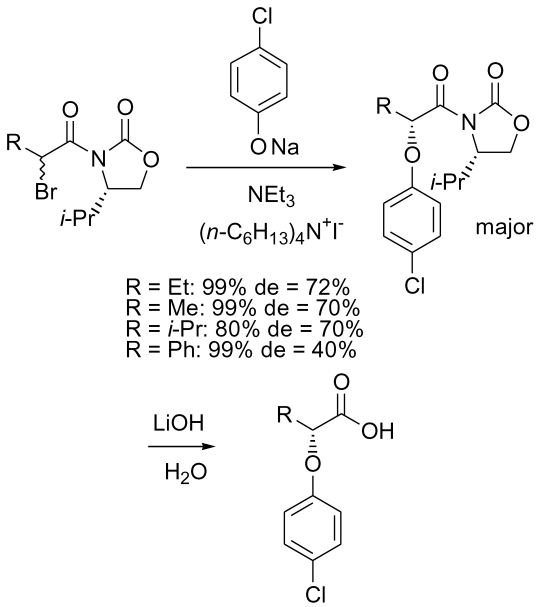
The synthesis of (*R*)-α-aryloxypropanoic acid herbicides was achieved by involving the same chiral auxiliary with the corresponding trisubstituted phenoxides. The DKR, which gave, in this case, moderate des was followed by mild acid hydrolysis (Scheme 6).[9]

A DKR was developed in 1999 by Bettoni et al. in order to prepare 2-aryloxyacid analogues of clofibrate which show markedly different biological activities, depending on the nature of the enantiomer. The key step of the synthesis was the condensation of sodium 4-chlorophenoxide on dia-



Scheme 6. DKR involving trisubstituted phenoxides.

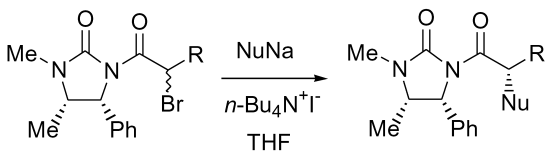
stereomeric 2-bromoimides.[10] (4*S*)-4-Isopropyl-1,3-oxazolidin-2-one was used as the chiral auxiliary (Scheme 7).



Scheme 7. Synthesis of 2-aryloxyacid analogues of clofibrate.

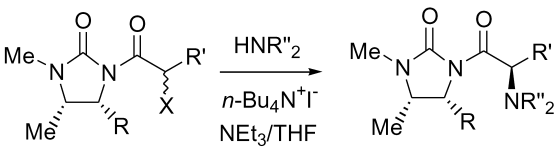
Recently, Caddick et al. have studied the DKR of α-haloacylimidazolidinones with a large variety of nitrogen, sulphur and carbon nucleophiles.[11] An unusual dichotomy of diastereoselection has been observed whereby the metallated nucleophiles preferentially reacted via the (5*S*,2′*R*) diastereomer (Scheme 8), whilst the amine nucleophiles reacted via the (5*S*,2′*S*) diastereomer (Scheme 9).

Extensive molecular modelling experiments have been carried out by Caddick et al.[12] in order to explain the stereochemical outcome of their DKR processes. It seems that a non-bifurcated H-bond model which minimises the bromine–phenyl interaction is probably the most accurate. The stereoselectivity of the reaction therefore arises from



R = Me, NuNa = $NaCH(CO_2Me)_2$: 78% de = 40-60%
R = Et, NuNa = $NaCH(CO_2Me)_2$: 93% de = 33%
R = *n*-Bu, NuNa = $NaCH(CO_2Me)_2$: 83% de = 52%
R = Et, NuNa = NaN_3: 100% de = 31%

Scheme 8. DKR involving ionic nucleophiles.



R	R'	X	$HNR"_2$	Yield (%)	de (%)
Ph	Me	Br	$BnNH_2$	100	74
Ph	Et	Br	piperidine	100	94
Ph	Et	Br	pyrrolidine	87	89
Ph	Me	I	pyrrolidine	79	68
Ph	Me	I	piperidine	91	81
Ph	Et	Br	pyrrolidine	87	90
Ph	*n*-Bu	Br	pyrrolidine	99	100
Ph	*n*-Bu	Br	piperidine	94	100
*c*Hex	Me	I	$BnNH_2$	97	86
Ph	Me	I	$BnNH_2$	96	79
Ph	Et	Br	$BnNH_2$	97	80

Scheme 9. DKR involving amine nucleophiles.

the interaction between the leaving group and the stereodifferentiating substituent of the chiral auxiliary (Fig. 4).

As the amine undergoes substitution, a twisting of the C_1-C_2 bond is required which potentiates these interactions in the 2′*R* isomer, but not in the 2′*S* isomer, thereby explaining its greater reactivity with H-bonding nucleophiles.

For the DKRs with metallated nucleophiles, a different result was observed. In fact, considering that the counterion of these nucleophiles can only be weakly complexed to the carbonyl group of the chiral auxiliary, direct attack of the anion should be more relevant and should take place preferentially from the less hindered side of the substrates in the anti-parallel carbonyls conformation. Therefore, the most reactive diastereomer was the 2′*R* and the selectivity depends mainly on the ability of the chiral auxiliary's substituent to generate steric/electrostatic repulsions with the nucleophile. In addition, the final outcome of the DKR reactions with metallated nucleophiles was the result of a competition between direct attack and complexed attack (through the sodium ion).

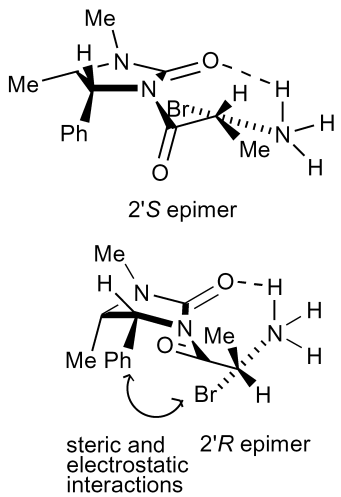
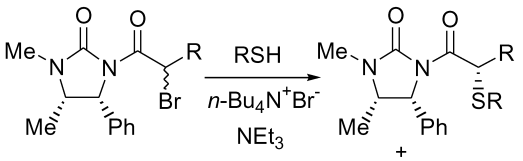


Figure 4. Transition states of both diastereomers using a semi-empirical PM3 approximation.

Disappointingly poor selectivities were observed with sulphur nucleophiles. The high reactivity of the sulphur nucleophiles resulted in rapid nucleophilic displacement reactions relative to the epimerisation process and this may explain the lack of selectivity (Scheme 10). Moreover, the results of DKR reactions using sulphur nucleophiles are in agreement with the observed dichotomy: methyl thioglycollate and benzyl mercaptan behaved similarly to amines, whereas thiophenol (which should be in the form of the thiophenolate anion under the reaction conditions used) showed the same preferential reactivity as the metallated nucleophiles.

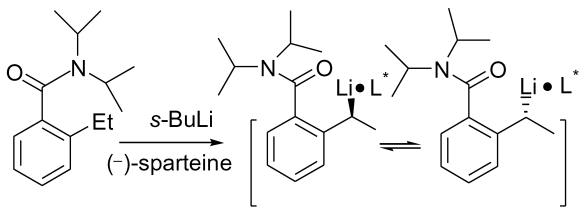


R = Ph: 96% (59.5:40.5)
R = Bn: 56% (44.5:55.5)
R = $MeOCOCH_2$: 80% (45:55)

Scheme 10. DKR involving sulphur nucleophiles.

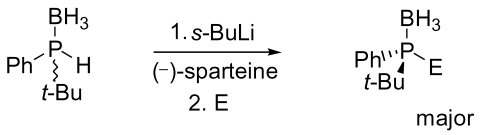
2.1.2. DKR of configurationally labile anions. The use of organometallic bases to effect asymmetric deprotonation in the presence of chiral complexing agents such as (−)-sparteine has been the focus of much attention in asymmetric synthesis.[13] The enantioselection can be achieved by deprotonation and subsequent complexation of the interconverting anions by the chiral ligand. The ligand may selectively complex one of the anionic enantiomers such that a single diastereomeric complex forms by virtue of the in situ enantiomerisation of the other uncomplexed anion. This complex is then trapped by rapid reaction with an electrophile. Alternatively, the rapidly interconverting anion enantiomers may both form complexes with the chiral ligand such that both diastereomeric complexes exist in rapid equilibrium in solution. Diastereoselective reaction of one of the complexes with an electrophile accompanied by in situ equilibration of the unreacted complex could result in enantiomerically enriched products.

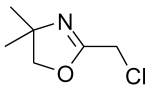
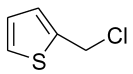
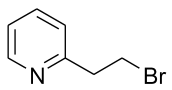
Highly enantioenriched substitution products could therefore be obtained by the (−)-sparteine-mediated



Electrophile (E)	Yield (%)	ee (%)
p-$MeOC_6H_4CH_2Cl$	79	92
CH_2=$CHCH_2Cl$	89	92
n-BuCl	95	80
n-Bu_3SnCl	78	92
Me_3SiCl	79	92
MeCOMe	64	40

Scheme 11. (−)-Sparteine-mediated lithiations.



Electrophile (E)	Yield (%)	ee (%)
o-$AnCH_2Cl$	80	95
	90	> 82
	85	95
	90	92

Scheme 12. Alkylations of resolved *tert*-butylphenylphosphine-borane.

lithiation-substitution reactions of the laterally lithiated *N*,*N*-diisopropyl-*o*-ethylbenzamide (Scheme 11).[13,14]

The pre-eminence of chiral phosphines as controller ligands for a wide range of asymmetric processes has become firmly established. In 1998, Livinghouse et al. showed that a variety of *P*-chiral phosphine-boranes could be directly prepared from a racemic 2°-phosphine-borane precursor with excellent enantiocontrol via DKR/alkylation of the corresponding lithium derivative in the presence of (−)-sparteine (Scheme 12).[15]

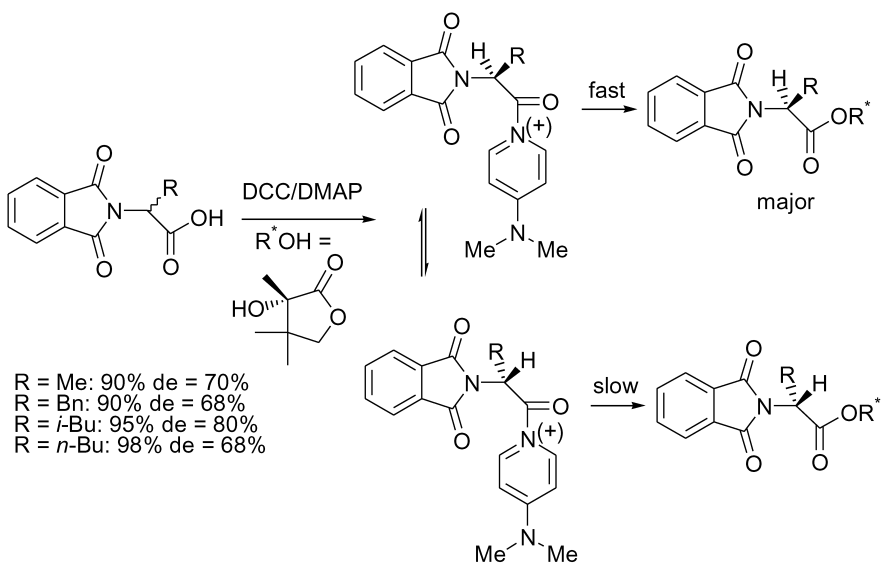
2.1.3. Other reactions. In 2000, Calmes et al. reported a DKR of racemic *N*-phthalylamino acids using dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP) and a chiral alcohol such as (*S*)-α-methylpantolactone.[16] This method provided an easy access to optically active α-amino acids (Scheme 13).

DKR of *N*-acylhemiaminals was performed by enantioselective acylation of the hydroxy groups with axially chiral twisted amides (Scheme 14).[17]

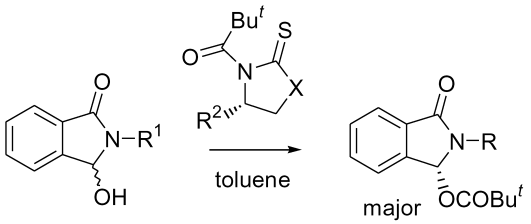
Surprisingly, the stereoselectivity of the acyl-transfer reaction was reversed in the presence of a catalytic amount of base such as DMAP. The effect of DMAP could be due to its strong coordination to the hydroxy group. This strong coordination would allow the complex to behave as if it were a single compound, as well as enhancing the nucleophilicity of the hydroxy group and, therefore, the selectivity might reverse only in the presence of DMAP (Scheme 15).

Cinchona alkaloids could serve dual catalytic roles to mediate both the enantioselective alcoholytic ring opening and the in situ racemisation of 5-aryl-1,3-dioxolane-2,4-diones involving DKR (Scheme 16).[18]

The same methodology has also been applied to urethane-protected α-amino acid *N*-carboxyanhydrides, offering a

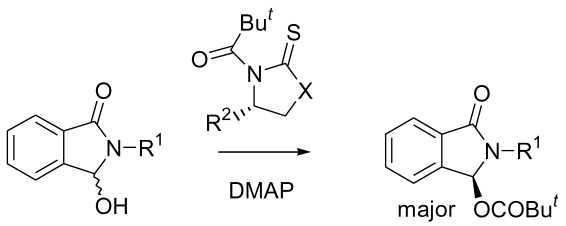


Scheme 13. DKR of *N*-phthalylamino acids using DCC/DMAP.



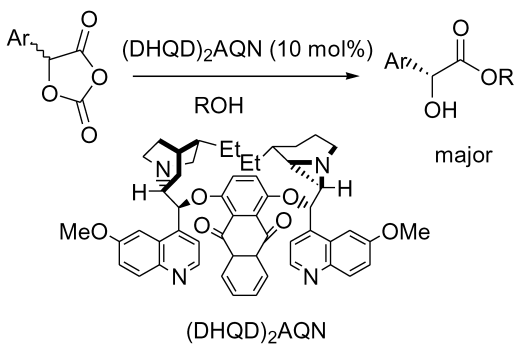
R^1	R^2	X	Yield (%)	ee (%)
COMe	*t*-Bu	O	62	62
COEt	*t*-Bu	O	70	62
$COCH(Me)_2$	*t*-Bu	O	74	66
$COC(Me)_3$	*t*-Bu	O	76	68
$COC(Me)_3$	*t*-Bu	S	94	64
$COC(Me)_3$	*i*-Pr	S	91	50

Scheme 14. DKR of hemiaminals with amides under neutral conditions.



R^1	R^2	X	Yield (%)	ee (%)
$COC(Me)_3$	*t*-Bu	S	99	70
$COCH(Me)_2$	*t*-Bu	S	99	72
$COC(Me)_3$	*t*-Bu	O	95	68
$COC(Me)_3$	*i*-Pr	O	99	68

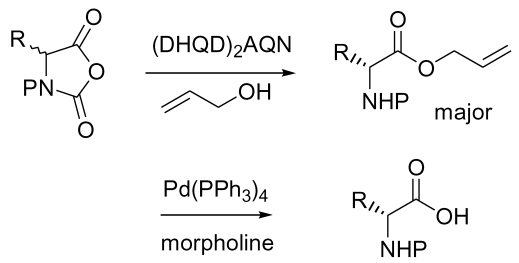
Scheme 15. DKR of hemiaminals with amides in the presence of DMAP.

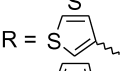
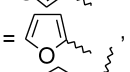
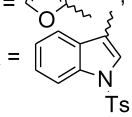


Ar = Ph, R = Et: 71% ee = 95%
Ar = 4-BrC_6H_4, R = Et: 80% ee = 96%
Ar = 4-FC_6H_4, R = Et: 65% ee = 95%
Ar = 4-*i*-PrC_6H_4, R = Et: 68% ee = 91%
Ar = 1-naphthyl, R = *n*Pr: 74% ee = 91%

Scheme 16. DKR of 5-aryl-1,3-dioxolane-2,4-diones.

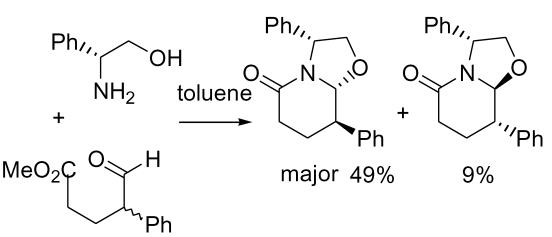
practical synthesis of a wide range of α-aryl- and α-heteroarylamino acids (Scheme 17).[19]



R = Ph, P = Cbz: 91% ee = 97%
R = *p*-FC_6H_4, P = Cbz: 90% ee = 96%
R = *p*-ClC_6H_4, P = Cbz: 92% ee = 97%
R = *p*-$CF_3C_6H_4$, P = Cbz: 90% ee = 95%
R = Ph, P = Fmoc: 90% ee = 98%
R =  , P = Cbz: 92% ee = 93%
R =  , P = Cbz: 91% ee = 95%
R =  , P = Cbz: 91% ee = 98%
R =  , P = Cbz: 90% ee = 95%

Scheme 17. Synthesis of α-arylamino acids via DKR.

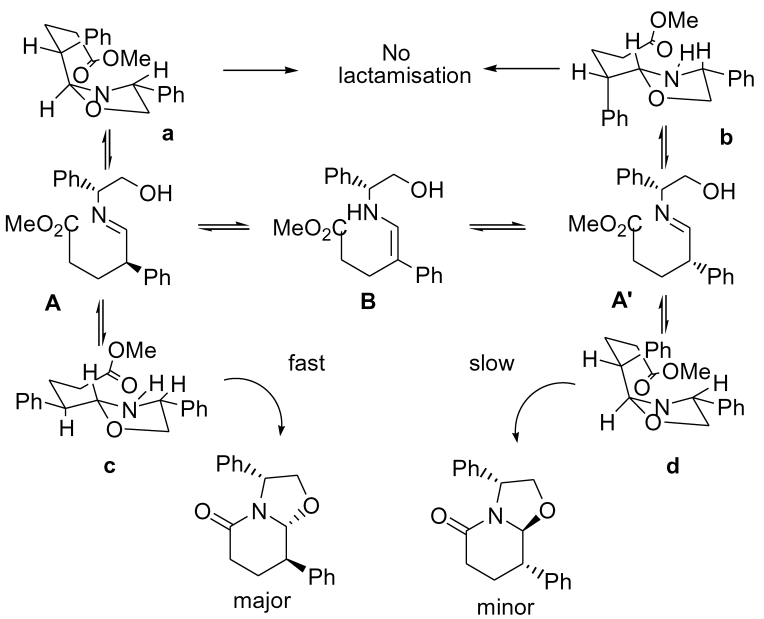
Cyclodehydration of racemic γ-aryl-δ-oxoesters with *R*-phenylglycinol efficiently led to enantiopure bicyclic δ-lactams, in a process that involved a DKR of the stereocenter α to the aldehydic carbonyl group (Scheme 18).[20]



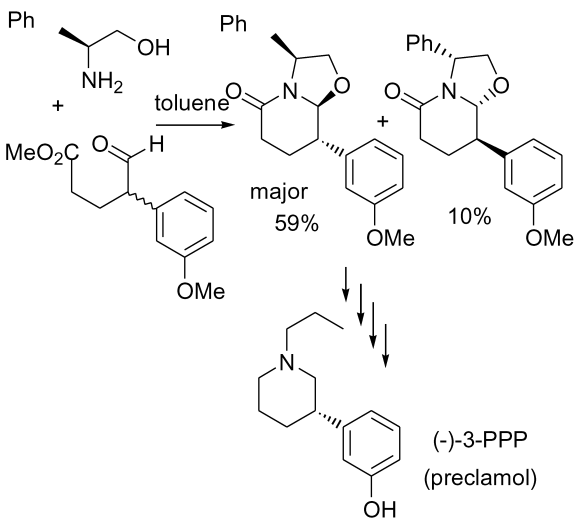
Scheme 18. Synthesis of enantiopure 3-phenylpiperidines.

The diastereomeric imines **A** and **A′** initially formed after the interaction of (*R*)-phenylglycinol with the racemic oxoester are in equilibrium via the enamine **B**. Consequently, a mixture of four equilibrating oxazolidines (**a**–**d**) at the two chirally labile stereogenic centres is formed. Subsequent lactamisation takes place via a transition state in which the phenyl substituent of the incipient chair-like six-membered lactam is equatorial, thus leading to the two compounds. The preferential formation of the major 3-phenylpiperidine is a consequence of lactamisation occurring faster from the diastereomeric oxazolidine that allows a less hindered approach of the ester group to the nitrogen atom (Scheme 19).

This reaction was applied to (*S*)-phenylglycinol and the racemic δ-oxoester bearing a *m*-methoxyphenyl substituent,



Scheme 19. Preferential transition state for lactamisation.



