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Kinetic resolution strategies using non-enzymatic catalysts

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Abstract—Recent advances in the use of non-enzymatic chiral catalysts for the kinetic resolution or dynamic kinetic resolution of racemic substrates are described. Successful protocols that afford recovered starting material or products in high enantiomeric excess are included, and mechanistic detail is discussed where appropriate. Relevant examples illustrate the wide range of different reaction scenarios where kinetic resolution has recently been employed as a strategy for the efficient synthesis of enantiopure compounds.

Contents

1. Introduction

The development of low molecular weight chiral catalysts for asymmetric synthesis has been one of the major breakthroughs in organic synthesis over the last 30 years. Within this context, a significant number of enantioselective catalysts are now available that afford excellent levels of stereocontrol that could only previously be achieved using biocatalysts. Whilst the use of enzymes for the kinetic resolution of racemic substrates to afford enantiopure compounds in high e.e. and good yields has emerged as a popular strategy in synthesis,[1] it is only relatively recently that the widespread application of non-enzymatic chiral catalysts for kinetic resolution[2] (or dynamic kinetic resolution[3]) has gained popularity within the synthetic community. Major developments using non-enzymatic catalysts for kinetic resolution prior to 2000 have been extensively reported,[4] and consequently it is the intention of this review to document comprehensively major developments within this fast moving area over the last three years.[5] No attempts have been made to discuss the fundamental principles associated with kinetic resolution strategies, since these concepts have been dealt with in great detail elsewhere.[6] We have confined ourselves to those reports that employ sub-stoichiometric amounts of catalyst or chiral ligand for kinetic resolution, and consequently do not include those protocols that require stoichiometric quantities of chiral ligand or chiral reagent for stereocontrol.[7] Neither, do we discuss recent developments in chemo-enzymatic strategies that employ biocatalysts for enantioselective catalysis in the presence of metal-catalysed racemisation processes to afford elegant dynamic kinetic resolution protocols.[8] Since it is our intention to not only describe the range of enantioselective catalysts that have been applied for resolution, but also to provide a synthetic perspective on how widely this methodology has been adopted as a tool for the preparation of enantiopure compounds, we have

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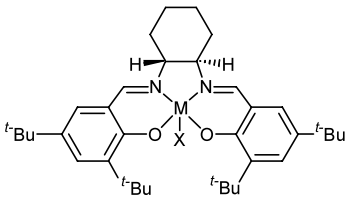


Figure 1. Salen complexes **1**–**4** used for HKR of terminal (*rac*)-epoxides.

concentrated primarily on reports that afford recovered starting materials or products in both high e.e. and in good yield.

2. Hydrolytic kinetic resolution of terminal racemic epoxides

Numerous reports have appeared over the last three years describing the use of Jacobsen's chiral (salen)–Co^{III} or –Cr^{III} complexes **1**–**4** (Fig. 1) for the stereoselective hydrolytic kinetic resolution (HKR) of terminal racemic epoxides.[9] HKR, using water as a nucleophile has been shown to be effective for the resolution of a wide range of racemic terminal epoxides, often affording both epoxides and their corresponding 1,2-diols in very high e.e. For example, HKR of racemic propylene oxide in the presence of 0.55 equiv. of water using only 0.2 mol% of salen catalyst (*R*,*R*)-**1**, affords recovered (*R*)-epoxide in >99% e.e. and in 46% yield (maximum 50%) after 18 h.[9] This approach has been applied to the kinetic resolution of a wide range of alkyl-, halo alkyl-, aryl-, vinyl- and alkynyl-racemic epoxides,[9] and has recently been extended to epoxides containing ω-sulfone,[10] and ω-diethyl phosphonate[11] functionalities, all of which afforded chiral epoxides in $\geq$93% e.e. (Fig. 2).

Unsurprisingly, the generality and broad substrate specificity of HKR has been exploited for the production of a wide range of chiral synthons for natural product synthesis, including recent strategies directed towards the synthesis of Epothilone A,[12] Laulimalide,[13] Fostriecin[14], Arachadonic acid metabolites,[15] (–)-Pyrenophorin,[16] Carquinostatin A[17] Bryostatins,[18] Ulapualide,[19] (–)-Mycalolide,[20] α,α-difluoroalkylphosphonate analogues of (Lyso)phosphatidic acid[21] and bicyclic lactones from parasitic wasps.[22] HKR has also been used for the production of a homochiral epoxide for the enantioselective synthesis of a chiral pyrrolidin-2-one for the treatment of hypertension and arrhythmia.[23] The use and range of chiral epoxides resolved in these natural product syntheses clearly stands as testament to the true power of HKR as *routine* methodology for stereoselective organic synthesis (Fig. 3).

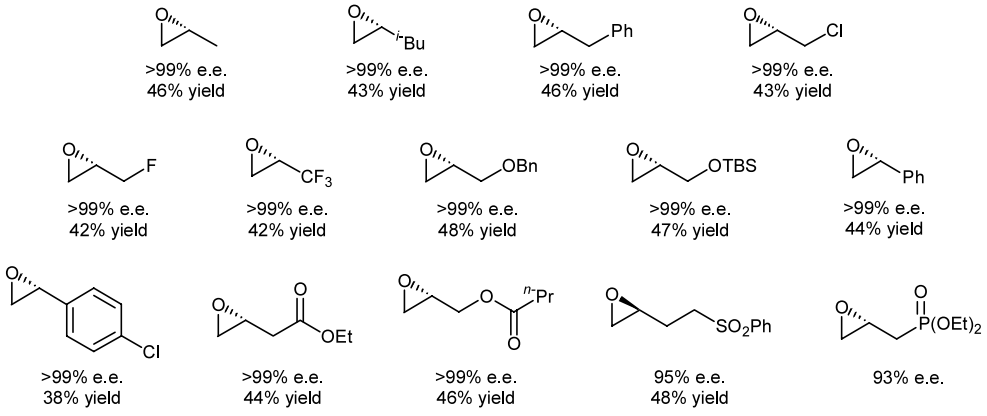


Figure 2. A representative range of (*rac*)-epoxides resolved using salen complexes (*R*,*R*)-**1** or (*S*,*S*)-**1**.

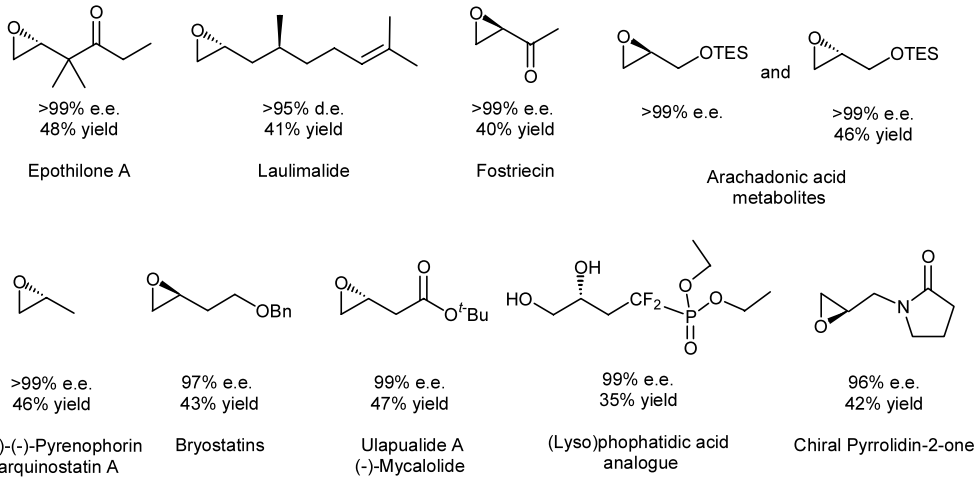


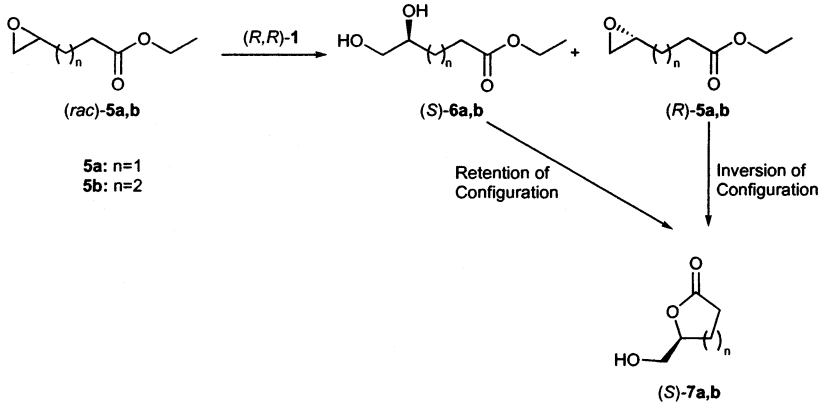
Figure 3. Range of chiral epoxides and diols resolved using HKR as synthons for natural product synthesis.

Liu et al. have demonstrated that judicious choice of substrate enables HKR to be compatible with enantioconvergent synthetic protocols in which both enantiomers of a racemic epoxide are converted to the same enantiopure product.[24] Thus, HKR of epoxide (*rac*)-**5a** under standard conditions afforded unreacted epoxide (*R*)-**5a** in 45% yield, and diol (*S*)-**6a** which cyclised in situ to afford δ-lactone (*S*)-**7a** in 94% e.e. and 50% yield. Subsequent treatment of recovered epoxide (*R*)-**5a** with aqueous TFA resulted in epoxide ring opening with inversion of configuration, followed by spontaneous cyclisation, to once again afford lactone (*S*)-**7a** in 96% e.e. and 44% yield (Scheme 1).