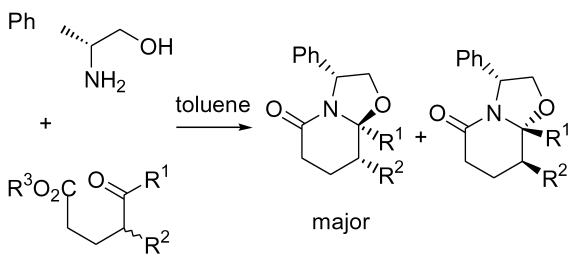
Scheme 20. Enantioselective synthesis of (−)-3-PPP.

allowing the synthesis of (−)-3-PPP (preclamol), an antipsychotic drug (Scheme 20).

The preceding methodology was extended to the synthesis of preclamol analogues bearing an alkyl substituent at the piperidine 2-position, starting from the appropriate racemic α-arylketones instead of the aldehydes. Interestingly, the stereochemical outcome of these reactions differed from that observed in the cyclodehydrations from the aldehyde esters, since lactams with a *cis* 3-C_6H_5/R^2 relationship were now formed as the major isomers (Scheme 21).

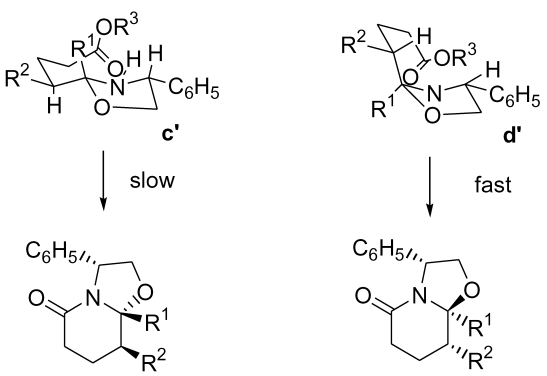
This result can be accounted for by considering that, when starting from the ketones, lactamisation of the diastereomeric oxazolidines in equilibrium occurs faster from **d′**, as this oxazolidine allows a less hindered approach of the ester (or acid) group to the equatorial substituent (Scheme 22).

In order to prepare the (+)-Rove beetle pheromone, Node et al. reported a novel tandem Michael/Meerwein–Ponndorf–Verley reduction, in which, for the first time, a DKR was involved when the reversibly formed Michael adduct carried a β-substituent. Indeed, the production of a single isomer was attributable to DKR via reversible Michael addition and kinetically controlled intramolecular reduction of one of the two Michael adducts (Scheme 23).[21]

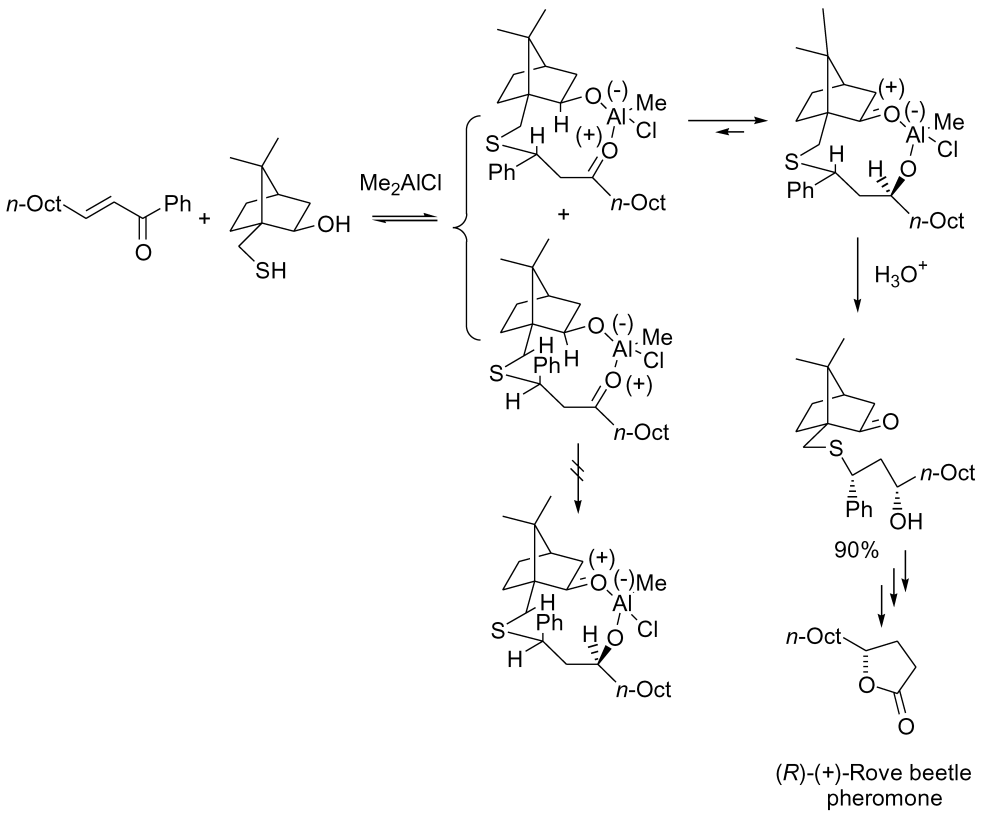


R^3 = H, R^1 = Me, R^2 = Et: 60% de = 56%
R^3 = Me, R^1 = Me, R^2 = *p*-MeOC_6H_4: 76% de = 60%
R^3 = H, R^1, R^2 = -$(CH_2)_4$-: 70% de = 58%

Scheme 21. Enantioselective synthesis of *cis*-2-alkylpiperidines.



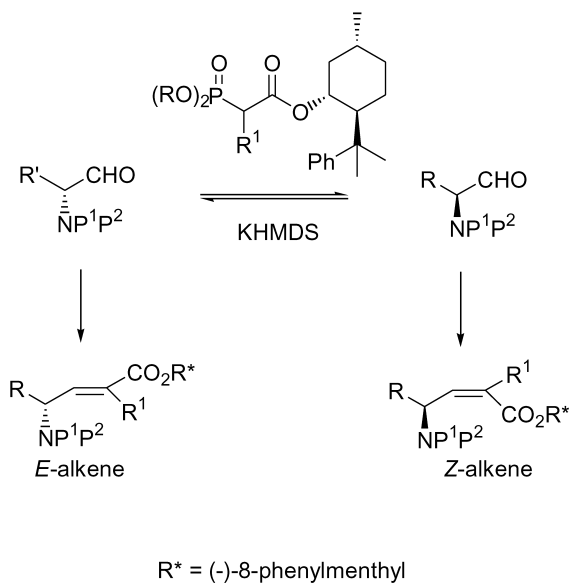
Scheme 22. Preferential transition state for the lactamisation starting from ketones.



Scheme 23. Asymmetric synthesis of the (+)-Rove beetle pheromone.

The first DKR of racemic α-aminoaldehydes was reported by Rein and Reiser by treating these aldehydes **1**-**3** with chiral phosphonates in the presence of a slight excess of base such as potassium hexamethyldisilazide (KHMDS). According to the nature of the phosphonate, the *E*- or the *Z*-product was selectively obtained (Scheme 24, Table 1).[22]

A key intermediate of diltiazem was efficiently synthesised by an asymmetric reduction of a 1,5-benzothiazepine derivative with $NaBH_4$ and chiral α-amino acids such as



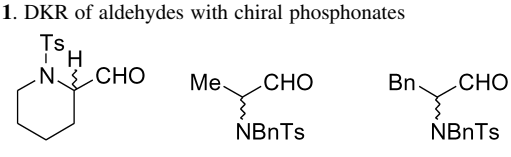
Scheme 24. DKR of aldehydes by reaction with chiral phosphonates.

(*S*)-*tert*-leucine.[23] This asymmetric reduction proceeded via DKR and made it possible to control the two adjacent asymmetric carbons through keto–enol tautomerism (Scheme 25). The role of AcOH was to promote the racemisation between the two enantiomeric ketones.

Another DKR was observed by Uemura et al. during the samarium iodide-induced reductive cross-coupling of *N*-tosylbenzylideneamines with planar chiral benzaldehyde-chromium complexes (Scheme 26).[24] This constitutes a new synthetic strategy for the preparation of enantiopure β-aminoalcohols.

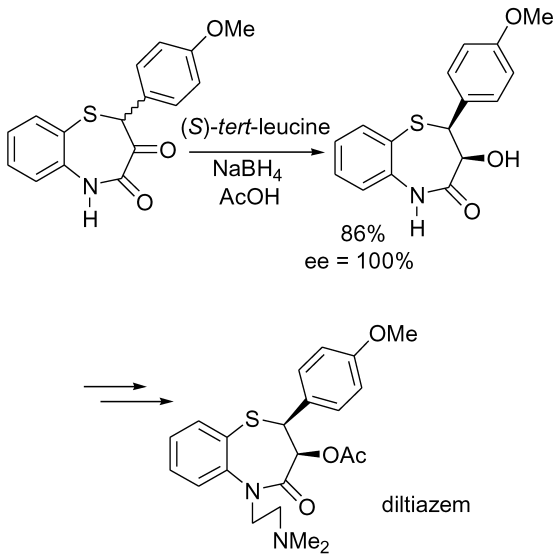
In 2000, Roland et al. developed a diastereoselective synthesis of *tert*-butyl-1,2-diamines from the addition of *tert*-butylmagnesium chloride to 1,2-bisimines derived from

Table 1. DKR of aldehydes with chiral phosphonates

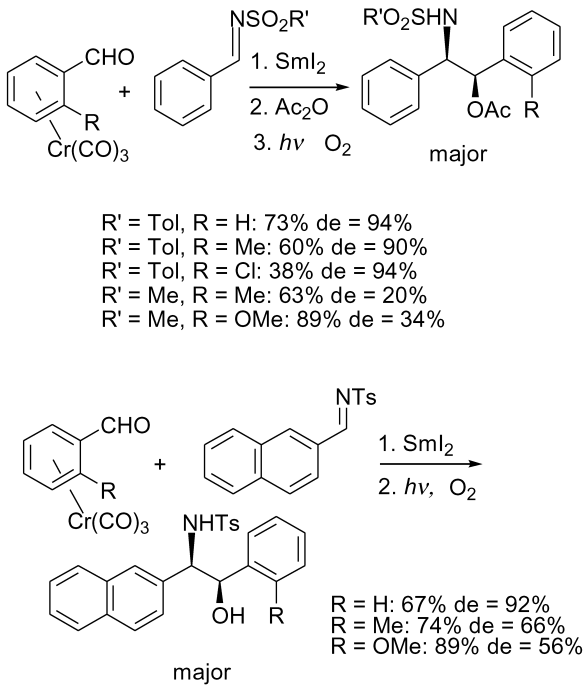


1 **2** **3**

Aldehyde	R	R^1	de (%)	Yield (%) (major isomer)
1	Et	H	96	96 (*E*)
1	*i*-Pr	H	98	87 (*E*)
1	CF_3CH_2	H	68	81 (*Z*)
1	CF_3CH_2	Me	66	69 (*Z*)
2	CF_3CH_2	H	88	86 (*Z*)
3	CF_3CH_2	H	80	81 (*Z*)



Scheme 25. Synthesis of a diltiazem intermediate.

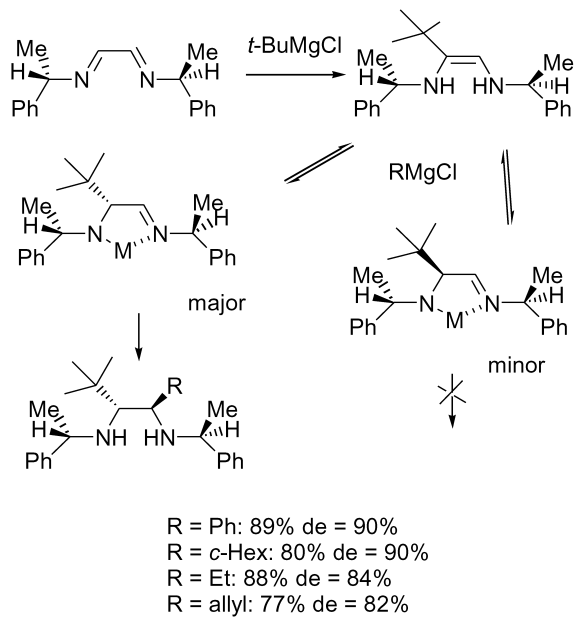


Scheme 26. Reductive cross-coupling reaction involving a DKR.

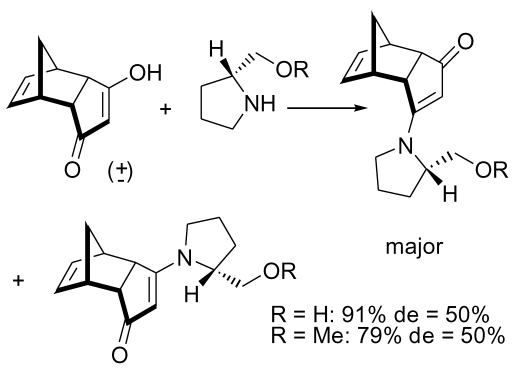
glyoxal and chiral amines. Evidence of a DKR during the bis-addition process of the organometallic reagent, leading to the 1,2-di-*tert*-butylethanediamine, as a single diastereomer, has been demonstrated (Scheme 27).[25]

A DKR of a 5-hydroxytricyclodecadienone using (*S*)-prolinol or its methyl ether as the chiral mediator led to the corresponding enaminones. This approach, which constituted an asymmetric desymmetrisation of a Diels–Alder adduct, was an attractive method to obtain the enantiopure tricyclodecadienones (Scheme 28).[26]

A DKR was observed during the aminolysis of α-sulphinyl-δ-unsaturated dithioesters by dimethylamine affording the (2*R**,S*S**)-thioamides.[27] It was demonstrated that the



Scheme 27. Diastereoselective addition of Grignard reagents to chiral 1,2-bisimines.

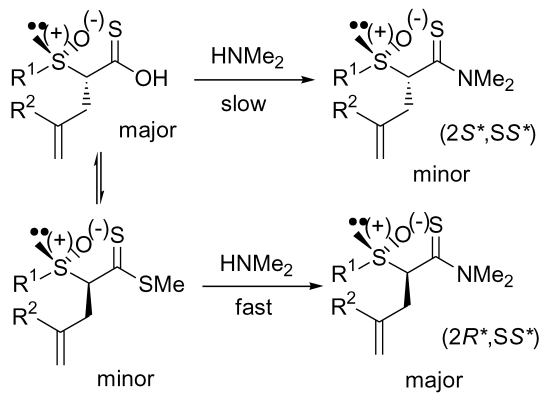


Scheme 28. Asymmetric desymmetrisation yielding tricyclic enaminones.

dithioesters underwent rapid equilibration and that the (2*R**,S*S**)-isomers reacted faster than the (2*S**,S*S**)-isomers, resulting in the preferential formation of thioamides of (2*R**,S*S**) configuration (Scheme 29).

In 2000, Khiar et al. reported the first enantiodivergent DKR of bis-sulphinyl chlorides with the simultaneous creation of two chiral centres.[28] According to the nature of the tertiary amine used to catalyse the reaction, the diastereoselectivity of the reaction was reversed. Indeed, in the presence of pyridine, the major compound was the C_2-symmetric (*R*,*R*) diastereoisomer. In contrast, a simple change of tertiary amine from pyridine to *i*-Pr_2NEt shifted the diastereoselectivity in favour of the C_2-symmetric bis-sulphinate ester (*S*,*S*). A further condensation of an organometallic reagent on the 1,2-bis-sulphinate esters led to the corresponding enantiomerically pure C_2-symmetric bis-sulphoxides (Scheme 30).

These results may represent an example of DKR that does not rely necessarily on the epimerisation of the starting substrate, as a consequence of the hypervalent intermediates being able to undergo pseudorotations.[29] As shown in



R^1	R^2	(2*S**)/(2*R**) dithioester ratio	(2*S**)/(2*R**) thioamide ratio
i-Pr	H	99:1	14:86
Me	H	80:20	5:95
Me	Me	83:17	8:92
c-Hex	H	88:12	17:83

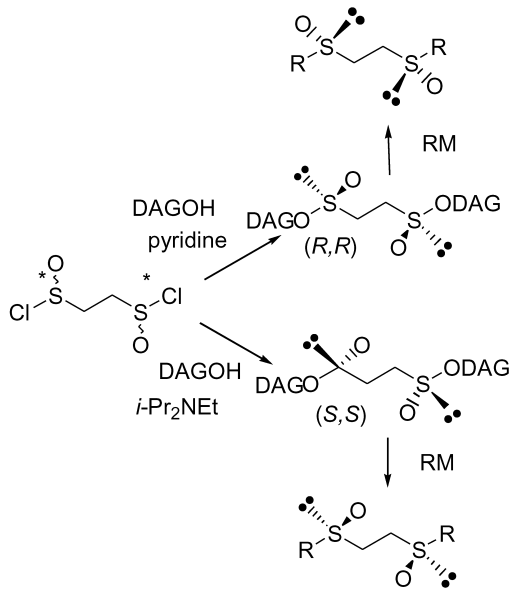
Scheme 29. Aminolysis of α-sulphinyl-δ-unsaturated dithioesters.

Scheme 31, depending on whether the base used was pyridine or *i*-Pr_2NEt, all the bis-sulphurane intermediates evolved by pseudorotation to the bis-sulphurane type **A** or bis-sulphurane type **B**, which yielded (*R*,*R*)- or (*S*,*S*)-bis-sulphinate esters, respectively, by extrusion of the amine.

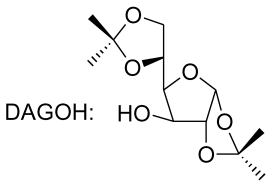
It was shown previously that α-amino acid esters could be prepared asymmetrically by the DKR of the appropriate zirconaaziridines, using a C_2-symmetric cyclic carbonate as an optically active CO_2 equivalent.[30] The same methodology was applied to the asymmetric synthesis of silicon-containing α-amino acid esters (Scheme 32).[31]

In 2000, Rao et al. reported for the first time that enantiopure β-aminoalcohols could be prepared from the racemic epoxides by DKR involving enantio-differentiating racemisation in cyclodextrin complexes under solid-state conditions.[32] When one of the enantiomeric forms of the epoxide in the β-cyclodextrin cavity, due to its favourable geometry, was captured selectively by the external amine, the phenomenon of DKR through racemisation of the starting epoxide made it possible to obtain the enantiomerically pure aminoalcohols (Scheme 33).

Enantiopure thio- and oxoflavopiridols were prepared via a very efficient DKR of the racemic intermediate piperidones in the presence of dibenzoyl-D-tartaric acid in methanol at reflux (Scheme 34).[33] The desired enantiomeric salt was quite insoluble in methanol, while the opposite enantiomeric salt was soluble. There was a difference not only in solubility between these two diastereomeric salts, but also in thermodynamic stability. It was reported that a facile in situ epimerisation of the C-4 chiral centre under the reaction conditions, the thermodynamic stability difference between



Configuration of major bis-sulphinate	RM	Yield (%)	de (%)	major bis-sulphoxide (ee,%)
(*R*,*R*)	MeMgI	40	> 98	(*S*,*S*) (> 96)
(*R*,*R*)	^{t}BuMgCl	46	> 98	(*R*,*R*) (> 98)
(*R*,*R*)	*o*-AnMgI	52	> 98	(*R*,*R*) (> 98)
(*S*,*S*)	TolMgBr	54	86	(*S*,*S*) (> 98)
(*R*,*R*)	*o*-pyr-CH_2Li	60	64	(*S*,*S*) (> 98)
(*S*,*S*)	*o*-pyr-CH_2Li	50	70	(*R*,*R*) (> 98)
(*R*,*R*)	^{t}BuO_2CCH_2Li	60	> 98	(*S*,*S*) (> 98)
(*S*,*S*)	^{t}BuO_2CCH_2Li	70	> 98	(*R*,*R*) (> 98)



Scheme 30. DKR route to optically pure C_2-symmetric bis-sulphoxides.

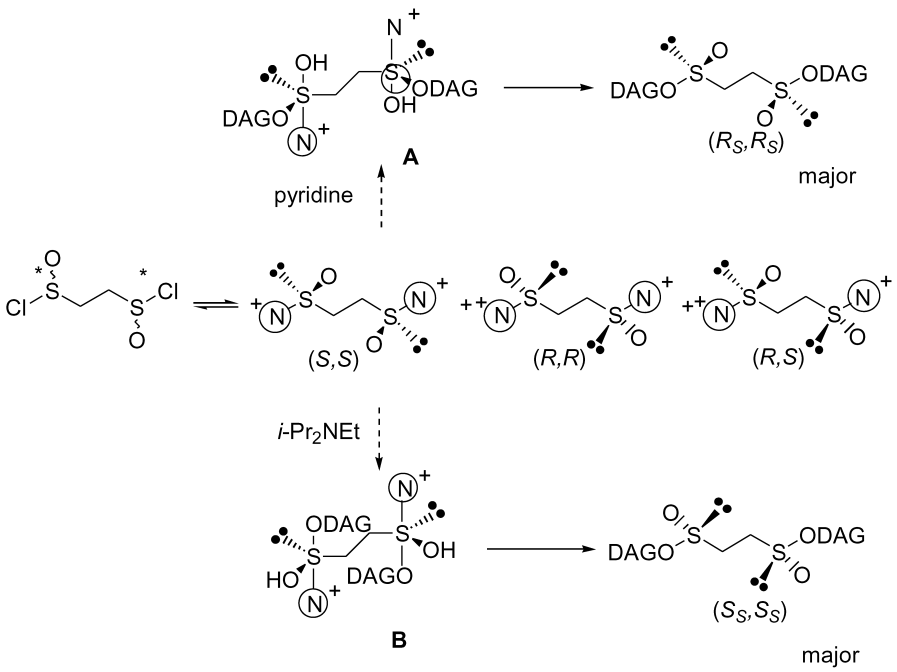
the two diastereomeric salts in favour of the desired 4*R*-enantiomer of the piperidone and a large solubility difference between the two diastereomeric salts in methanol enabled the DKR to be very efficient.

2.2. Chiral metal catalysts

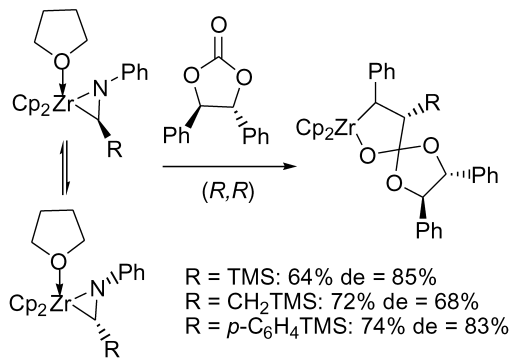
2.2.1. Ruthenium-catalysed DKR. The ruthenium-catalysed hydrogenation has been widely used in the DKR of β-ketoesters.[1] The catalysts are prepared in situ under mild conditions, in a one-step sequence from a commercially available starting material (COD)Ru(η^3-$(CH_2)_2CMe)_2$ (Scheme 35).[34]

The first example of DKR of α-acetamido-β-ketoesters was reported in 1989 simultaneously by Noyori[35] and Genêt (Scheme 36).[36]

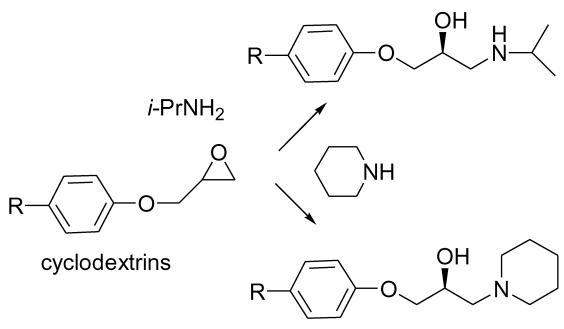
The DKR of α-acetamido-β-ketoesters was successfully applied to produce an important intermediate for the synthesis of carbapenems (Scheme 37).[37]



Scheme 31. Possible pathways for the DKR of ethane-1,2-bis-sulphinyl chloride.

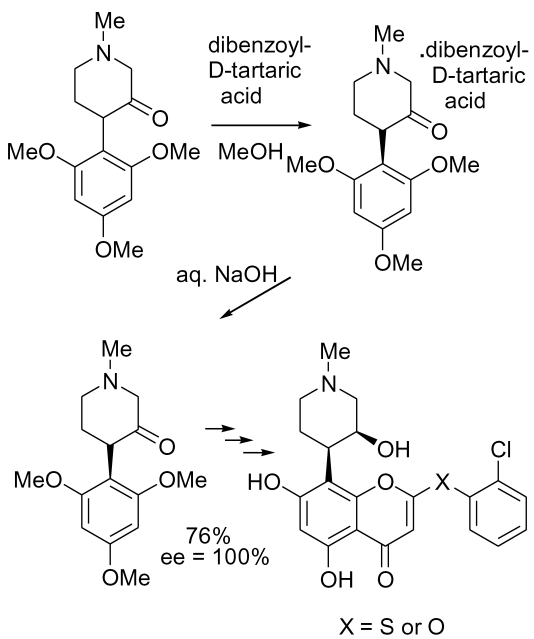


Scheme 32. Asymmetric synthesis of silylated α-amino acid esters through DKR.



R	Amines	Yield (%)	ee (%)
H	*i*-PrNH$_2$	79	74
Cl	*i*-PrNH$_2$	75	100
Me	*i*-PrNH$_2$	72	89
CH_2CH_2OMe	*i*-PrNH$_2$	70	85
Cl	piperidine	70	100

Scheme 33. Solid-state asymmetric synthesis of β-aminoalcohols.

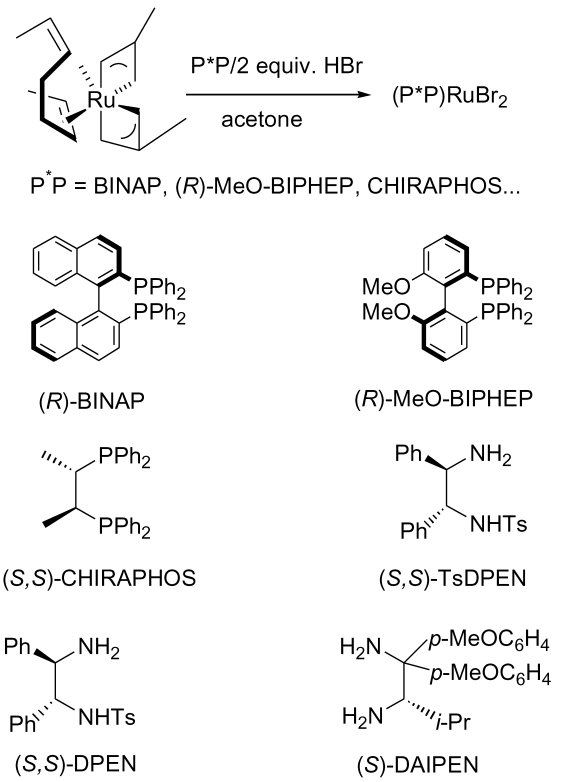


Scheme 34. Asymmetric synthesis of thio- and oxoflavopiridols via DKR.

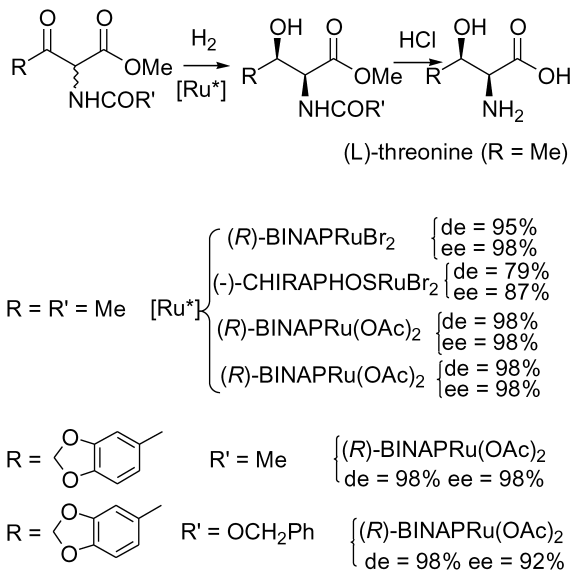
The synthesis of (2*S*,3*R*)-methyl *p*-chloro-3-hydroxy-tyrosinate, a component of vancomycin, was achieved using the DKR of an α-acetamido-β-ketoester prepared from *m*-chloro-*p*-hydroxybenzoic acid (Scheme 38).[38]

A quantitative yield of (2*S*,3*R*)-3-hydroxylysine was obtained by Genêt et al. by DKR of racemic methyl 2-acetamido-3-keto-6-phtalimidohexanoate (Scheme 39).[39]

The DKR applied to racemic cyclic β-ketoesters such as 2-substituted-3-oxo carboxylic esters revealed that the stereochemical course of the reaction was influenced by

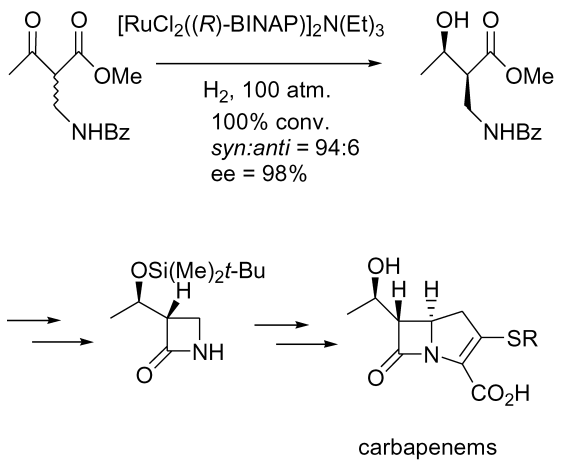


Scheme 35. Synthesis of chiral ruthenium-catalysts.

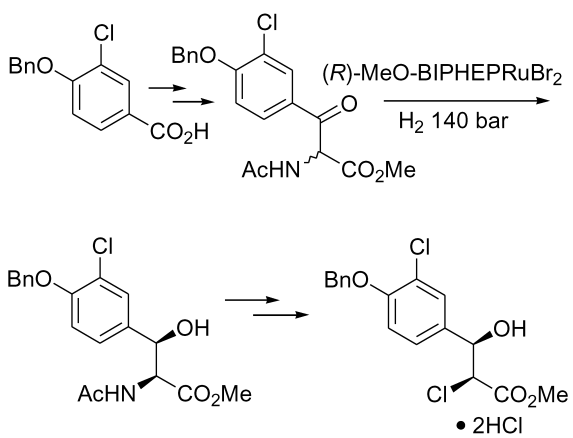


Scheme 36. Ru-catalysed hydrogenation of 2-substituted 3-oxocarboxylic esters.

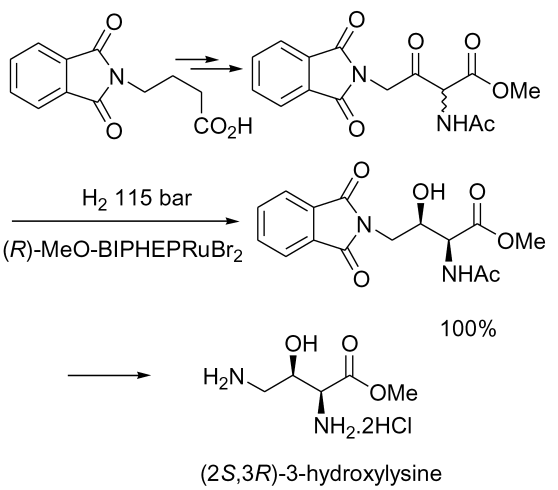
the structures of the substrates.[40,41] When comparing the asymmetric hydrogenation of the five-membered ring to those obtained with cyclic six-membered rings, the following comment can be made: in the case of 2-(ethoxycarbonyl)cyclopentanone or 2-(methoxycarbonyl)cyclopentanone, the hydrogenation reaction proceeded with high diastereo- and enantioselectivity (de=92%, ee=85% and de=98%, ee=92%, respectively) by using (*R*)-BINAP as the chiral auxiliary, leading to the corresponding (2*R*,3*R*) *trans* product. In increasing the ring size to a six-membered



Scheme 37. Synthesis of carbapenems via DKR.

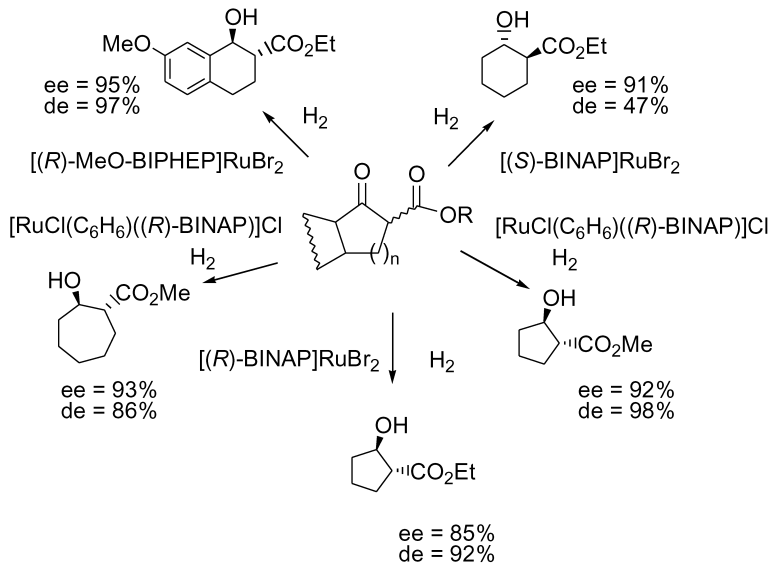


Scheme 38. Synthesis of a component of vancomycin via DKR.

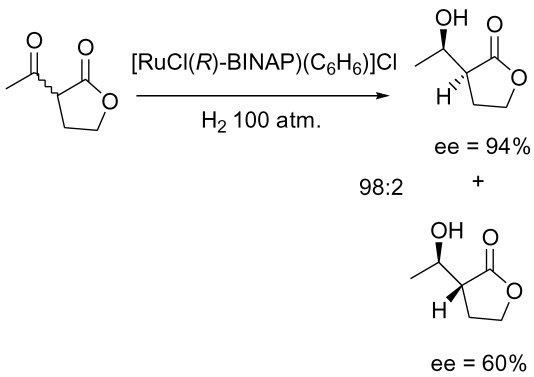


Scheme 39. Synthesis of (2*S*,3*R*)-3-hydroxylysine via DKR.

ring with (*S*)-BINAPRu(II) catalyst, however, the diastereoselectivity decreased to some extent (de=47%). Nevertheless, significant enantiomeric excess was reached for the ruthenium-promoted hydrogenation reaction of 2-(ethoxycarbonyl)cyclohexanone, affording the (2*S*,3*S*) *trans* product (ee=91%). On the other hand, the reduction of the corresponding seven-membered ring with (*R*)-BINAP



Scheme 40. DKR involving cyclic β-ketoesters.

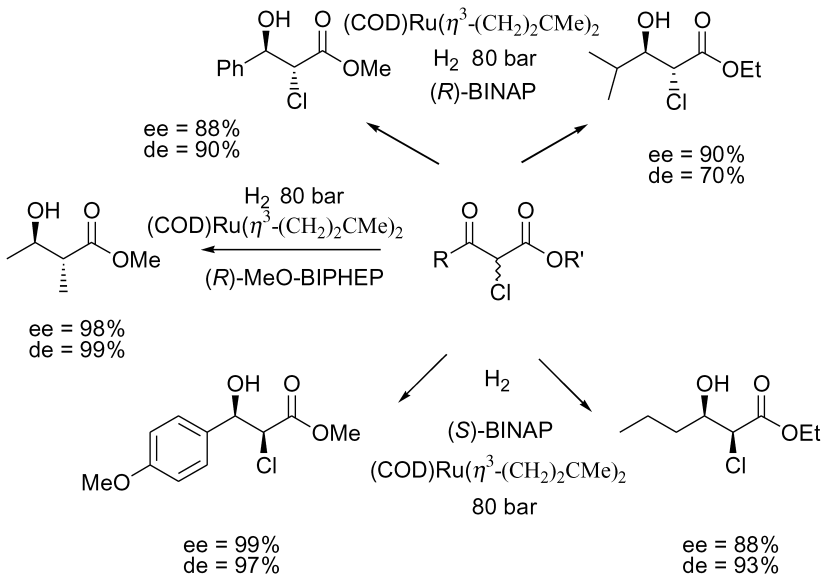


Scheme 41. Synthesis of a butanolide via DKR.

gave better results (de=86%, ee=93%). A relevant DKR was achieved for cyclic β-ketoesters containing a tetralone moiety, i.e. 7-methoxy-2(ethoxycarbonyl)tetralone. Indeed, using (*R*)-MeO-BIPHEP as the chiral auxiliary provided the *trans* cyclic β-hydroxyester with excellent enantio- and diastereofacial discrimination (de=97%, ee=95%) (Scheme 40).

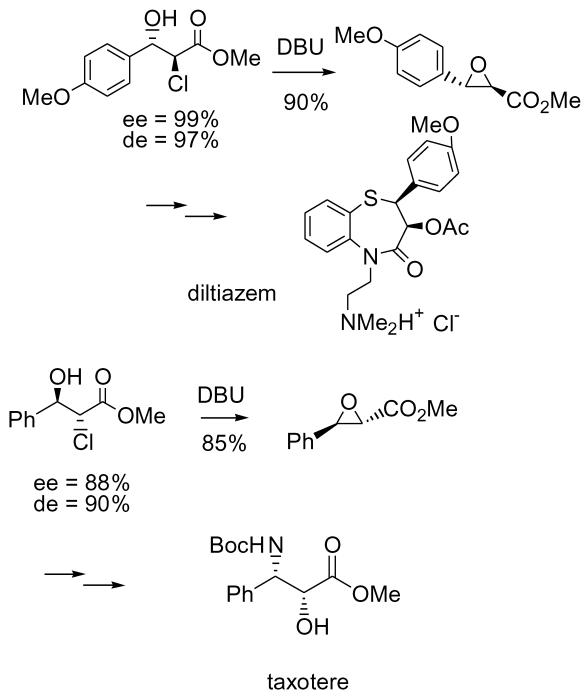
An original example of DKR was observed during the hydrogenation of 2-acetyl-4-butanolide proceeding with 96% *syn* diastereoselectivity and good enantiomeric excesses (Scheme 41).[41a]

The hydrogenation of α-chloro-β-ketoesters has also been widely studied.[42] In this case, a catalytic system was prepared by mixing (COD)Ru(η^3-$(CH_2)_2CMe)_2$ and the chiral diphosphine (BINAP or MeO-BIPHEP). Under these conditions, the corresponding *anti* α-chloro-β-hydroxyesters bearing an alkyl or an aromatic substituent were synthesised with high levels of enantio- and diastereoselections varying from 70 to 99%. A *syn* diastereoselectivity was also reported using an [(*R*)-BINAP]Ru(II) catalyst (Scheme 42).[43]



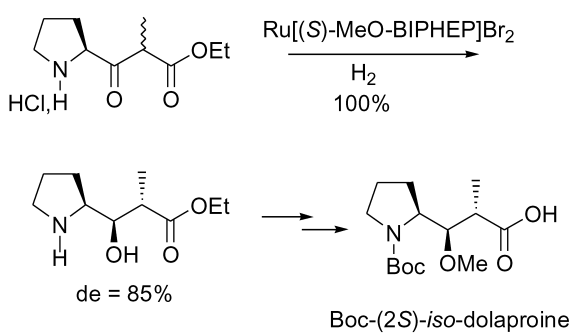
Scheme 42. DKR involving α-chloro-β-ketoesters.

These enantiomerically enriched α-chloro-β-hydroxyesters were used to synthesise optically active glycidates such as (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate, a key intermediate for the synthesis of diltiazem, a potent channel blocker. The preparation of *trans* (2*S*,3*R*)-methyl-3-phenylglycidate under similar conditions provided an efficient route to the taxotere side chain (Scheme 43).[42]



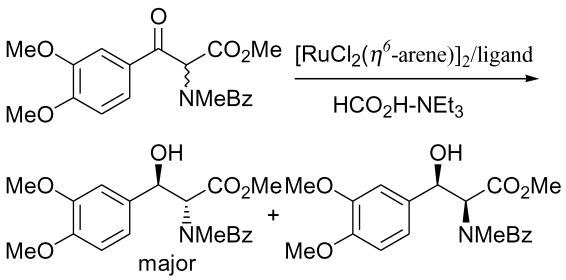
Scheme 43. Synthesis of diltiazem and taxotere.

DKR of α-substituted-β-ketoesters has also allowed the synthesis of several other natural products such as the HMG-CoA synthase inhibitors 1233 A,[44] biphenomycin A[45] and roxaticin.[46] More recently, the first asymmetric Ru(II)-catalysed hydrogenation of α-substituted-β-keto-esters bearing an asymmetric centre in the δ-position was reported by Genêt et al. and was applied to the synthesis of *iso*-dolaproine (Scheme 44).[47]

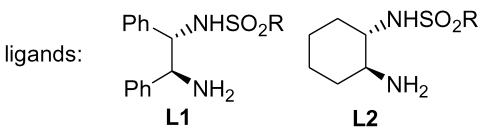


Scheme 44. Synthesis of *iso*-dolaproine via DKR.