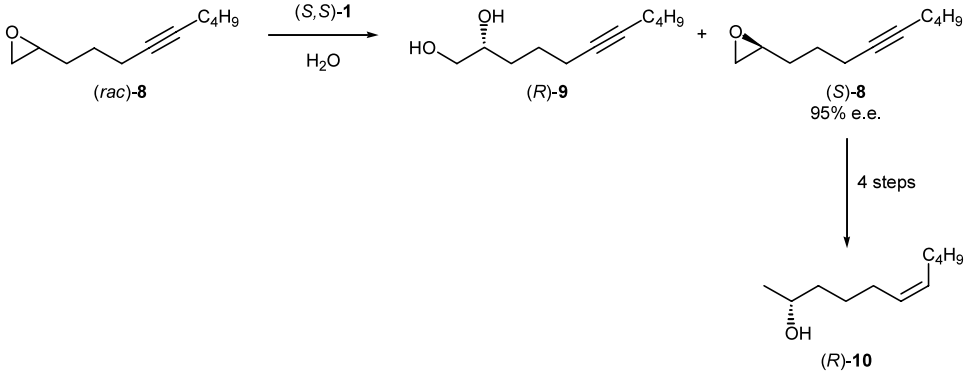
The HKR of mono- and bis-epoxides catalysed by catalyst (*S*,*S*)-**1** has also been used as the key step in the synthesis of a range of insect pheromones, demonstrating that structurally more complex racemic epoxides respond equally well to these procedures.[25] A representative example is the HKR of mono-epoxide (*rac*)-**8** for the synthesis of a pheromone of ant-lions, nostrenol (*R*)-**10**. The HKR of epoxide (*rac*)-**8** using (*S*,*S*)-**1** and 0.55 equiv. of H_2O furnished (*S*)-**8** in 95% e.e. (and (*R*)-**9**) which was converted to nostrenol (*R*)-**10** over four steps (Scheme 2).

The HKR of a diastereoisomeric mixture of bis-epoxides containing (*meso*)-**11** and bis-epoxide (*rac*)-**12** with (*R*,*R*)-**1** and 0.8 equiv. of water produced bis-epoxide (*R*,*R*)-**12**, epoxydiol (2*R*,8*S*)-**13** and tetrol (*S*,*S*)-**14** in 24, 46 and 15% yields, respectively. This approach therefore employs catalyst (*R*,*R*)-**1** for the simultaneous enantioselective desymmetrisation of *meso*-**11** and the kinetic resolution of (*rac*)-**12**, thus affording useful quantities of epoxydiol (2*R*,8*S*)-**13** which was subsequently transformed into 1,7-dimethylnonyl propanoate (*R*,*R*)-**15** (the sex pheromone of the female western corn rootworm) in seven steps (Scheme 3).[26]

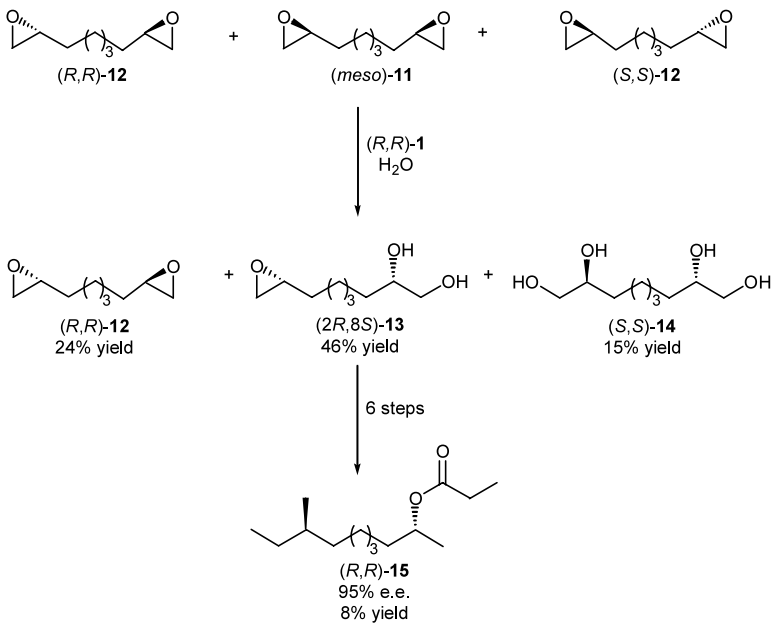
The potential of salen catalysts to 'resolve' mixtures of diastereoisomeric terminal epoxides (2*S*)-**16** and (2*R*)-**17** has been further demonstrated for the synthesis of diastereoisomers of aminohydroxyiminocarane (2*R*)-**19** and (2*S*)-**20** both of which exhibit localised anaesthetic activity. This approach involved treatment of diastereoisomeric epoxyiminocarene (2*S*)-**16** and (2*R*)-**17** with (salen)CoOAc (*R*,*R*)-**1** under standard HKR conditions to yield epoxide (2*R*)-**17** (>99% e.e.) and diol (2*S*)-**18** (>97% e.e.), respectively. Separation and subsequent synthetic manipulation of (2*R*)-**17** or (2*S*)-**18** using *iso*-propylamine as a nucleophile resulted in their stereoselective conversion into either



Scheme 1. Enantioconvergent transformation of (*rac*)-**5a**,**b** into γ- and δ-lactones (*S*)-**7a** and (*S*)-**7b** via HKR.



Scheme 2. Synthesis of nostrenol (*R*)-**10** via HKR.

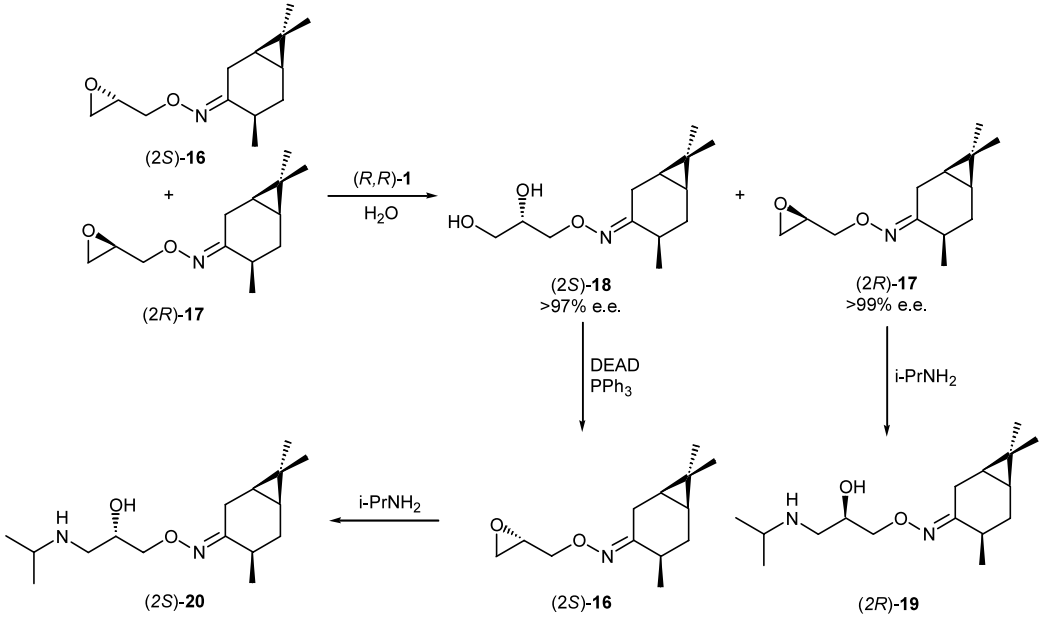


Scheme 3. Synthesis of the sex pheromone of the female western corn rootworm (*R*,*R*)-**15** via HKR.

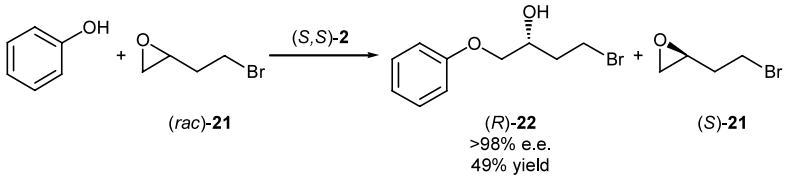
diastereoisomer of aminohydroxyiminocarane (2*R*)-**19** and (2*S*)-**20**, respectively (Scheme 4).[27]

Salen catalysts may also be employed for the ring opening of racemic epoxides using a variety of other nucleophiles, such as phenol, or azide.[28] For example, treatment of epoxide (*rac*)-**21** with 0.5 equiv. of phenol in the presence of catalyst (*S*,*S*)-**2** produced (*R*)-**22** in >98% e.e. in near quantitative yield (with respect to phenol), which was then used for the synthesis of a Prostaglandin $F_{1\alpha}$ analogue (Scheme 5).[29]

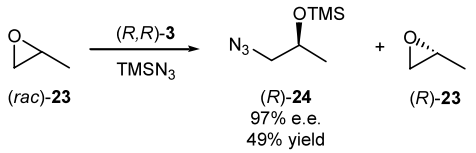
A representative example of the kinetic resolution of terminal racemic epoxides via enantioselective ring



Scheme 4. Synthesis of either diastereoisomer of aminohydroxyiminocarane (2*R*)-**19**/(2*S*)-**20** via HKR.



Scheme 5. Synthesis of Prostaglandin $F_{1\alpha}$ precursor (*R*)-**22** via HKR using phenol as a nucleophile.



Scheme 6. Kinetic resolution of propylene oxide (*rac*)-**23** with $TMSN_3$.