Another ruthenium catalyst such as an Ru(η^6-arene)-*N*-perfluorosulfonyl-1,2-diamine was involved in the hydrogenation of racemic *threo*-β-hydroxy-α-amino acids, affording β-(3,4-dimethoxyphenyl)serine methyl esters (Scheme 45).[48]



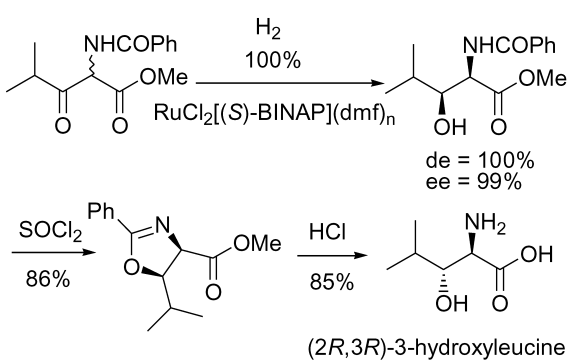
Ligand	η^6-Arene	Conv. (%)	de (%)	ee (%)
L1a	*p*-cymene	80	90	94
L1b	*p*-cymene	100	90	90
L1c	*p*-cymene	90	90	94
L1c	benzene	95	56	50
L1d	*p*-cymene	100	90	98
L1d	*p*-cymene	100	90	> 99
L2a	*p*-cymene	50	90	88
L2b	*p*-cymene	65	90	88
L2d	*p*-cymene	95	90	97
L2d	benzene	100	76	86
L2e	*p*-cymene	100	90	> 99
L2e	benzene	100	68	90
L2e	*p*-cymene	100	90	99



a: R = *p*-MeC_6H_4-
b: R = *p*-$CF_3C_6H_4$-
c: R = C_6F_5
d: R = CF_3
e: R = $CF_2CF_2CF_2CF_3$

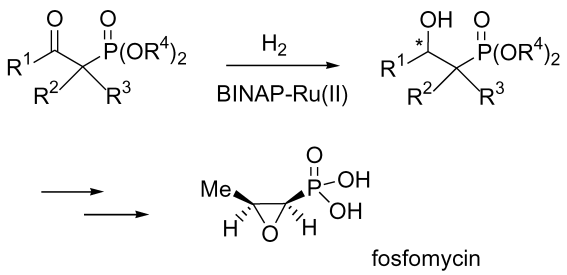
Scheme 45. Stereoselective hydrogenation of β-keto-α-methylamino acid esters via DKR.

(2*R*,3*R*)- and (2*S*,3*S*)-3-Hydroxyleucines, components of cyclodepsipeptides, papuamides and polyoxypeptins, were efficiently synthesised along with their diastereomers from the corresponding β-keto-α-amino acid esters through DKR using $RuCl_2$(BINAP)-catalysed hydrogenation (Scheme 46).[49]



Scheme 46. Synthesis of (2*R*,3*R*)-3-hydroxyleucine.

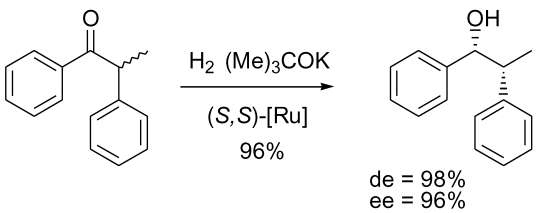
Finally, a practical route to fosfomycin was described by Noyori et al. based on a very efficient DKR of β-ketophosphonates (Scheme 47).[50]



a: $R_1 = R_4 = Me$, $R_2 = R_3 = H$: 99% ee = 98%
ester (*R*) from BINAP (*R*)
b: $R_1 = Me$, $R_2 = R_3 = H$, $R_4 = Et$: 98% ee = 96%
ester (*R*) from BINAP (*R*)
c: $R_1 = R_2 = R_3 = R_4 = Me$: 97% ee = 98%
ester (*R*) from BINAP (*R*)
d: $R_1 = n\text{-}C_5H_{11}$, $R_2 = R_3 = H$, $R_4 = Me$: 98% ee = 94%
ester (*S*) from BINAP (*S*)
e: $R_1 = (Me)_2CH$, $R_2 = R_3 = H$, $R_4 = Me$: 96% ee = 96%
ester (*S*) from BINAP (*S*)
f: $R_1 = Ph$, $R_2 = R_3 = H$, $R_4 = Me$: 96% ee = 95%
ester (*R*) from BINAP (*R*)
g: $R_1 = Me$, $R_2 = Br$, $R_3 = H$, $R_4 = Me$: 95% ee = 98%
ester (1*R*,2*S*) from BINAP (*S*)

Scheme 47. Synthesis of fosfomycin via DKR.

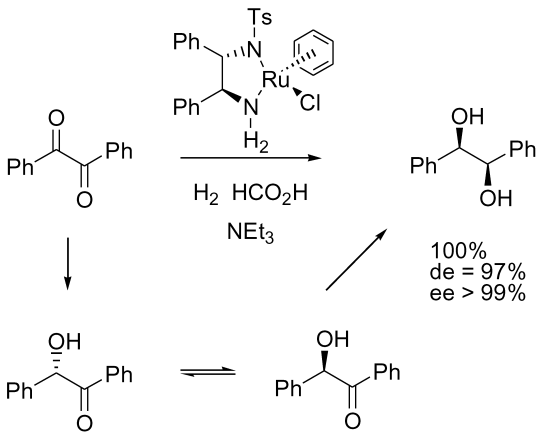
The application of dynamic kinetic discrimination to the ruthenium-catalysed hydrogenation of simple ketones such as substituted cyclohexanones was reported by Noyori in 1996.[51] In one example, hydrogenation of 2-isopropyl-cyclohexanone in the presence of an (*S*)-BINAP/(*R*,*R*)-DPEN-ruthenium catalyst under 4atm. H_2 gave quantitatively the *cis* (*R*,*R*)-alcohol (93% ee). Another example was the hydrogenation of 2-phenyl-propiophenone with an (*S*)-XylBINAP/(*S*)-DAIPEN-ruthenium catalyst (structures of DPEN- and DAIPEN-ruthenium catalysts in Scheme 35) under basic, protic conditions, which gave the corresponding (*R*,*R*)-alcohol in excellent yield and selectivity (Scheme 48).[52]



(*S*,*S*)-[Ru]: *trans*-[$RuCl_2$((*S*)-xylBINAP)((*S*)-DAIPEN)]

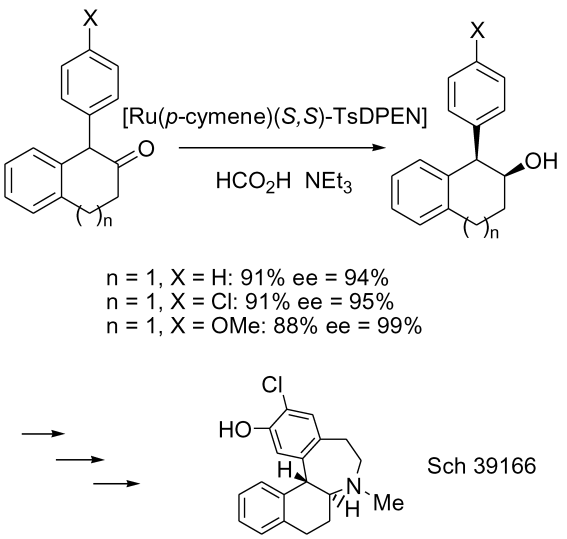
Scheme 48. Hydrogenation of 2-phenyl-propiophenone via DKR.

Enantiomerically pure hydrobenzoin could be prepared from benzyl by employing a diamino-type ruthenium(II) complex (Scheme 49).[53] The success of this reaction was made possible due to the stepwise reduction of benzyl to hydrobenzoin via the intermediate benzoin. This latter derivative was itself configurationally labile and stereomutated rapidly.



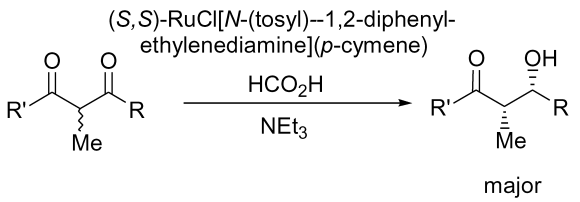
Scheme 49. Synthesis of hydrobenzoin via DKR.

Very recently, a range of 1-aryl-2-tetranols have been generated in high yields and enantiomeric excess from the corresponding racemic ketones via a DKR-hydrogenation process, using Ru(II)-TsDPEN. This provided a potential entry to an asymmetric total synthesis of benzazepines such as Sch 39166 (Scheme 50).[54]



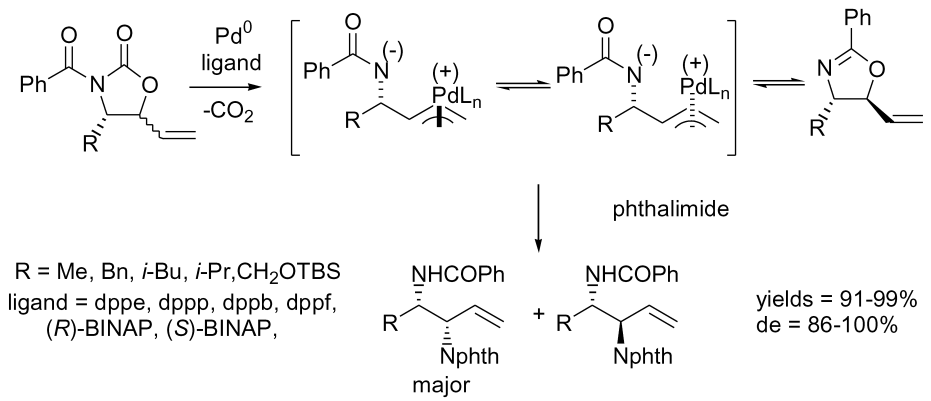
n = 1, X = H: 91% ee = 94%
n = 1, X = Cl: 91% ee = 95%
n = 1, X = OMe: 88% ee = 99%

Scheme 50. Synthesis of Sch 39166 via DKR.



R' = Ph, R = CH_2OMe: 95% de = 54% ee = 92%
R' = Ph, R = CH_3: 84% de = 84% ee = 98%
R' = Ph, R = $(CH_2)_2CH{=}CH_2$: 82% de = 82% ee = 98%
R' = Ph, R = CH_2NHCBz: 81% de =66% ee = 89%
R' = Ph, R = $(CH_2)_2NHBoc$: 88% de = 94% ee = 97%
R' = *i*-Pr, R = CH_2OBn: 92% de = 44% ee = 94%

Scheme 51. Hydrogenation of 2-alkyl-1,3-diketones via DKR.

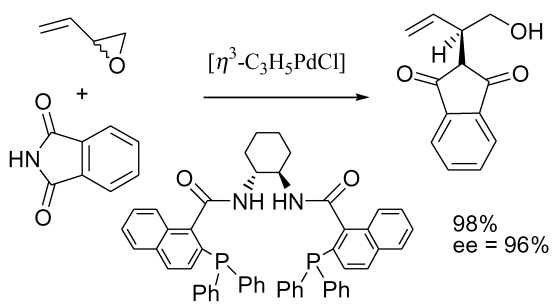


Scheme 52. Synthesis of chiral *syn*-1,2-diamines via DKR.

The same conditions have been successfully applied to 2-alkyl-1,3-diketones by Cossy et al., leading to *syn*-2-alkyl-3-hydroxyketones.[55] These reactions offer an alternative preparation of aldol-type intermediates by a non-aldol pathway under easily scalable conditions (Scheme 51).

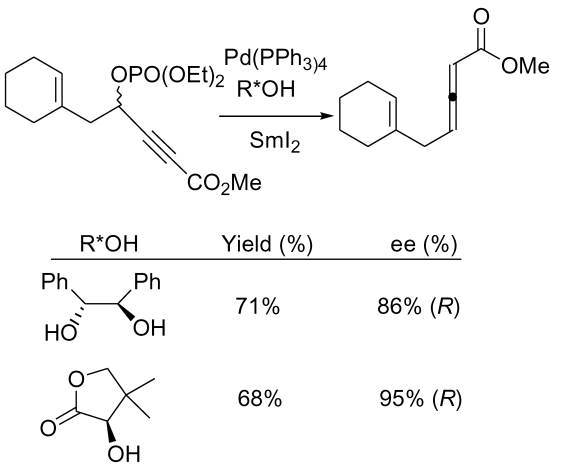
2.2.2. DKR catalysed by metals other than ruthenium. Chiral palladium complexes have also been used in the context of DKR. In 1999, Cook reported the palladium-mediated synthesis of chiral vicinal diamines from the chiral oxazolidinones.[56] The process involved successive oxidative insertion, loss of CO_2 and subsequent cyclisation at the amide oxygen atom. The intermediate π-allyl palladium complexes were undergoing rapid equilibration. Moreover the intermediate oxazoline was also ionised by the palladium catalyst and was in equilibrium with the π-allylpalladium complexes, giving rise to thermodynamically controlled product ratios. These dynamic intermediates could be trapped with phthalimide under kinetic control to afford enantio- and diastereoselectively the *syn*-chiral 1,2-diamines (Scheme 52).

In 2000, Trost reported that exposing butadiene monoepoxide and phthalimide to a catalyst formed in situ from π-allylpalladium chloride dimer and a chiral ligand led to the corresponding chiral phthalimide with very high selectivity (Scheme 53).[57] This reaction constituted a practical synthesis of vinylglycinol and was also applied to the preparation of vigabatrin or ethambutol.



Scheme 53. Synthesis of protected vinylglycinol via DKR.

The first example of the asymmetric synthesis of allenic esters by a samarium(II)-mediated reduction of propargylic compounds through dynamic kinetic protonation was reported by Mikami et al.[58] Various chiral proton sources were involved and gave enantio-enriched allenic esters (Scheme 54).

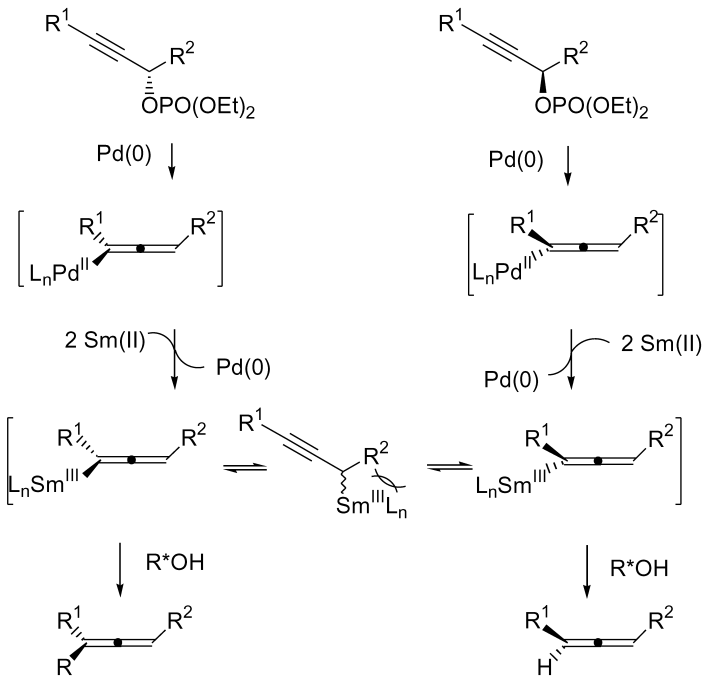


Scheme 54. Enantioselective SmI_2-mediated reduction–protonation.

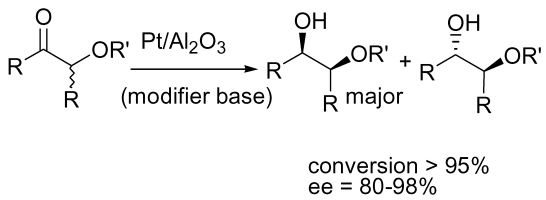
The stereochemical course for racemisation could be explained as follows. First, oxidative addition to the propargylic phosphate gave allenylpalladium(II) through back side attack of palladium(0). Thus, the enantio-enriched allenylpalladium(II) was stereospecifically formed starting from the enantio-enriched propargylic phosphate without loss of enantiopurity. The cationic allenylpalladium(II) species were converted to anionic organosamarium(II). This carbanionic samarium(III) species was readily racemised and the racemic allenic compound was obtained after protonation with an achiral proton source such as *tert*-butyl alcohol (Scheme 55).

Recently, the first successful example of the asymmetric hydrogenation of substituted α-ketoethers with Cinchona-modified Pt/Al_2O_3 was reported. The immobilisation of the OH^- ions on solid ion exchangers allowed a DKR (Scheme 56).[59]

A new practical methodology to prepare enantiopure 1,2-hydrazinoalcohols based on a diastereoselective Ni(II)-catalysed Michael addition step followed by stereoselective reduction of the keto function has been reported. In this process, a DKR was involved during the reduction of chiral α-hydrazino-β-ketoacid derivatives (Scheme 57).[60]



Scheme 55. Proposed mechanism for enantioselective SmI_2-mediated reduction–protonation.



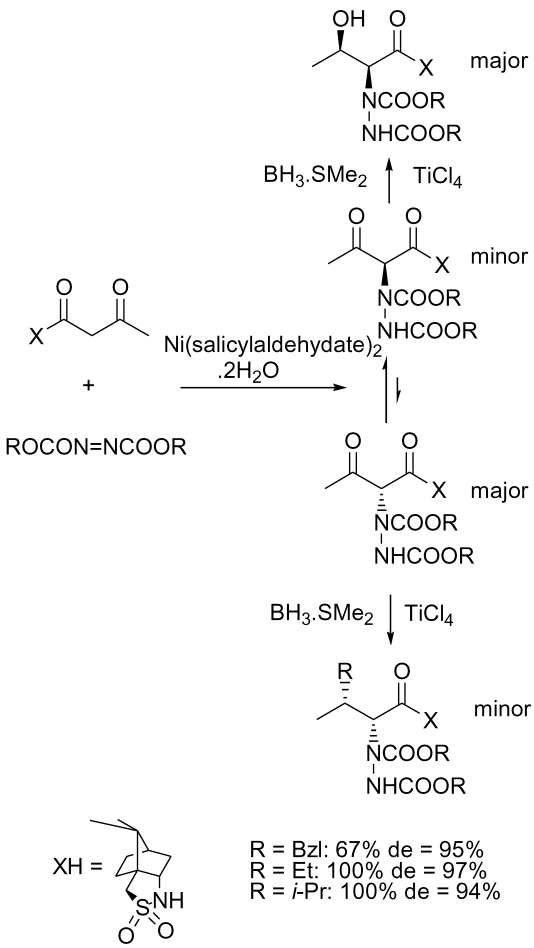
Scheme 56. DKR with a heterogeneous modified catalyst and a heterogeneous base.

On the other hand, optically active cobalt(II) complexes were used as catalysts for the enantioselective borohydride reduction of aromatic ketones employing pre-modified borohydride.[61] A DKR was observed for the reduction of a 2-ethoxycarbonyl-1-tetralone derivative using pre-modified borohydride arising from $NaBH_4$, tetrahydrofurfuryl alcohol (THFA) and ethanol (Scheme 58).

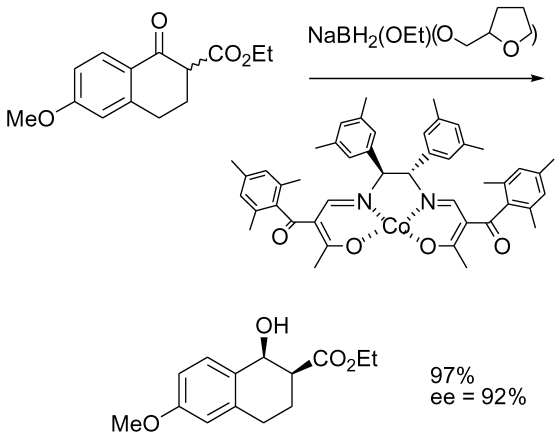
The same methodology has been applied to the reduction of 2-substituted-1,3-propanediones[62] and 2-alkyl-3-keto-esters[63] affording, respectively, the optically active 2-substituted-1,3-diaryl-3-hydroxypropanones and optically active *anti*-2-alkyl-3-hydroxyesters (Scheme 59).

Very recently, Buchwald has reported the DKR of racemic 3,5-dialkylcyclopentenones employing catalytic (*S*)-*p*-tol-BINAP/CuCl/NaO*tert*-Bu and poly(methylhydrosiloxane) as a stoichiometric reductant.[64] This process was a unique approach to simultaneously establish two non-adjacent stereocentres in dialkylcyclopentanones (Scheme 60).

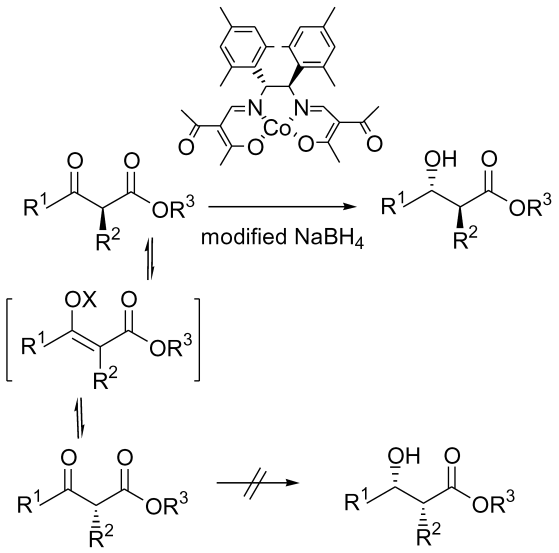
In order to explain this DKR, it was proposed that, upon asymmetric conjugate reduction of the enone, a copper enolate intermediate was formed. Subsequent σ-bond metathesis with silane yielded the silyl enol ether and



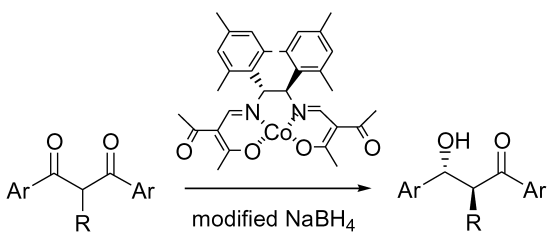
Scheme 57. Reduction of chiral α-hydrazino-β-ketoacid derivatives via DKR.



Scheme 58. Enantioselective borohydride reduction promoted by cobalt(II) catalysts.

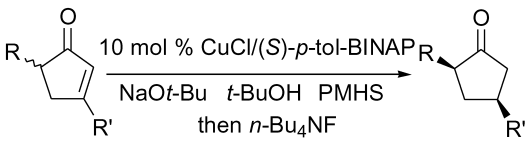


R^1	R^2	R^3	Yield (%)	de (%)	ee (%)
naphth	Me	Et	91	92	95
Ph	Me	Et	91	89	93
p-MeOPh	Me	Et	93	87	94
p-BrPh	Me	Et	91	90	90
Ph	allyl	Et	84	87	95



Ar = Ph, R = Me: 93% de = 99% ee = 99%
Ar = *p*-tol, R = Me: 97% de = 99% ee = 99%
Ar = naphth, R = Me: 73% de = 99% ee = 99%
Ar = *p*-MeOPh, R = Me: 96% de = 99% ee = 97%
Ar = Ph, R = Et: 88% de = 98% ee = 97%
Ar = Ph, R = Bn: 96% de = 99% ee = 98%

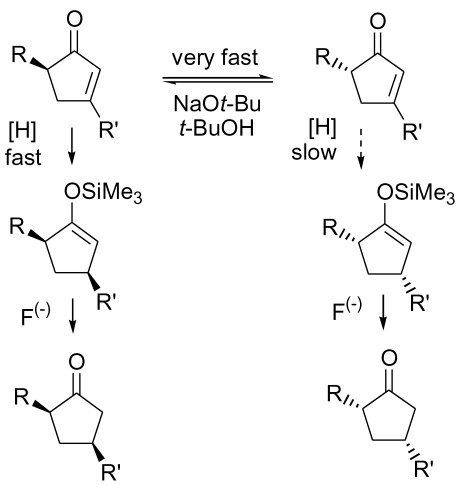
Scheme 59. Catalytic borohydride reduction in the presence of cobalt(II) complexes via DKR.



R = Me, R' = $(CH_2)_2$Ph: 89% de = 82% ee = 91%
R = *i*-Pr, R' = $(CH_2)_2$Ph: 94% de = 86% ee = 93%
R = *t*-Bu, R' = $(CH_2)_2$Ph: 94% de = 87% ee = 94%
R = Bn, R' = *i*-Pr: 95% de = 83% ee = 93%
R = Me, R' = Ph: 90% de = 93% ee = 91%

Scheme 60. DKR of 3,5-dialkylcyclopentenones using CuCl as catalyst.

regenerated the Cu-hydride catalyst. Under basic conditions, a rapid racemisation of the starting material should occur. Furthermore, since the product ketone was masked as a silyl enol ether, epimerisation at the α-stereocenter of the desired product would be obviated (Scheme 61).

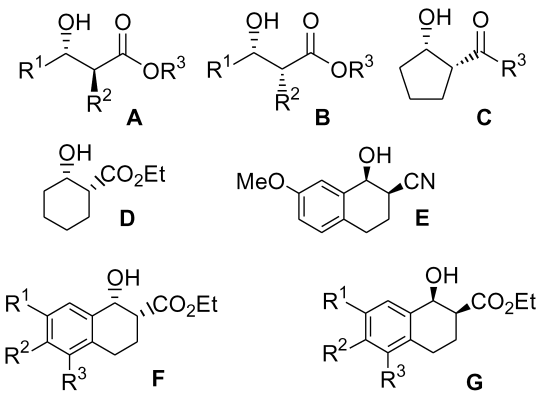


Scheme 61. DKR of 3,5-dialkylcyclopentenones.

3. Enzymatic methods

3.1. Enzymatic reduction reactions via DKR

The reduction of β- and α-ketoesters[65] can be accomplished using baker's yeast or other microorganisms, and a wide range of applications of this methodology have been reported.[66] 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.[67] Figure 5 summarises some products which were obtained in excellent diastereomeric and enantiomeric purity and in acceptable yields via biocatalytic dynamic kinetic reduction of the corresponding racemic α-substituted carbonyl compounds.[68–75] α-Monosubstituted β-oxoesters are excellent substrates and as long as the α-substituent is an alkyl or an aryl group, DKR may easily be achieved. On the other hand, DKR is impossible due to the lack of in situ racemisation for electronic reasons, with α-thioalkyl[76] or α-azido derivatives.[77] The same proviso holds for derivatives which are fully substituted at the *a*-position for obvious reasons. With cyclic β-oxoesters

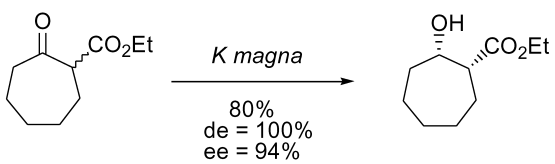


Product	R^1	R^2	R^3	Microorganism	Yield (%)	de (%)	ee (%)	Ref.
A	Me	Me	Et	*Geotrichum candidum*	80	98	98	68
B	Me	Me	Et	*baker's yeast*	94	94	99	69
B	Me	allyl	Et	*baker's yeast*	94	92	99	69
B	Me	Me	n-octyl	*baker's yeast*	82	90	98	70
B	Me	propargyl	Et	*Escherichia coli*	87	-	98	74
B	Me	CH_2NHBz	Et	*Rhodotorula glutinis*	90	84	100	75
C	-	-	SEt	*baker's yeast*	88	100	96	71
D	-	-	-	*baker's yeast*	72-85	99	99	72
E	-	-	-	*Rhizopus arrhizus*	97	98	99	73
F	H	H	H	*Saccharomyces*	95	98	98	73
G	H	H	MeO	*Mucor racemosus*	75	98	99	73

Figure 5. Optically active alcohols obtained by DKR enzymatic reduction.

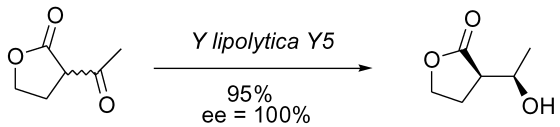
and α-cyanoketones, the formation of the corresponding *cis*-β-hydroxyesters is predominant and the *trans*-products are usually not formed due to steric hindrance.

While good results were previously obtained with 5- or 6-membered ring cyclic β-oxoesters by using baker's yeast, in the case of the larger cyclic β-oxoesters such as 2-carbethoxycycloheptanone, a microorganism such as *Kloekera magna* gave better yields and selectivities (Scheme 62).[78]



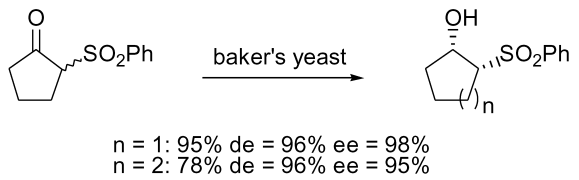
Scheme 62. Microbial reduction of 2-carbethoxycycloheptanone via DKR.

An original reduction via supposed DKR was reported by Medici et al. involving enolisable α-acetoxy-δ-butyrolactone and *Yarrowia lipolytica* as the microorganism (Scheme 63).[79]



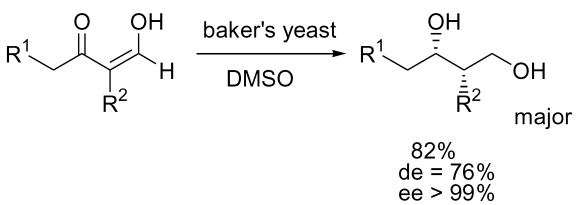
Scheme 63. Microbial reduction of α-acetoxy-δ-butyrolactone via DKR.

In 1999, an efficient DKR in baker's yeast-mediated reductions of 2-benzenesulphonylcycloalkanones was reported. Again, the best results were observed with 5- or 6-membered ring derivatives, whereas the 7- and 8-membered ring compounds showed much less efficiency (Scheme 64).[80]



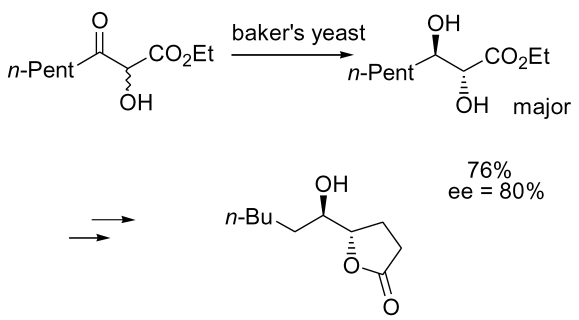
Scheme 64. Reduction of 2-benzenesulphonylcycloalkanones via DKR.

The first baker's yeast reduction of α-substituted β-ketoaldehydes was reported by Shimizu et al. using a sulphur compound such as DMSO as an additive. This reaction allowed an easy access to chiral 2-substituted-1,3-diol derivatives which are useful intermediates (Scheme 65).[81]



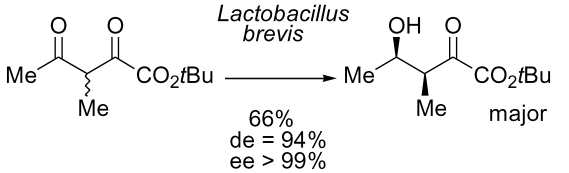
Scheme 65. Baker's yeast reduction of β-ketoaldehydes via DKR.

The key step in a simple approach to chiral *anti*-(4*S*,5*R*)-5-hydroxy-δ-decalactone was based on the baker's yeast reduction of an α-hydroxy-β-ketoester yielding the *anti*-2*R*,3*R*-dihydroxy ester with high selectivities (Scheme 66).[82]



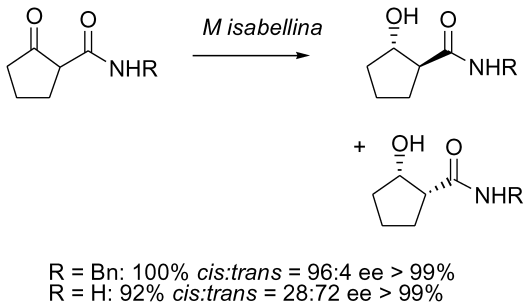
Scheme 66. Synthesis of (4*S*,5*R*)-5-hydroxy-δ-decalactone.

An entirely new method for the DKR of a racemic 2-methyl-substituted unsymmetrical 1,3-diketone via enzymatic reduction was described in 2001 by Müller et al. (Scheme 67).[83]



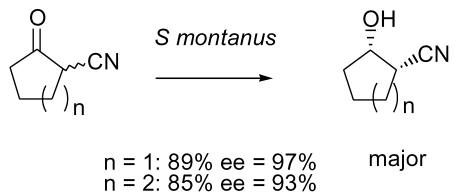
Scheme 67. DKR of *tert*-butyl 4-methyl-3,5-dioxohexanoate.

The fungus *Mortierella isabellina* NRRL 1757 catalysed the reduction of 2-oxocyclopentanecarboxamides with very high selectivities via DKR. The presence or absence of a substituent on the amidic nitrogen had a strong influence on the diastereoselectivity achieved in this process (Scheme 68).[84]



Scheme 68. Reduction of 2-oxocyclopentanecarboxamides via DKR.

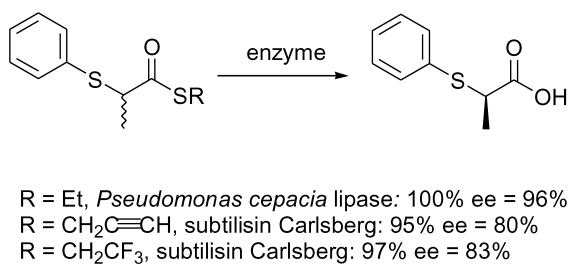
The bioreduction of α-monosubstituted β-ketonitriles has been rarely reported in the literature. In this way, Gotor studied the DKR of 2-oxocycloalkanecarbonitriles by reduction with the yeast *Saccharomyces montanus* (Scheme 69).[85]



Scheme 69. DKR of 2-oxocycloalkanecarbonitriles.

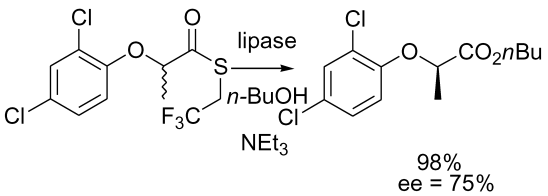
3.2. Enzymatic hydrolysis and esterification reactions via DKR

The α-hydrogens of thioesters are more acidic than those of (non-activated) oxoesters, although the rates of base-catalysed hydrolysis of thioesters and oxoesters are very similar. Although several thioesters have been subjected to enzymatic resolution by lipases, their exceptional α-H-acidity having only recently been exploited for a dynamic resolution process,[86,87] this concept having been verified with several thioesters of α-(phenylthio)propionate (Scheme 70).



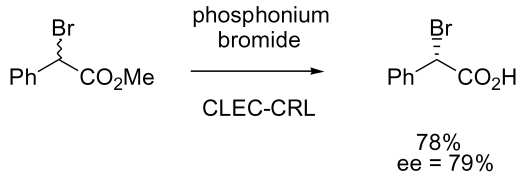
Scheme 70. DKR of thioesters.

A dynamic enzymatic transesterification procedure was also demonstrated in the resolution of the trifluoroethyl thioester of α-(2,4-dichlorophenoxy)propionate (Scheme 71).[87]



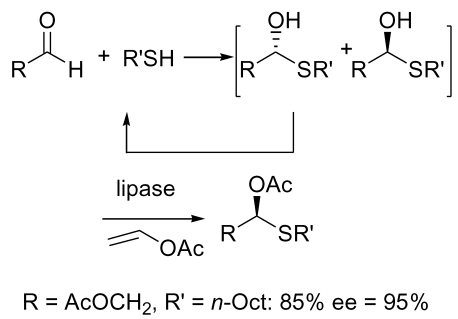
Scheme 71. Transesterification of thioesters via DKR.

Racemisation via S_N2 displacement has been used for the DKR of an α-bromoester by enzymatic hydrolysis.[88] The product, an α-bromoacid, was less reactive in the S_N2 process. Investigations of the bromide source and the lipase employed led to an optimised system where an immobilised phosphonium bromide was used, together with cross-linked enzyme crystals from *Candida rugosa* lipase (CLEC-CRL), to afford the corresponding α-bromocarboxylic acid (Scheme 72). This procedure was extended to the α-chloroesters.



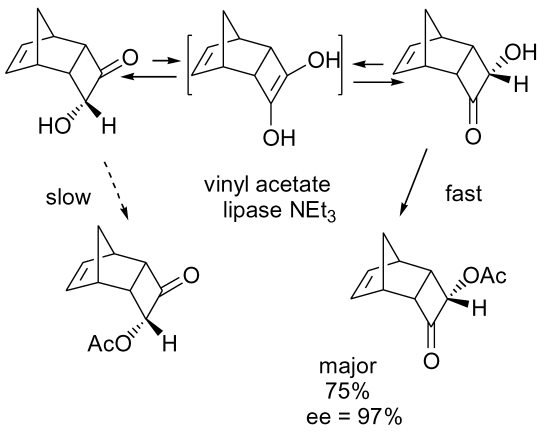
Scheme 72. Hydrolysis of α-bromoesters via DKR.

The resolution of in situ-formed hemithioacetals has been investigated by Brand et al.[89] As shown in Scheme 73, different thiols and aldehydes were mixed together to form racemic hemithioacetals of which essentially a single enantiomer was acylated by *Pseudomonas fluorescens* lipase. Racemisation of the unreactive hemithioacetal isomer was obtained by a dissociation–recombination process catalysed by silica gel.



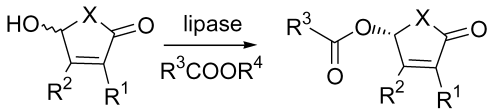
Scheme 73. DKR of in situ-formed hemithioacetals.

In 1997, Ogasawara demonstrated that the tricyclic racemic acyloin *endo*-3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-en-4-one was dynamically acylated with vinyl acetate in an enantiospecific manner via transient *meso*-enediol in the presence of lipase and triethylamine, leading to the corresponding single *endo*-acetate (Scheme 74).[90]



Scheme 74. Transesterification of a tricyclic acyloin via DKR.

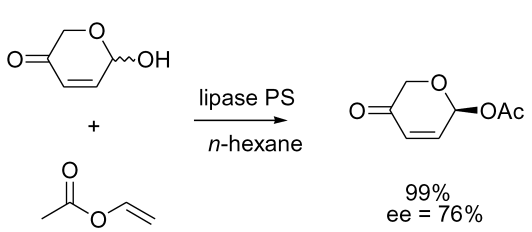
5-Hydroxy-2(5H)-furanones were successfully involved in DKRs with lipase PS offering an attractive route to the enantioselective synthesis of a series of 5-acyloxy-2(5H)-furanones with optimal chiral economy.[91–94] In the same way, the corresponding 5-(acyloxy)pyrrolinones were submitted to esterification using *Candida antarctica* lipase B via DKR (Scheme 75).[92,94]



Lipase	X	R^1	R^2	R^3	R^4	Yield (%)	ee (%)	Ref.
PS	O	H	H	Me	COR^3	90	> 99	92
PS	O	H	H	Me	$CH=CH_2$	70	> 99	93
PS	O	H	H	Et	COR^3	100	83	92
PS	O	Me	Me	Me	$CH=CH_2$	100	78	91
PS	O	Me	H	Me	$CH=CH_2$	100	84	91
PS	O	H	Me	Me	$CH=CH_2$	100	86	91
CA	NAc	H	H	Me	$CH=CH_2$	100	> 99	92,94

Scheme 75. DKR of 5-acyloxy-2(5H)-furanones and 5-(acyloxy)pyrrolinones.

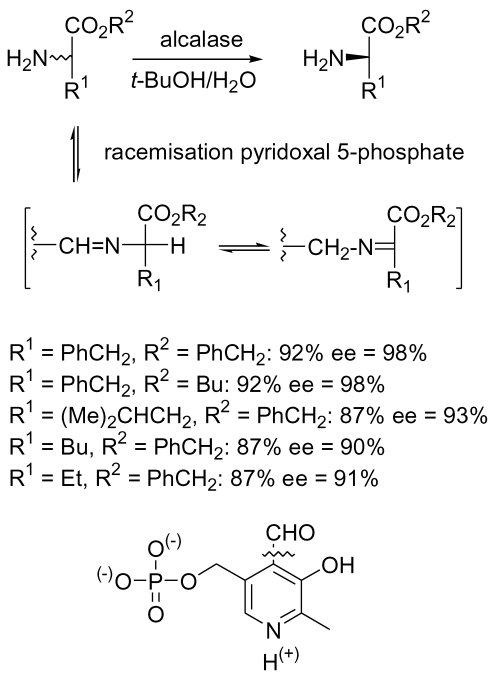
These results were successfully applied to 6-acetyloxy-2*H*-pyran-3(6*H*)-one (Scheme 76).[95]



Scheme 76. DKR of 6-acetyloxy-2*H*-pyran-3(6*H*)-one.

A considerable number of optically pure L-amino acids were prepared by using enzymatic methods. An elegant DKR process for α-amino acids made use of the esterase method, i.e. the enantioselective hydrolysis of α-amino acid esters catalysed by proteases. The remaining unhydrolysed

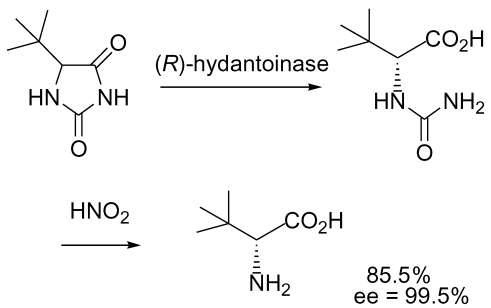
D-enantiomer of the substrate was racemised in situ in the presence of pyridoxal 5-phosphate (Scheme 77).[96]



Scheme 77. Synthesis of L-amino acids via DKR.