opening with $TMSN_3$ is described in Scheme 6, involving treatment of propylene oxide (*rac*)-**23** with 0.5 equiv. of $TMSN_3$ in the presence of (*R*,*R*)-**3** (1 mol%) which resulted in essentially quantitative conversion to a mixture of ring opened product (*R*)-**24** and epoxide (*R*)-**23** after 18 h at 0°C. The unreacted volatile epoxide was removed in vacuo leaving 1-azido-2-trimethyl-siloxypropane (*R*)-**24** in 97% e.e. and 49% yield. A representative range of ring-opened products that can be prepared in high e.e. using this variant of HKR methodology are shown in Fig. 4.[28] From a mechanistic perspective, it has been reported that HKR epoxide ring opening reactions using salen catalysts exhibit a second-order kinetic dependence on the catalyst, and that these resolutions also demonstrate non-linear effects when scalemic salen ligands are used for catalysis.[28,30] In order to explain these observations it has been proposed that one metal–salen complex acts as a Lewis acid to activate the epoxide towards ring opening, whilst another metal–salen complex serves to deliver the incipient nucleophile (Fig. 5). Consequently, it was proposed that catalysts derived from cyclic ligands that contained more than one metal centre in close proximity to each other might display enhanced reactivity relative to conventional monomeric salen catalyst systems. Thus, a range of oligomeric (salen)Co complexes **25** and **26** (Fig. 6) were prepared and shown to be highly effective catalysts for the asymmetric ring opening of epoxides, affording catalytic systems with higher enantioselectivities, and reactivities than those observed for monomeric catalyst (*R*,*R*)-**4** (Table 1). For example, cyclic oligosalen catalyst **25**, which exists as a complicated mixture of diastereoisomeric oligomers of varying ring size ($n=1$–5), was found to catalyse the HKR of various terminal epoxides (*rac*)-**28a**–**e** with a range of alcohols **27a**–**e** as nucleophiles to afford ring opened products **29a**–**e** in >98% e.e. and in 46–50% yield (Scheme 7).[31] Subsequent investigations revealed that a monomeric pimelate linked trimeric oligosalen complex **26** (X = csa, $n=2$) demonstrated even higher enantioselectivity and reactivity than those observed for the oligomeric mixture of cyclic salen catalysts **25**.[32]

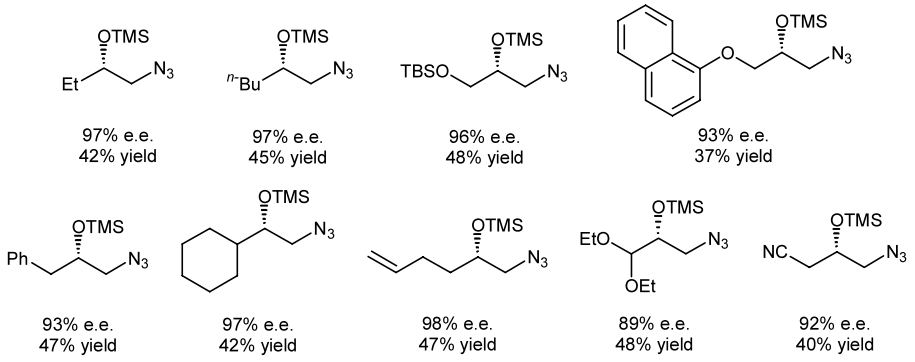


Figure 4. Synthons produced via HKR using $TMSN_3$ as a nucleophile.

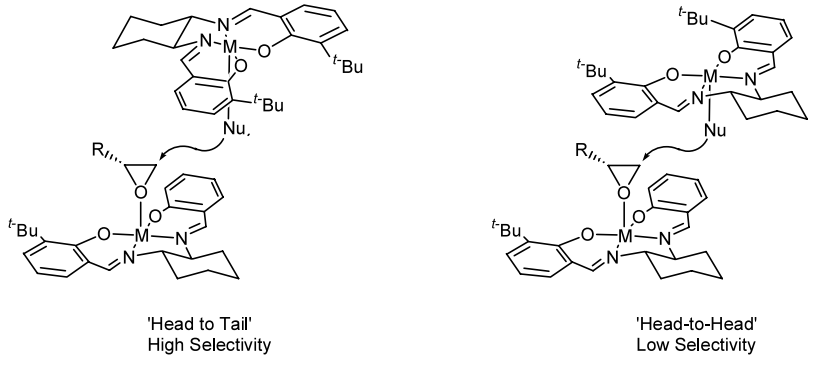
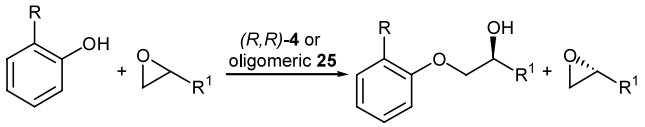
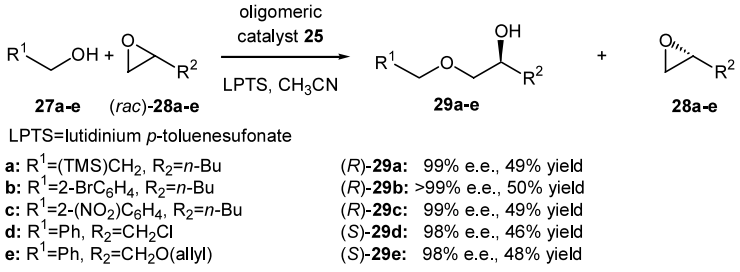


Figure 5. Competing transition states for epoxide ring-opening using salen catalysts.

Table 1. Kinetic resolution of racemic epoxides with phenol catalysed by (salen)Co complexes (*R*,*R*)-**4** or **25**



R	R^1	Catalyst	Co (mol%)	e.e. α-aryloxy-alcohol	% Yield α-aryloxy-alcohol
H	CH_2Cl	(*R*,*R*)-**4**	4.0	99	48
		25	0.25	99	50
H	*c*-Hexyl	(*R*,*R*)-**4**	8.0	94	45
		25	0.5	98	49
Cl	^{n}Bu	(*R*,*R*)-**4**	4.0	68	40
		25	0.8	99	0.8



Scheme 7. Kinetic resolution of racemic epoxides with alcohols catalysed by oligomeric catalyst **25**.