The enzyme-catalysed hydrolysis of Schiff bases derived from racemic amino acid esters and aromatic aldehydes was studied by Parmar et al.[97] The L-amino acid precipitated out from the solution as the reaction progressed and the liberated aldehyde and unhydrolysed D-ester remained in solution. The addition of an organic base (DABCO) in the solution resulted in the racemisation of the remaining D-ester and the additional hydrolysis of the substrate, leading to the effective asymmetric transformation of the initial ester (Scheme 78).

Approaches to the synthesis of the non-proteinogenic amino acid *tert*-leucine were made possible by the DKR of racemic 5-*tert*-butyl-hydantoin.[98] The hydantoin racemised in situ and was opened enantioselectively using (*R*)-hydantoinase. Decarbamoylation then yielded the expected (*R*)-*tert*-leucine (Scheme 79).



Scheme 79. Synthesis of (*R*)-*tert*-leucine via DKR.

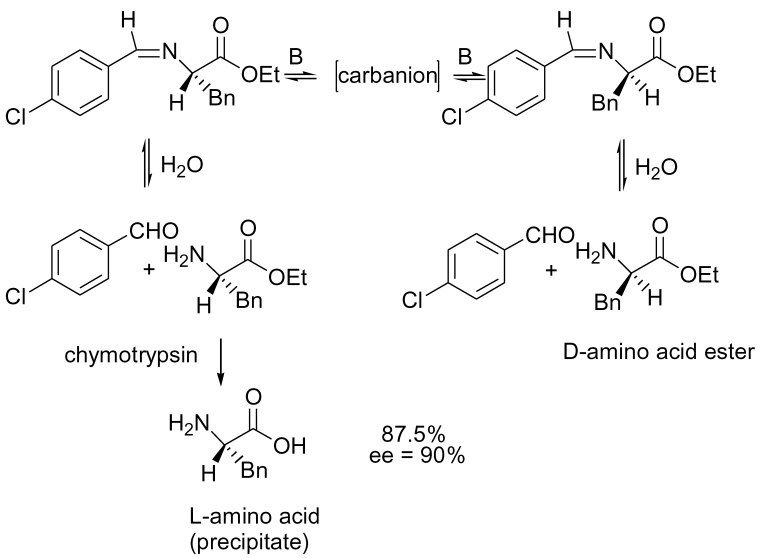
Basic conditions have also been exploited to effect equilibration between DL-hydantoins. Building on these known protocols for hydantoin racemisation, Azerad and Garcia have developed an efficient route to a number of D-phenylglycine derivatives, which are mono- or disubstituted in the aromatic ring (Scheme 80).[99]

A new route to (*R*)-4-benzyloxazolidinone was developed starting from DL-phenylalanine, using the D-hydantoinase-catalysed enantioselective hydrolysis of 5-benzyl-hydantoin under the DKR conditions (Scheme 81).[100]

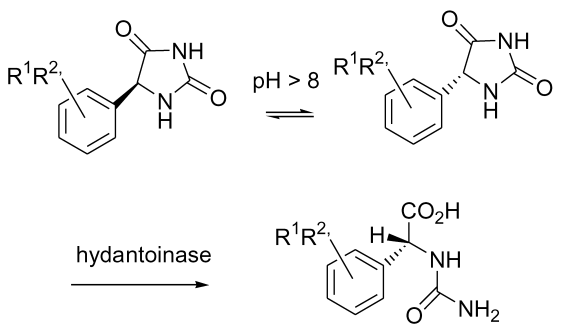
Turner et al. have used lipozyme and novozyme as effective catalysts for the DKR of various racemic 2-phenyl-4-substituted-5(4*H*)-oxazolones in the presence of an alcohol, yielding the optically active *N*-benzoylamino acid esters (Scheme 82).[101,102]

3.3. Other enzymatic reactions via DKR

A new approach to DKR mediated by enzymes was reported

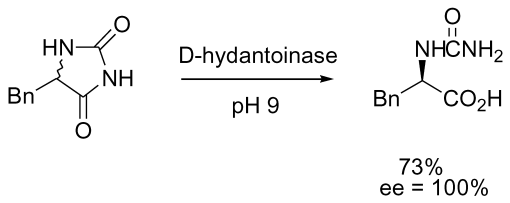


Scheme 78. DKR of Schiff bases of amino acid esters.

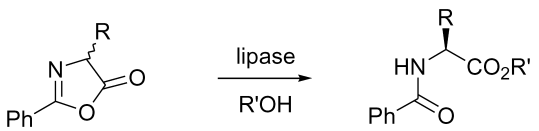


R^1,R^2 = 2-Cl: 65% ee = 99%
R^1,R^2 = 3-Cl: 83% ee = 96%
R^1,R^2 = 3-Me: 79% ee = 99%
R^1,R^2 = 3-OMe: 60% ee = 99%
R^1,R^2 = 3,5-$(OMe)_2$: 63% ee = 97%

Scheme 80. Synthesis of D-phenylglycine derivatives via DKR.



Scheme 81. Hydrolysis of hydantoin derived from DL-phenylalanine via DKR.

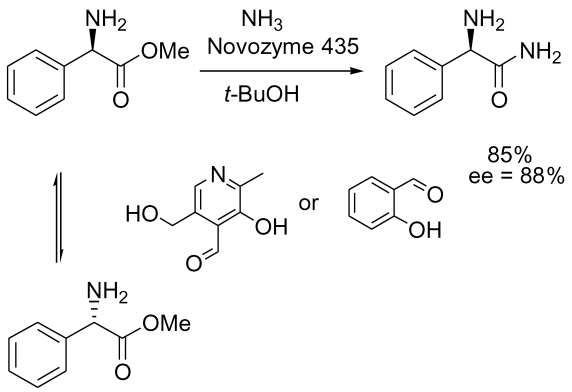


Lipase	R	R'	Yield (%)	ee (%)
Lipozyme + NEt_3	*t*-Bu	*n*-Bu	94	99.5
Novozyme + NEt_3	Bn	*n*-Bu	81	95
Novozyme	Bn	Me	88	98
Novozyme	*i*-Bu	Me	96	97
Novozyme	*i*-Pr	Me	83	97
Novozyme	*indolemethylene*	Me	90	90
Novozyme	$(CH_2)_2SMe$	Me	69	80

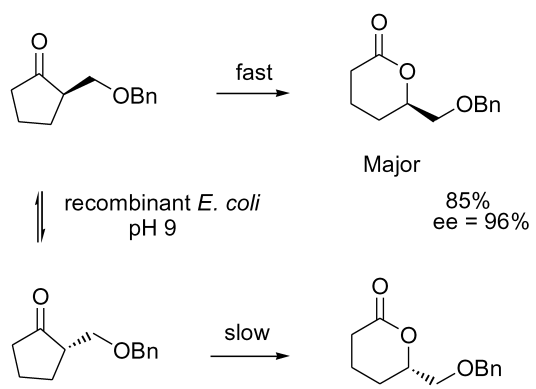
Scheme 82. DKR of 2-phenyl-4-substituted-5(4*H*)-oxazolones.

by Sheldon et al. in the lipase-catalysed ammonolysis of a phenylglycine ester.[103] Thus, the amino acid ester was racemised via Schiff base formation with pyridoxal or salicylaldehyde under the aforementioned ammonolysis conditions (Novozyme 435 in the presence of NH_3) yielding the corresponding D-phenylglycine amide (Scheme 83).

Very recently, Furstoss et al. reported the first example of a DKR process applied to a microbiological Baeyer–Villiger oxidation using a recombinant *E. coli* strain overexpressing the well-known cyclohexanone monooxygenase enzyme.[104] Thus, 2-benzyloxymethylcyclopentanone could be converted to nearly enantiopure (*R*)-6-benzyloxymethyltetrahydropyran-2-one (Scheme 84).



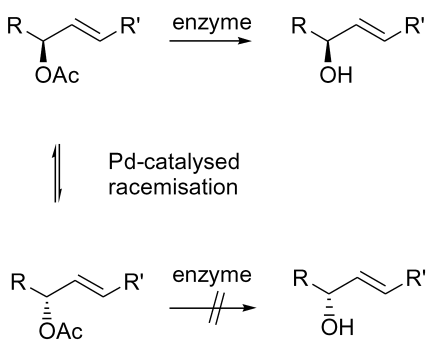
Scheme 83. Lipase-catalysed ammonolysis of a phenylglycine ester via DKR.



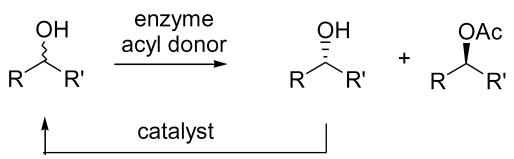
Scheme 84. DKR of 2-benzyloxymethylcyclopentanone using a recombinant *E. coli*.

3.4. Use of transition metals and enzymes in tandem

Williams et al. demonstrated in 1996 the compatibility of enzymes and transition metal complexes. Two examples illustrated the concept: the palladium-catalysed racemisation of an allylic acetate in the presence of a hydrolase[105] (Scheme 85), and the racemisation of a secondary alcohol[106] through Oppenhauer oxidation/



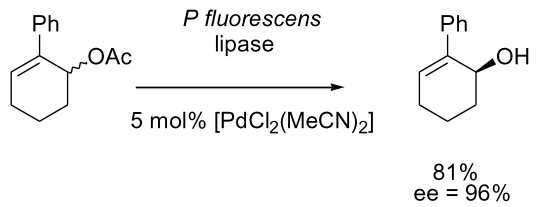
Scheme 85. Pd-catalysed racemisation of a secondary alcohol via DKR.



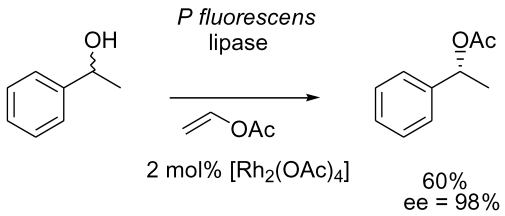
Scheme 86. Racemisation of a secondary alcohol via DKR.

Meerwein–Ponndorf–Verley reduction with concomitant acylation of one enantiomer with a lipase from *Pseudomonas fluorescens* (Scheme 86).

In order to utilise 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. Scheme 87 provides a specific example of the enzymatic hydrolysis outlined in Scheme 85. The substituted allylic acetate was hydrolysed with a lipase from *Pseudomonas fluorescens* in the presence of 5 mol% palladium complex. Scheme 88 depicts a specific example for the racemisation shown in Scheme 86 using a rhodium complex.



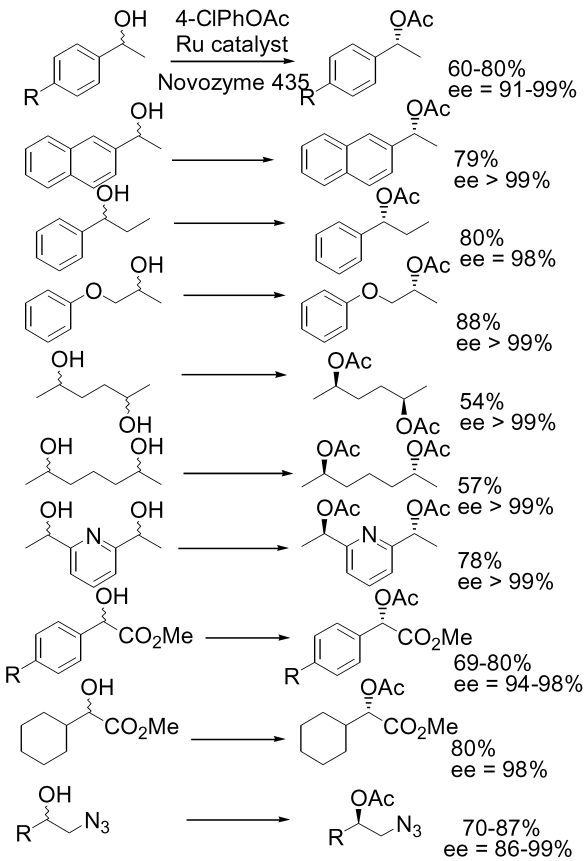
Scheme 87. Specific example for the racemisation shown in Scheme 86.



Scheme 88. Specific example for the racemisation shown in Scheme 87.

Bäckvall et al. have recently reported substantial improvements in this process.[107] A range of 1-phenylethanol derivatives could be synthesised from the racemates in excellent yields and >99% ee by using a binuclear ruthenium complex combined with an immobilised lipase and a specifically designed acyl donor (4-ClPhOAc). A variety of benzylic- and phenoxy-substituted sec-alcohols were resolved under such conditions (Scheme 89). Treatment of *meso*/*dl* mixtures of symmetrical diols in comparable conditions resulted in the enantiomerically pure (*R*,*R*)-diacetates (Scheme 89).[108] The dynamic resolution of α-hydroxycarboxylic acid esters by a similar method has been described recently.[109] A number of ring-substituted (*S*)-*O*-acetylmandelic acid esters were obtained in 70–80% yields and 94–98% ee (Scheme 89). Moreover, the DKR of β-azidoalcohols led to the corresponding enantiomerically pure-β-azidoacetates, providing an efficient route to the chiral aziridines (Scheme 89).[110]

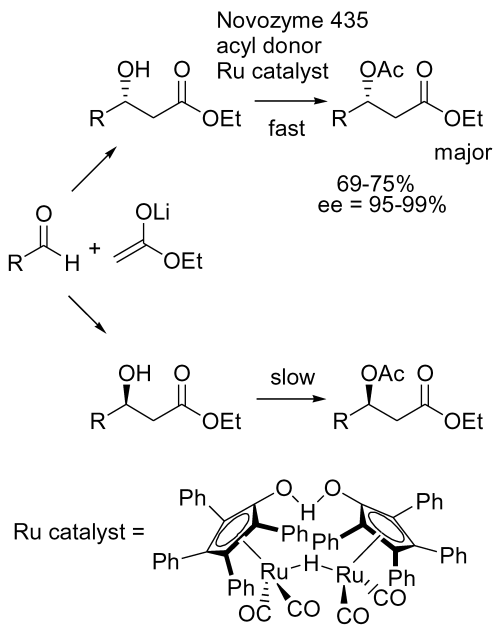
The same methodology has also been applied to the DKR of β-hydroxyesters.[111] The reaction was carried out in tandem with an aldol reaction and the β-hydroxyester formed, after neutralisation, underwent DKR using the immobilised



Scheme 89. DKR of various sec-alcohols by enzymatic transesterification in the presence of a ruthenium complex catalyst.

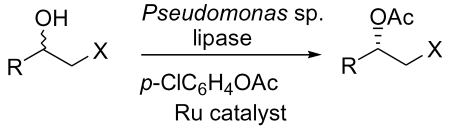
lipase from *Candida antarctica* (Novozyme 435) and a ruthenium catalyst (Scheme 90).

This concept was also extended by Reetz et al. to the resolution of phenylethylamine.[112] In this case, an



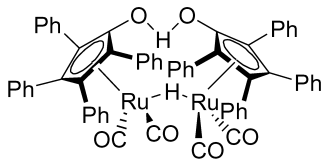
Scheme 90. DKR of β-hydroxyesters using Novozyme 435 and a ruthenium catalyst.

immobilised lipase and ethyl acetate as the acyl donor were used; the non-acylated (*S*)-enantiomer of the amine was racemised in situ by palladium on charcoal and (*R*)-*N*-acetylphenylethylamine was isolated in 64% yield and 99% enantiomeric excess. Very recently, an efficient route to chiral epoxides was reported by Bäckvall et al. based on the DKR of β-haloalcohols (Scheme 91).[113]



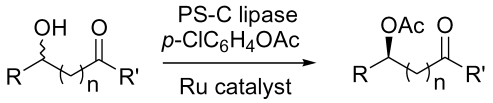
R = *p*-FC_6H_4, X = Cl: 99% ee = 93%
R = Ph, X = Cl: 93% ee = 95%
R = 1-naphthyl-OCH_2, X = Cl: 98% ee = 87%

Ru catalyst =



Scheme 91. DKR of β-haloalcohols.

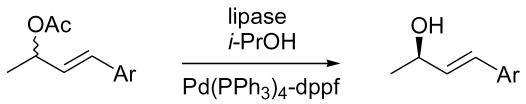
The same authors recently demonstrated that a combination of *Pseudomonas cepacia* lipase and the ruthenium catalyst allowed the DKR of δ- or γ-hydroxyacid derivatives (Scheme 92).[114,115]



n = 2, R = Me, R' = O*t*-Bu: 70% ee = 94%
n = 2, R = Me, R' = N(*i*-Pr)$_2$: 93% ee = 98%
n = 3, R = Me, R' = O*t*-Bu: 89% ee = 98%
n = 3, R = Et, R' = O*t*-Bu: 91% ee = 95%

Scheme 92. DKR of δ- and γ-hydroxyacid derivatives.

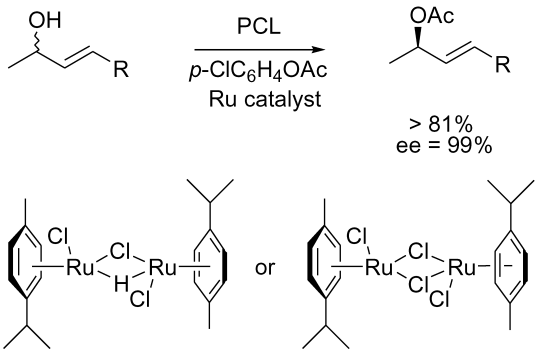
Kim et al. have applied the concept first introduced by Williams (Scheme 87) for the DKR of acyclic allylic acetates (Scheme 93).[116] In this case, a palladium(0) complex racemised allylic acetates via a π-allylpalladium intermediate.



Ar = Ph: 83% ee = 98%
Ar = *p*-ClPh: 77% ee = 97%
Ar = *p*-MePh: 82% ee = 98%
Ar = 1-naphthyl: 70% ee = 98%

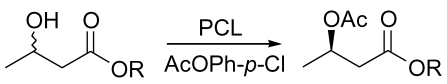
Scheme 93. DKR of acyclic allylic acetates in the presence of a palladium catalyst.

A reverse reaction to that depicted in Scheme 93 was reported by the same authors using ruthenium catalysts, whereas the enzymatic resolution was achieved with PCL using *p*-chlorophenyl acetate as an acyl donor (Scheme 94).[117]

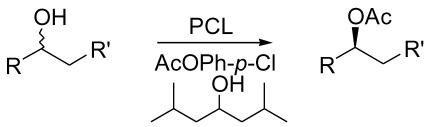


Scheme 94. Esterification of allylic alcohols via DKR.

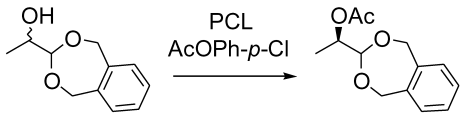
One of the useful strategies for enhancing the enzyme enantioselectivity is the use of structurally modified substrates. In this way, various substrates such as β-hydroxyacids, diols and hydroxyaldehydes were protected with a bulky group and then submitted to lipase/ruthenium-catalysed DKR.[118] In all cases, the reactions provided the products of *R* configuration in good yields and high enantioselectivities (Scheme 95).



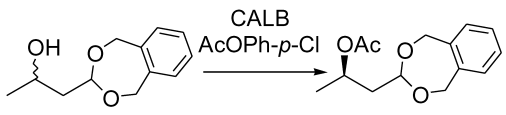
R = Bn: 88% ee = 86%
R = CH_2-*p*-$MeOC_6H_4$: 91% ee = 93%
R = $CH_2C_6H_4$-*p*-C_6H_4: 92% ee = 94%
R = *t*-Bu: 88% ee > 99%



R = Me, R' = OTr: 96% ee > 99%
R = Et, R' = OTr: 91% ee = 99%
R = Me, R' = CH_2OTr: 97% ee = 95%



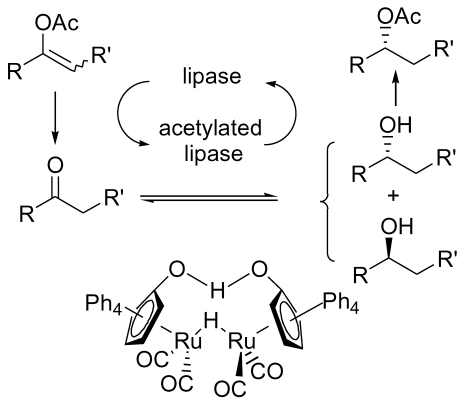
95% ee = 98%



90% ee = 96%

Scheme 95. Lipase/ruthenium-catalysed DKR of substrates bearing a bulky group.