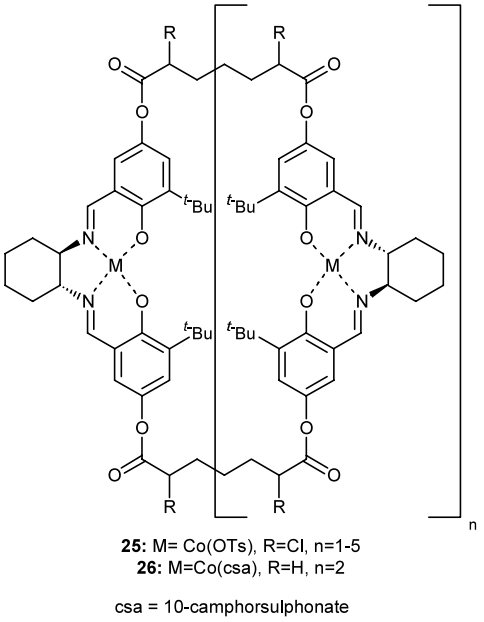
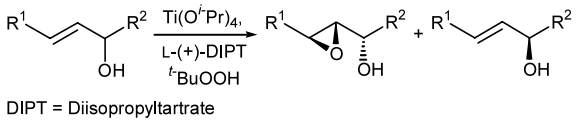


Figure 6. Oligomeric (salen)Co catalysts **25** and **26** for HKR.

Given their broad substrate specificity and wide usage, it is unsurprising that there have been concerted efforts by a number of different research groups to transfer this methodology to solid-support to afford easily recoverable and fully recyclable homogeneous or heterogeneous salen catalysts for asymmetric synthesis. Jacobsen et al. have immobilised salen catalysts onto polystyrene resin or silica supports, affording a recyclable homogeneous catalyst that was employed for the kinetic resolution of a range of racemic epoxides in excellent e.e. using either water or phenol as a nucleophile.[33] Zheng et al. have also employed a range of easily recyclable homogeneous oligomeric poly-salen–Co(III) complexes that catalyse the kinetic resolution of racemic epoxides in high e.e. using water as a nucleophile.[34] An alternative approach to immobilisation involving the preparation of dendrimeric salen catalysts also gave enhanced reactivity when compared to monomeric salen catalysts to afford chiral epoxides and diols in >98% e.e.,[35] whilst the use of 'light fluorous' chiral Co(salen) complexes for the HKR of terminal epoxides under essentially solvent free conditions has also been investigated.[36]

3. Oxidative kinetic resolution via asymmetric epoxidation strategies

The seminal protocol for the catalytic kinetic resolution of allylic alcohols first reported by Sharpless et al. in 1981 (Scheme 8)[37] continues to find favour amongst synthetic chemists for the preparation of a wide range of chiral synthons directed towards the synthesis of chiral drugs;[23] as substrates for new synthetic methodology;[38] or for natural product synthesis.[37a]



Scheme 8. Kinetic resolution of racemic allylic alcohols using Sharpless asymmetric epoxidation.

For example, over the last two years a range of non-racemic chiral allylic alcohol or epoxides have been prepared using this methodology as synthons for the asymmetric synthesis of a wide range of natural products such as (+)-Grandisol,[39] Korormicin,[40] (+)-Isoaltholactone,[41] (+)-Methynolide,[42] and Methyl isosartortuoate[43] (Fig. 7).

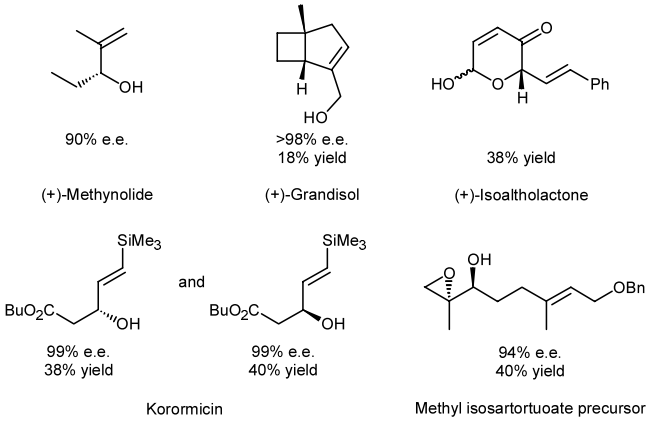
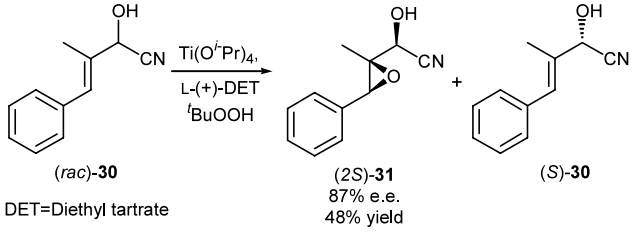


Figure 7. Synthons produced via Sharpless asymmetric epoxidation for natural product synthesis.

Williams et al. have reported the efficient kinetic resolution of allylic cyanohydrin (*rac*)-**30** via Sharpless asymmetric epoxidation to afford (2*S*)-**31** in 87% e.e. and 48% yield (Scheme 9).[44] Attempts to incorporate this kinetic resolution into an elegant 'one-pot' catalytic electronic activation strategy involving reversible interconversion of an achiral α,β-unsaturated aldehyde into its corresponding racemic allylic cyanohydrin, followed by kinetic resolution via stereoselective epoxidation, and subsequent transformation into a chiral α,β-epoxy aldehyde, were ultimately unsuccessful however.



Scheme 9. Kinetic resolution of allylic cyanohydrin (*rac*)-**30**.

In 1995 Jacobsen et al. reported the first example of a catalytic kinetic resolution using (salen)-Mn catalyst (*S*,*S*)-**32** (Fig. 8), *m*-CPBA and *N*-methyl-morpholine-*N*-oxide for the stereoselective epoxidation of 2,2-dialkyl chromene (*rac*)-**34** with a modest *s* value of 3.1 to afford the two diastereoisomeric epoxychroman products (*R*,*S*,*S*)-**35** and (*S*,*S*,*S*)-**36** both in >97% e.e. (Scheme 10).[45]

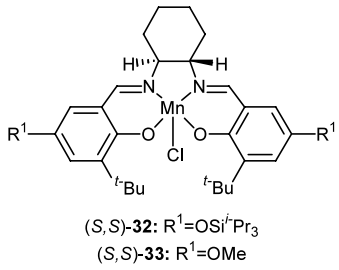
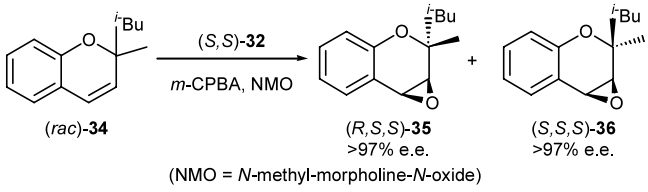
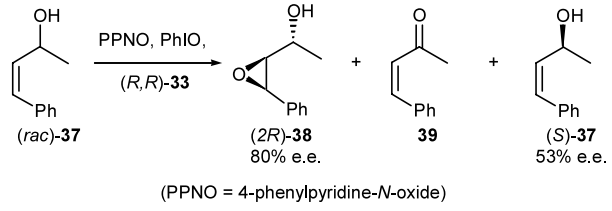


Figure 8.



Scheme 10. Kinetic resolution of 2-methyl-2-isobutyl chromene (*rac*)-**34** with catalyst (*S*,*S*)-**32**.

This Mn–salen complex mediated epoxidation resolution was later successfully applied to the kinetic resolution of 1,2-dihydronaphthalenes for the synthesis of lignans,[46] whilst Adam et al. have recently applied it to the kinetic resolution of aryl-substituted allylic alcohols.[47] For example, *cis*-allylic alcohol (*rac*)-**37** was resolved using catalyst (*R*,*R*)-**33** where its (*R*)-enantiomer was preferentially epoxidised to give the *threo* or *cis*-epoxy alcohol (2*R*)-**38** in 80% e.e., whilst the unreacted enantiomer (*S*)-**37** was recovered in 53% e.e. (Scheme 11). A small amount of the over-oxidation product enone **39** was also recovered in a ratio of (2*R*)-**38**:**39** of 95:5.



Scheme 11. Kinetic resolution of allylic alcohol (*rac*)-**37** via Jacobsen–Katsuki epoxidation.

An alternative method of kinetic resolution via alkene epoxidation was reported in 1999 by Shi et al.[48] using their chiral dioxirane epoxidising agent generated in situ from the action of Oxone™ on fructose derived ketone (–)-**40** (Fig. 9).[49] Thus, 1-phenyl-6-(trimethylsiloxy)cyclohexene (*rac*)-**41** was treated with 35 mol% of (–)-**40** and Oxone™ at –10°C for 2.5 h which gave recovered (*S*)-**41** in 96% e.e. at 49% conversion. *trans*-Epoxide (*S*)-**42** was shown to be formed as the predominant diastereoisomeric product in 95% e.e., with >20:1 selectivity over the corresponding *cis*-epoxide (Scheme 12).

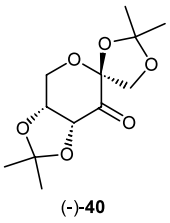
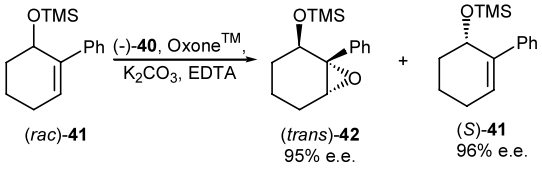


Figure 9.



Scheme 12. Kinetic resolution of (*rac*)-**41** via dioxirane-catalysed epoxidation.