An original concerted catalytic reaction for the conversion of ketones or enol acetates to chiral acetates was developed by Kim and Park.[119] This conversion proceeds through a five-step process, as shown in Scheme 96, which comprises: deacetylation of the enol acetate to give the corresponding enol and the acetylated lipase, keto–enol tautomerisation for the formation of ketone, reduction of the ketone to the



starting from ketones:

R' = H, R = Ph: 97% ee = 98%
R' = H, R = *p*-MeOC$_6$H$_4$: 94% ee = 99%
R' = H, R = *p*-ClC$_6$H$_4$: 97% ee = 99%
R' = H, R = Bn: 82% ee = 90%
R' = H, R = (CH$_2$)$_2$Ph: 100% ee = 99%
R' = H, R = *c*-Hex: 98% ee = 99%
R' = H, R = *c*-Hex: 95% ee = 95%

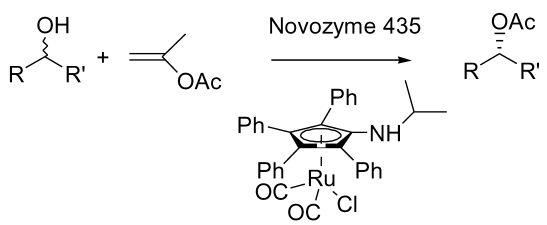
starting from enol acetates:

R = Ph, R' = H: 85% ee = 98%
R = *p*-MeOC$_6$H$_4$, R' = H: 70% ee = 98%
R = *p*-ClC$_6$H$_4$, R' = H: 84% ee = 97%
R = Me, R' = Ph: 89% ee = 79%
R = Me, R' = Bn: 89% ee = 94%
R = Me, R' = *n*-Pent: 89% ee = 91%

Scheme 96. Concerted catalytic reactions for the conversion of enol acetates or ketones to chiral acetates.

racemic mixture of alcohols, enantioselective acetylation of the (*R*)-alcohol with the acetylated lipase to produce the chiral acetate and reversible transformation between the two enantiomeric alcohols.

Finally, a novel ruthenium catalyst was developed involving a new mode of catalytic racemisation allowing the use of more reactive isopropenyl acetate as an acyl donor and much less lipase.[120] This catalytic system was particularly efficient for the DKR of various aliphatic or aromatic alcohols as shown in Scheme 97.



R = Me, R' = Ph: 97% ee > 99%
R = Me, R' = *p*-ClC$_6$H$_4$: 94% ee > 99%
R = Me, R' = *c*-Hex: 86% ee > 99%
R = Me, R' = *n*-Hex: 89% ee = 90.5%

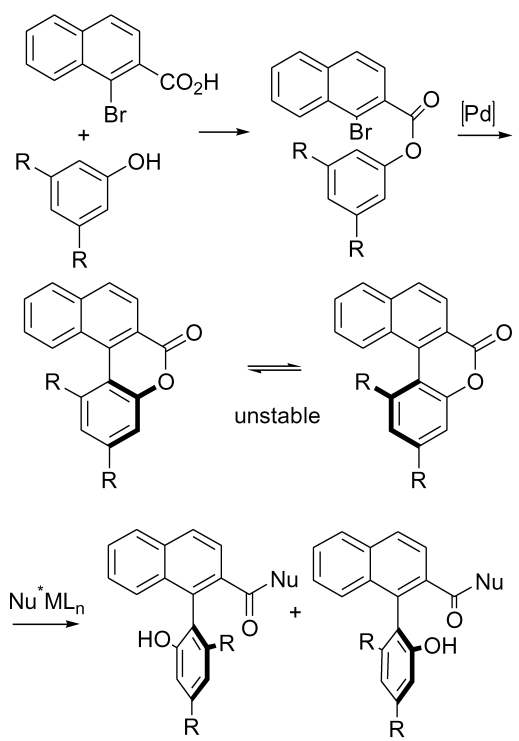
Scheme 97. Aminocyclopentadienylruthenium chloride as a catalyst for the DKR of alcohols.

Other novel ruthenium-based catalytic systems such as [TosN(CH$_2$)$_2$NH$_2$]RuCl(*p*-cymene)/TEMPO, capable of catalysing the in situ racemisation during enzymatic resolution, were recently reported and employed for the same reaction, providing similar results (for 1-phenylethanol: 91% yield and >99% ee were obtained in the presence of Novozyme 435).[121]

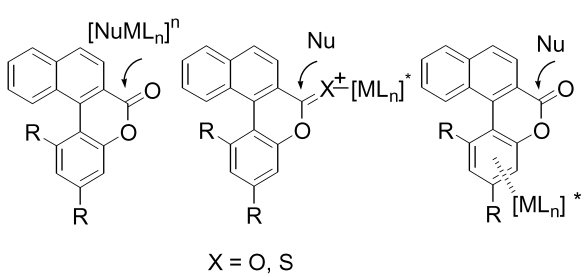
4. Atroposelective reactions

4.1. 'Lactone concept'

Among the few established methods for the atroposelective construction of biaryl systems, the 'lactone concept', introduced by Bringmann et al., holds a unique position since it separates the biaryl bond formation step from the actual introduction of stereo-information. The fundamental concept is shown in Scheme 98. A bromoarene carboxylic acid reacts with a phenol to give the corresponding ester. This array permits the biaryl coupling to occur intramolecularly, even against strong steric hindrance, providing the corresponding lactones which are configurationally unstable. These lactones are the key intermediates in the concept since they can be ring opened with chiral nucleophiles according to the principle of DKR, yielding the now configurationally stable biaryls.[2] The cleavage can



Scheme 98. 'Lactone concept'.

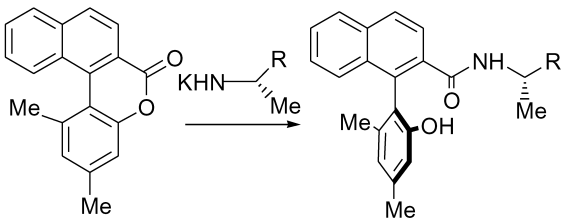


Scheme 99. Three possibilities for the metal-assisted ring opening of biaryl lactones.

be achieved highly atropo-enantio- or -diastereoselectively by the three principal possibilities summarised in Scheme 99, namely by involving a wide range of chiral metallated nucleophiles including metallated amines, alcohols, C-nucleophiles or hydride transfer reagents (see Section 4.2); by using uncharged chiral or achiral nucleophiles after Lewis acid activation of the lactone C═O function (see Section 4.4); or by involving a η^6-coordination of a transition metal fragment to one of the aromatic rings of the biaryl lactone (see Section 4.5).

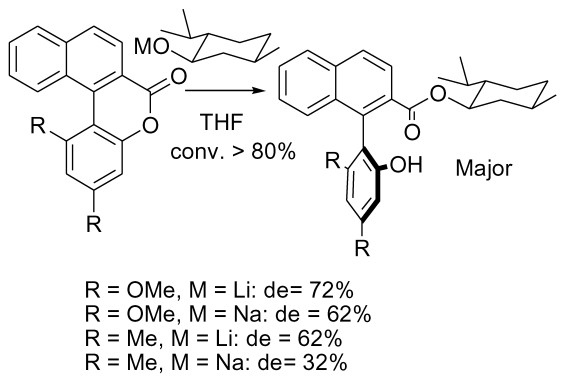
4.2. Atroposelective ring-opening reactions with metallated nucleophiles

Potassium-activated chiral *N*-nucleophiles such as (*S*)-phenylethylamine, (*S*)-1-naphthylethylamine or (*S*)-2,3,4-trimethoxyphenylethylamine were condensed on biaryl lactones, leading to the corresponding biaryl amides in good yields and selectivities (Scheme 100).[122,123]



Scheme 100. Atropo-diastereoselective amidolyses of biaryl lactones.

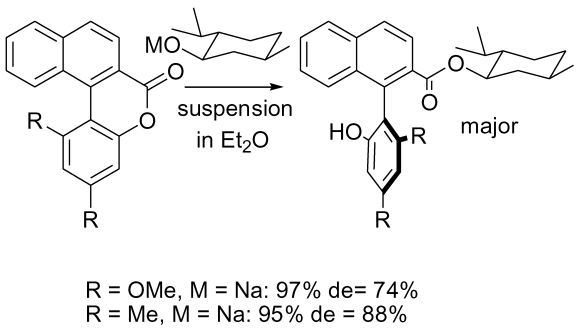
In the same way, chiral *O*-nucleophiles such as alkali menthoxides led to the corresponding esters with good to moderate asymmetric inductions (Scheme 101).[124]



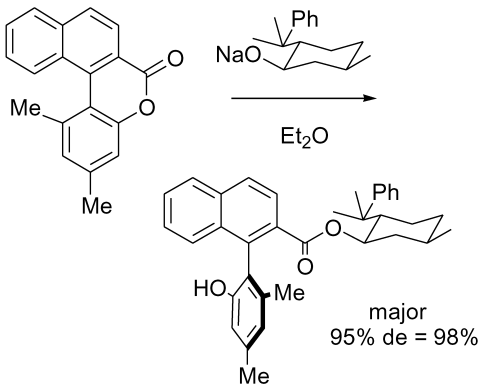
Scheme 101. Alcoholysis of biaryl lactones with metallated (*R*)-menthoxides.

Unexpectedly, when the reaction was carried out in suspension instead of in solution, an inverse asymmetric induction was observed, along with a higher degree of stereo-differentiation (Scheme 102).[124]

The best stereocontrol with *O*-nucleophiles was achieved with sodium (*R*)-8-phenylmenthoxide bearing a bulky dimethylphenyl group, since it gave exclusively and in 95% yield the atropodiastereomer shown in Scheme 103.[124]

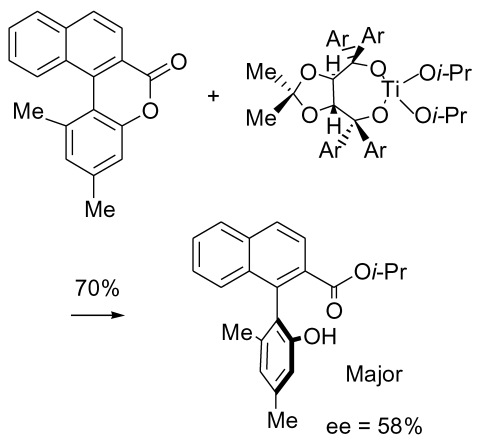


Scheme 102. Alcoholysis of biaryl lactones with sodium (*R*)-menthoxides.



Scheme 103. Alcoholysis of biaryl lactones with sodium (*R*)-8-phenylmenthoxide.

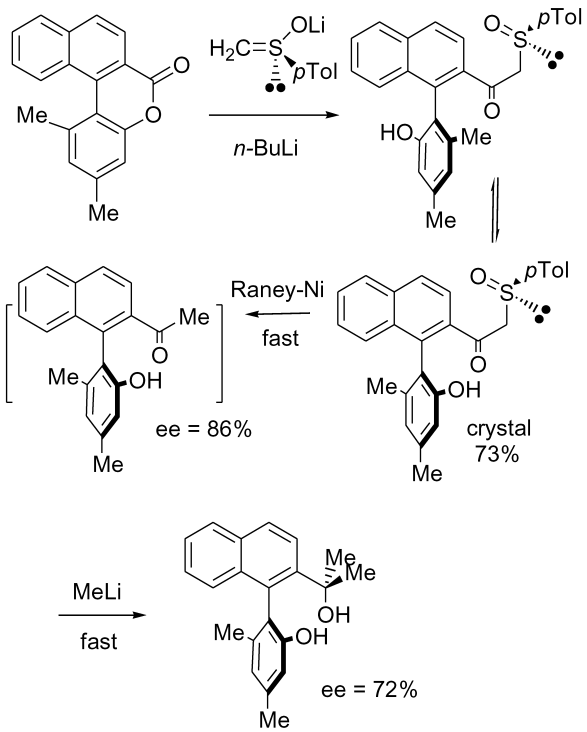
The first successful approach to a directly enantioselective variant of the method was achieved with Seebach's $(i\text{Pr})_2$Ti-TADDOLate, which served both as a chiral Lewis acid and as the *O*-nucleophile (Scheme 104). This Ti complex reacted with biaryl lactones, yielding the corresponding ester with a moderate selectivity.[125]



Scheme 104. Atropo-enantioselective alcoholysis of biaryl lactones with $(i\text{PrO})_2$Ti-TADDOLate.

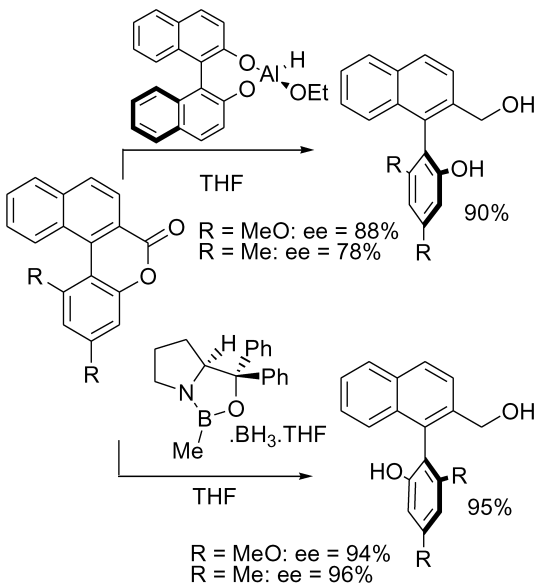
The reaction of biaryl lactones with *C*-nucleophiles was interesting since it allowed an extension of the carbon framework. For the condensation of the chiral lithiated sulphoxide depicted in Scheme 105, a 1:1 mixture of the two diastereomeric β-ketosulphoxides was formed due to the

interconversion of the atropisomers at room temperature. The problem was overcome by converting essentially the entire material of one isomer into the other by fractional crystallisation. Reductive desulphurisation then led to the corresponding configurationally unstable ketone, which was finally converted to the now configurationally stable corresponding alcohol (Scheme 105).[126]



Scheme 105. Condensation of a lithiated sulphoxide on biaryl lactones.

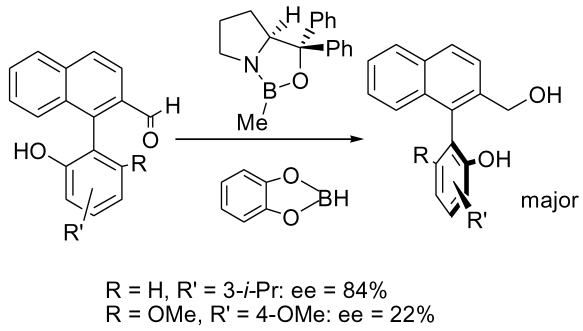
On the other hand, it was possible to cleave the biaryl lactones with chiral hydride transfer reagents such as Noyori's BINAL-H[127] or borane-THF in the presence of Corey's CBS reagent,[128] furnishing the alcohols in excellent yields and selectivities (Scheme 106).



Scheme 106. Reduction of biaryl lactones with BINAL-H and with the CBS reagent.

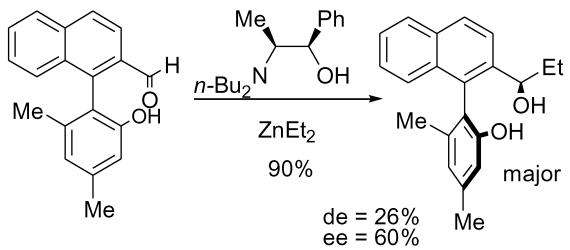
4.3. Application of the lactone concept to biaryl hydroxy aldehydes

The strategy based on the lactone concept is not restricted to biaryl lactones as substrates, but can be applied to other configurationally unstable biaryls such as biaryl hydroxy aldehydes. As an example, the CBS reduction of biaryl hydroxy aldehydes in the presence of a CBS catalyst and catecholborane yielded the corresponding alcohols (Scheme 107).[129]



Scheme 107. CBS reduction of biaryl hydroxy aldehydes.

The first catalytic atropo-enantioselective addition of a *C*-nucleophile such as diethylzinc in the presence of 10 mol% (−)-DBNE to biaryl hydroxy aldehydes was reported by Bringmann et al., providing the corresponding secondary alcohols (Scheme 108).[130]



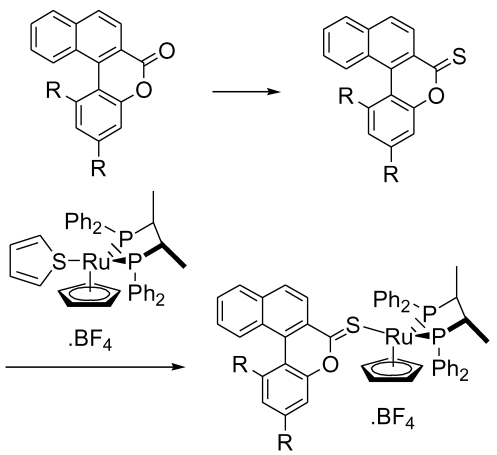
Scheme 108. Catalytic enantioselective addition of Et_2Zn to biaryl hydroxy aldehydes.

4.4. Ring opening of biaryl lactones activated by Lewis acids

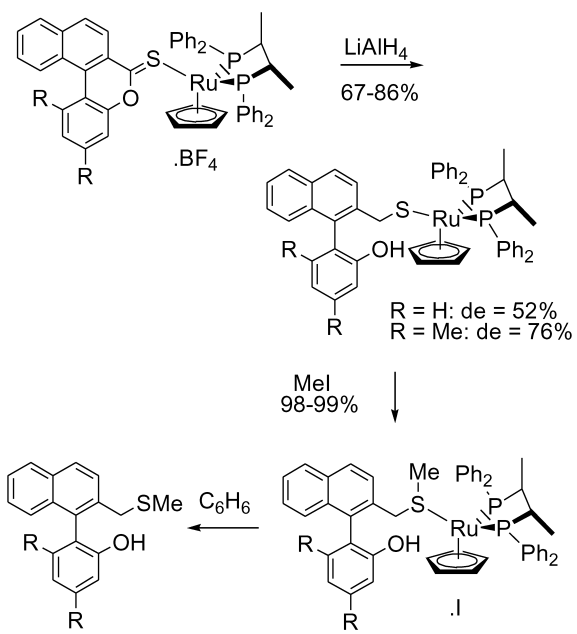
Atropo-diastereoselective ring opening of chiral thionolactone–ruthenium complexes prepared according Scheme 109[131] was investigated.

The 2-fold hydride addition to biaryl-thionolactone complexes followed by decomplexation of the generated rutheniumthiolates yielded the enantiomerically enriched corresponding biaryl thioethers in quite good diastereoselectivities in some cases (Scheme 110).[2b]

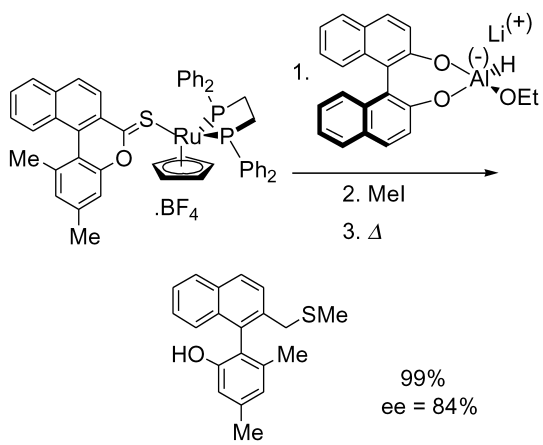
On the other hand, an achiral ruthenium fragment in combination with a chiral hydride source could also be involved. Thus, atropo-enantioselective ring cleavage of achiral thionolactone–ruthenium complexes with chiral *H*-nucleophiles such as BINAL-H provided the corresponding thioether in quantitative yield and excellent enantioselectivity (Scheme 111).[2b]



Scheme 109. Preparation of biaryl-thionolactone–ruthenium complexes.



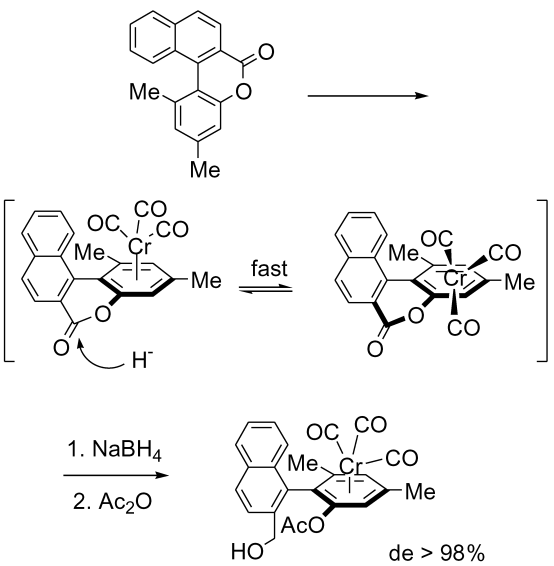
Scheme 110. Two-fold hydride addition to biaryl-thionolactone complexes.



Scheme 111. Enantioselective reductive cleavage of an achiral ruthenium complex with BINAL-H.

4.5. Ring opening of lactones activated by transition metal complexes

The biaryl lactones could also be activated by a η^6-coordination of a transition metal fragment which added an additional element of planar chirality to the system. For instance, coordination of a tricarbonyl chromium unit to the phenolic part of biaryl lactones delivered corresponding η^6-complex. This latter complex was configurationally unstable and existed as a mixture of the two atropodiastereomeric forms. Out of this equilibrium, the ring cleavage with sodium borohydride proceeded highly stereoselectively, yielding the biaryl alcohol *exo*-complex exclusively (Scheme 112).[132]

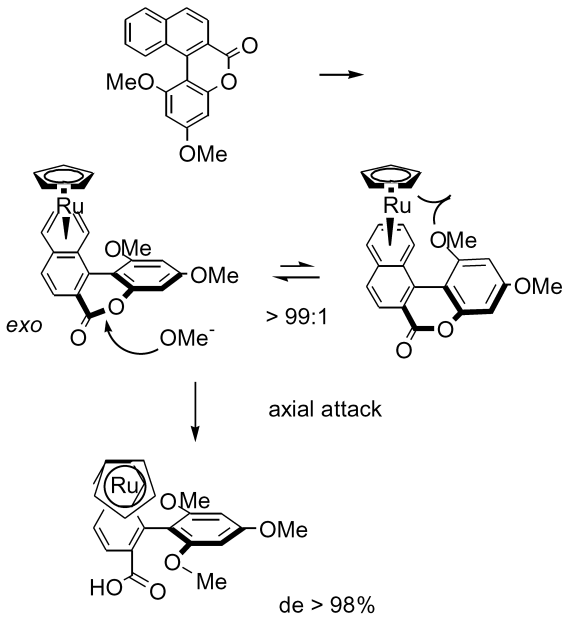


Scheme 112. Atropo-diastereoselective reduction of a η^6-complexed lactone with $NaBH_4$.

On the other hand, the complexation with Cp*-ruthenium implied a better efficiency along with a different regioselectivity.[133] In this case, the η^6-complexation of the biaryl lactones led to the *endo*-complex, with the sterically more-demanding metal fragment now located on the distal naphthalene, i.e. on the more-sterically accessible group. In contrast to the $Cr(CO)_3$ complex of Scheme 112, in which the two atropoisomers were nearly equally populated, the corresponding equilibrium in the RuCp* complex was entirely pushed towards the sterically less-constrained atropo-diastereomer *exo*-complex. Thus, an axial attack of the nucleophile *anti* to the RuCp* fragment took place, leading exclusively to the biaryl ester *exo*-complex (Scheme 113).

4.6. Application to the synthesis of natural products and chiral auxiliaries

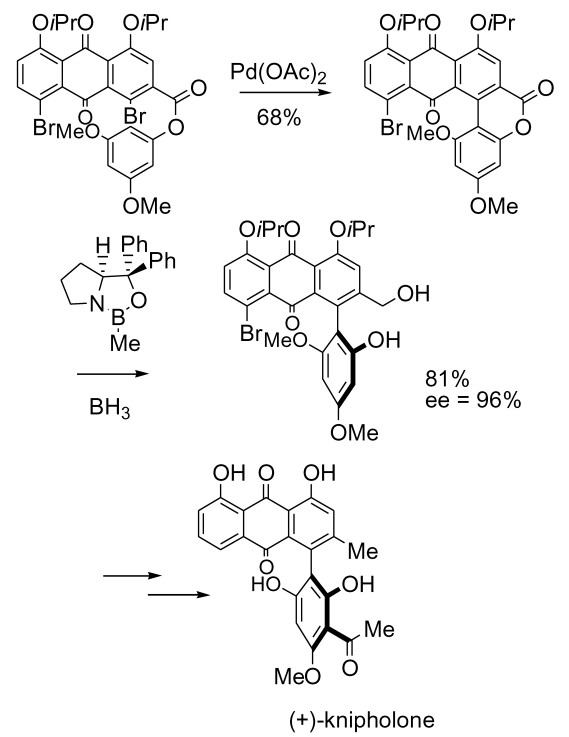
4.6.1. Synthesis of natural products. Besides its conceptual novelty, the most exciting feature of the 'lactone methodology' is its applicability to the stereocontrolled synthesis of a wide variety of target biaryls from quite different classes of natural products,[134] the method allowing the synthesis of naphththylisoquinoline alkaloids, sesquiterpenoid biphenyls like mastigophorenes A and B,



Scheme 113. Ring opening of a racemic *exo* Cp*-ruthenium-complexed lactone with NaOMe.

bicoumarins like isokotanin, biarylic biscarbazoles like bismurrayaquinone-A and phenylanthraquinones like knipholone. Very recently, the AB-biaryl fragment of vancomycin, a glycopeptide antibiotic, was prepared. Furthermore, the method was also applied to the synthesis of natural products without C_1-substituents next to the biaryl axis like dioncophylline C or korupensamine B.

One of the most recent applications of the concept in natural product synthesis was the first and atropo-enantioselective total synthesis of (+)-knipholone, an antimalarial phenylanthraquinone.[135] Against the steric hindrance by the C-10 keto function, the Pd-catalysed intramolecular coupling produced the key intermediate in good yields and without affecting the additional bromo function at C-5. A chemoselective reduction of the lactone function then yielded the corresponding diol, which was further converted into (+)-knipholone (Scheme 114).



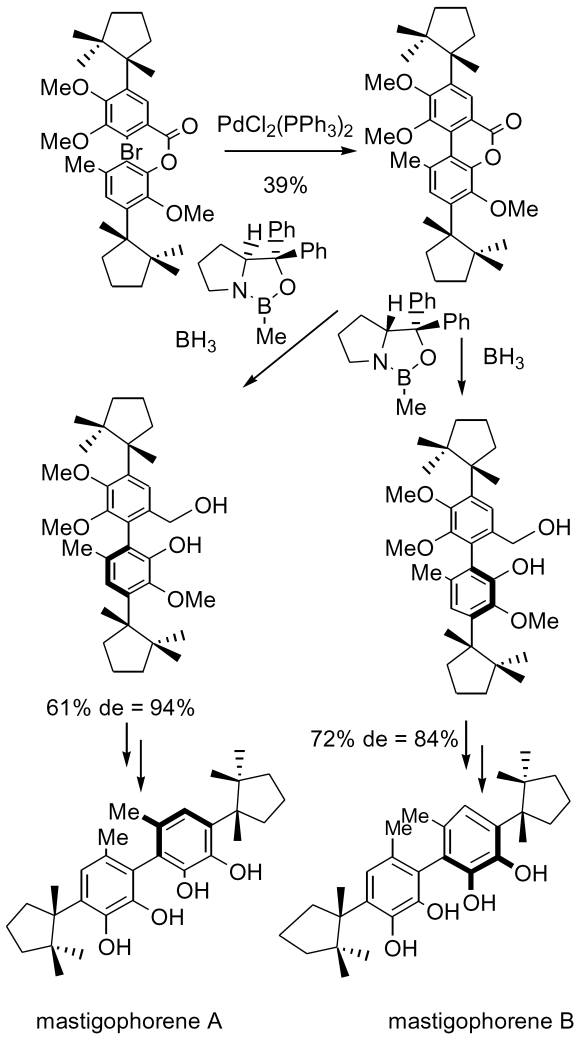
Scheme 114. Total synthesis of (+)-knipholone.

Mastigophorenes have attracted interest for their nerve growth-stimulating activity, triggering numerous synthetic efforts. In this way, Bringmann et al. reported a stereoselective total synthesis of these compounds based on the same methodology (Scheme 115).[136]

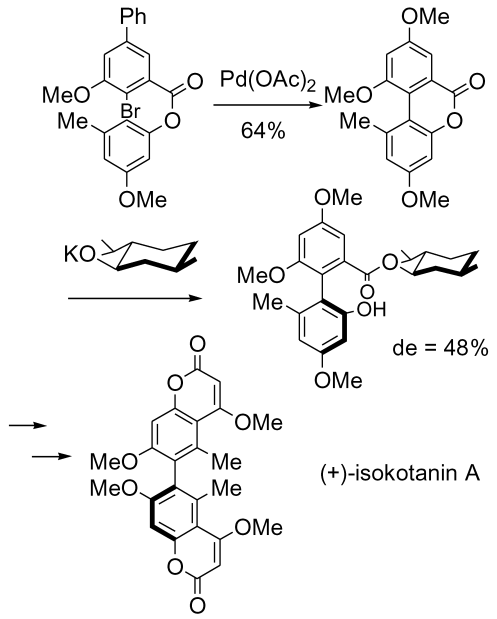
Using the same concept, the biaryl portion of isokotanin A was prepared.[137] In this case, the atropisomer-selective ring cleavage reaction was achieved by using an *O*-nucleophile such as potassium (1*R*)-mentholate (Scheme 116).

Alkali mentholates were also involved in the first stereoselective synthesis of bismurrayaquinone A, an axially chiral biscarbazole alkaloid (Scheme 117).[138]

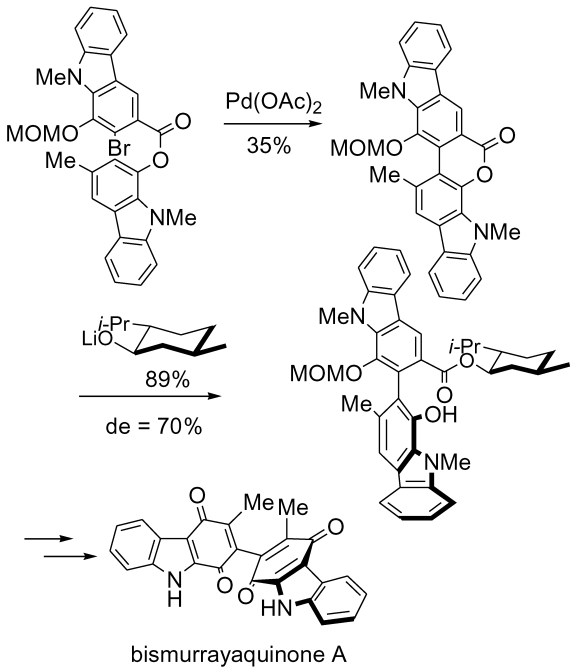
Naphthylisoquinoline alkaloids show interesting bioactivities, including strong antimalarial and antileishmanial



Scheme 115. Synthesis of mastigophorenes A and B.



Scheme 116. Synthesis of isokotanin A.

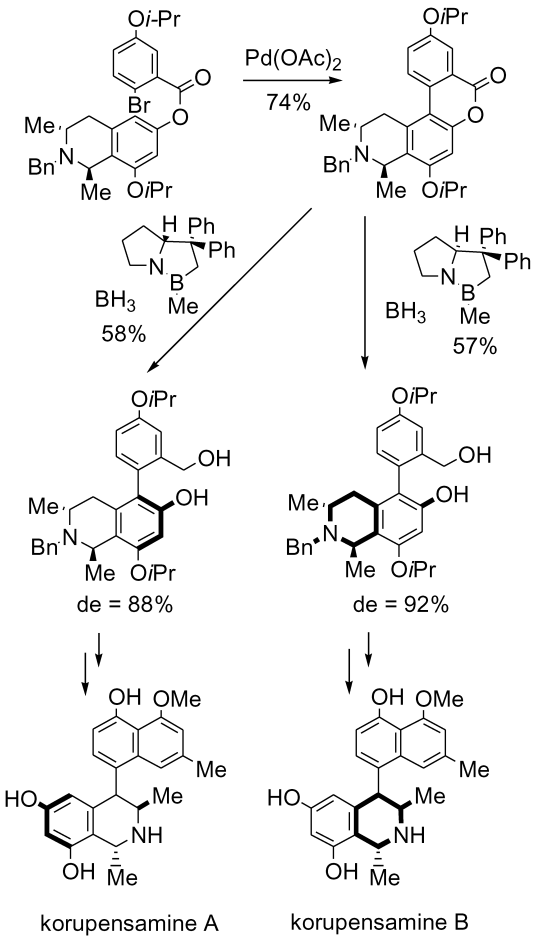


Scheme 117. Synthesis of bismurrayaquinone A.

properties. Some of their dimers also exhibit high anti-HIV activities. The lactone concept allowed an efficient synthetic access to this class of alkaloids such as korupensamines A and B (Scheme 118),[139] but also to ancistrocladine,[140] dioncophylline[141] and further naphthylisoquinoline alkaloids.[142]

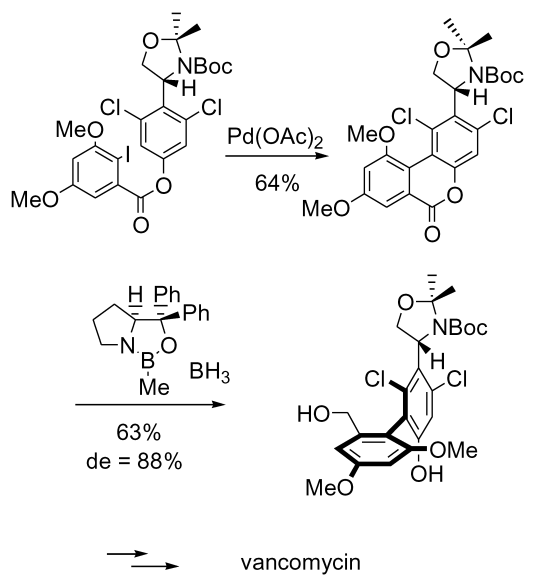
Very recently, Bringmann et al. reported a highly stereoselective approach to the AB-biaryl fragment of vancomycin, a glycopeptide antibiotic (Scheme 119).[143]

4.6.2. Synthesis of axially chiral reagents. A most rewarding advantage of the lactone methodology is that it

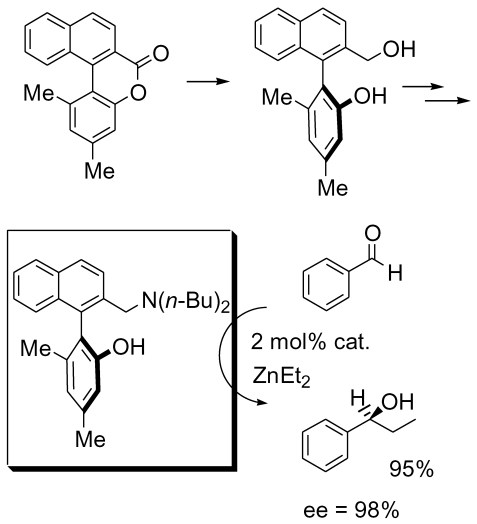


Scheme 118. Synthesis of korupensamines A and B.

gives rise to constitutionally symmetric and -unsymmetric biaryls and therefore also to promising novel non C_2-symmetric reagents and ligands for asymmetric synthesis. In one example, bidentate ligands bearing both *N*- and *O*-functionalities (Scheme 120) were easily prepared in stereochemically pure forms by enantioselective ring cleavage of a standard lactone, followed by subsequent



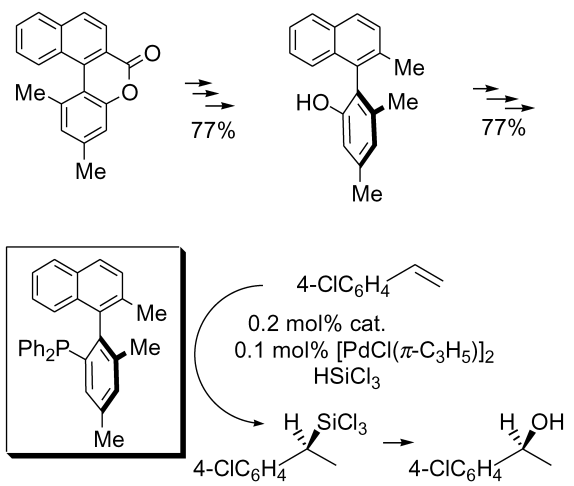
Scheme 119. Atroposelective approach to vancomycin.



Scheme 120. Synthesis and application of novel *N*,*O*-ligands.

introduction of the amino function onto the intermediate diols. These chiral ligands efficiently catalysed diethylzinc additions to various aldehydes.[144]

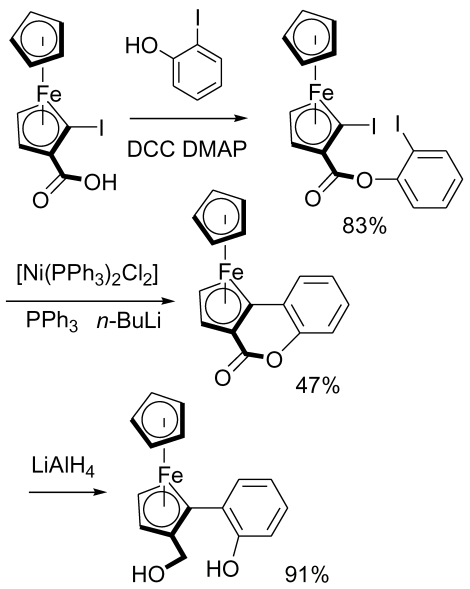
The lactone concept also allowed an easy access to monodentate phosphine ligands with sterically hindered biaryl axes which catalysed the asymmetric hydrosilylation of styrenes in the presence of palladium (Scheme 121).[145]



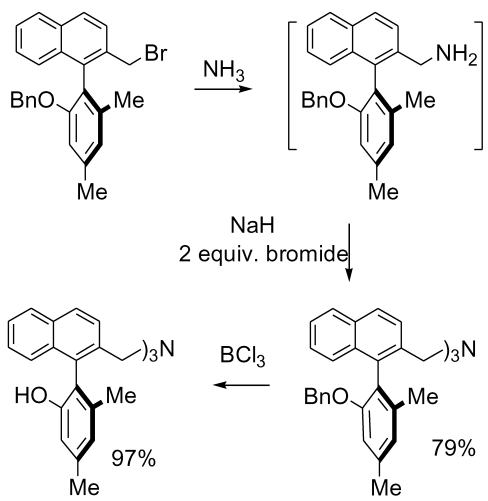
Scheme 121. Synthesis and application of monodentate phosphine ligands.

In 2001, the synthesis of novel ferrocenyl ligands combining a chiral ferrocene unit with an axially chiral biaryl moiety was described (Scheme 122).[146]

The same author also developed the synthesis of 3-fold axially chiral tripodal ligands, since virtually no studies have been reported on the combination of C_3-symmetry and axial chirality (Scheme 123).[134] The first step was the reaction between a chiral bromide with liquid ammonia giving the corresponding primary amine, which was further alkylated in situ with two additional equivalents of the chiral bromide. A final deprotection with BCl_3 furnished the required tripodal ligand, the biarylic portions of which form a cavity capable of incorporating oxophilic Lewis acidic elements.



Scheme 122. Synthesis of aryl-ferrocenyl ligands.

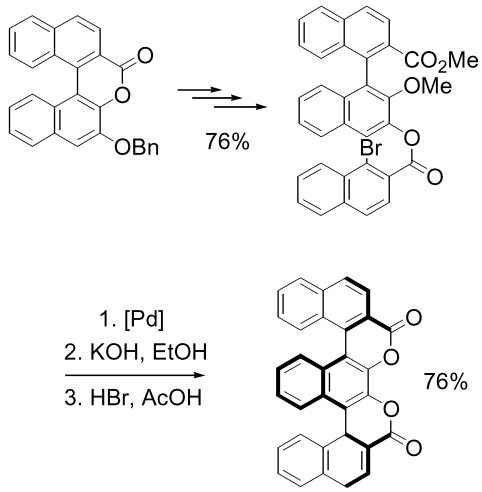


Scheme 123. Synthesis of axially chiral tripod ligands.

Finally, the lactone concept was extended to the synthesis of 2-fold lactone-bridged teraryls which may be suitable precursors for the formation of C_2-symmetric teraryls. The synthesis was accomplished by palladium-catalysed intramolecular coupling, with subsequent ester saponification, methyl ether cleavage and 2-fold ring closure to give the expected bislactone (Scheme 124).[147]

5. Conclusions

This review hightlights and updates the principal techniques used to obtain DKR by either enzymatic or non-enzymatic methods and illustrates the diversity of useful products that can be obtained through this concept. Unlike its predecessors, this review includes the atroposelective reactions recently reported by Bringmann and their application in the synthesis of natural products and chiral auxiliaries. The



Scheme 124. Synthesis of a novel ternaphthyl bislactone.

resolution of stereoisomers has always been a reliable method of obtaining enantiomerically pure compounds, but the fundamental limitation of yield has made it thoroughly unfashionable. The use of DKRs seems to be increasing and it would appear that these strategies become serious alternatives to conventional methods for asymmetric synthesis.

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Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K. P. C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.