Yang et al. subsequently employed dioxiranes derived from C_2-symmetric binaphthyl-ketones (*R*)-**43** and (*R*)-**44** for the enantioselective epoxidation of racemic α-trichloromethyl allylic alcohols to afford synthetically useful *erythro*-epoxides in excellent e.e.[50] High selectivities were observed for substrates that contained electron donating or sterically demanding aryl groups, whilst *tert*-butyl- and trifluoromethyl substituted allylic-TBDMS ethers also afforded acceptable levels of stereoselectivity using (*R*)-**43** or (*R*)-**44** (Fig. 10) as a catalyst precursor (Table 2).

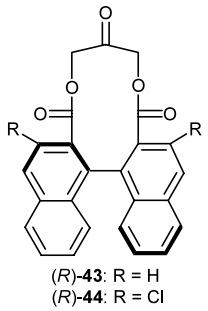
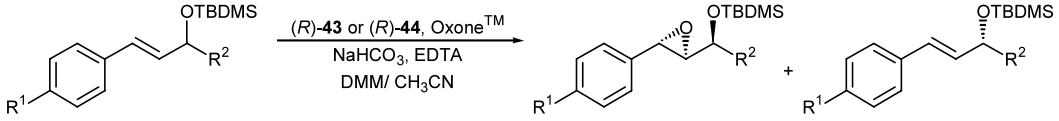


Figure 10.

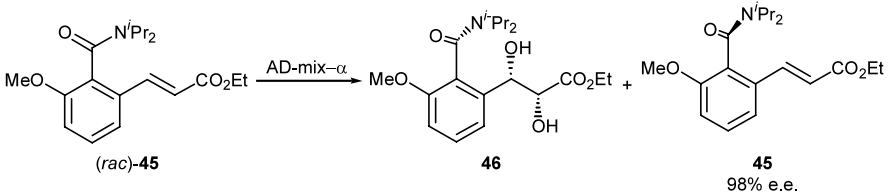
3.1. Kinetic resolution via asymmetric dihydroxylation

The Sharpless asymmetric dihydroxylation mechanism has proven to be a highly effective catalyst for the stereoselective dihydroxylation of alkenes, but has found only limited success as a strategy for kinetic resolution.[51] However, AD-mix-α has recently been employed for the catalytic kinetic resolution of atropisomeric amides with excellent levels of enantioselection for certain substrates. The most impressive results were obtained for α,β-unsaturated ester (*rac*)-**45**, containing an *N*,*N*-diiso-propylamide fragment, which proceeded with a k_{rel} of 32 using AD-mix-α affording chiral amide **45** (and diol **46**) in 98% e.e. at 57% conversion (Scheme 13).[52]

Table 2. Kinetic resolution of acyclic secondary allylic silyl ethers via chiral dioxirane-mediated epoxidation



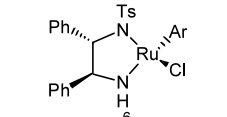
R^1	R^2	Catalyst	Epoxide		Recovered allylic ether		*s*
			% Yield	e.e.	% Yield	e.e.	
^{t}Bu	CCl_3	(*R*)-**43**	41	–	41	96	13
OMe	CCl_3	(*R*)-**43**	26	–	42	98	13
H	CCl_3	(*R*)-**44**	43	77	42	96	30
Et	CCl_3	(*R*)-**44**	38	77	43	99	37
^{t}Bu	CCl_3	(*R*)-**44**	41	93	44	94	100
H	^{t}Bu	(*R*)-**44**	44	76	43	63	14
H	CF_3	(*R*)-**44**	41	–	43	75	9



Scheme 13. Kinetic resolution of atropisometric amide (*rac*)-**45** using AD-mix-α.

3.2. Kinetic resolution via asymmetric oxidation of racemic secondary alcohols

A large number of kinetic resolution strategies that rely on the use of chiral catalysts for the enantioselective oxidation of one enantiomer of a racemic secondary alcohol to its corresponding ketone have been reported to date.[53] Since Noyori's seminal report in 1997 on reversible catalytic asymmetric transfer hydrogenation complexes for asymmetric catalysis, the use of chiral diamine Ru(II) complexes to transfer hydride from a racemic alcohol substrate to acetone has been widely used as a method for the kinetic resolution of secondary alcohols.[54] For example, Ogasawara et al. have employed complexes (*S*,*S*)-**47** or (*S*,*S*)-**48** (Fig. 11) for the kinetic resolution of a range of cyclic allylic alcohols in good e.e., which were subsequently used as synthons for the asymmetric synthesis of a wide range of natural products including (−)-Chokol G,[55] (+)-Frontalin and (−)-Malyngolide,[56] (+)-Tanikolide[57] (−)-Morphine,[58] 25-hydroxy-Grundmann's ketone,[59] and (+)-Vernolepin (Fig. 12).[60]



(*S*,*S*)-**47**: Ar=η^6-mesitylene
(*S*,*S*)-**48**: Ar=η^6-cymene

Figure 11.

The use of Wills' amino-2-indanol derived catalyst (1*R*,2*S*)-**49**[61] (Fig. 13) for the kinetic resolution of secondary alcohols has also been investigated and shown to afford excellent levels of enantioselectivity for the oxidation of a range of racemic α- and β-aryl alcohols.[62] Interestingly, Faller et al. have employed this catalyst to develop a tandem protocol employing 'mirror image catalysts' to enhance the enantiomeric excess of target

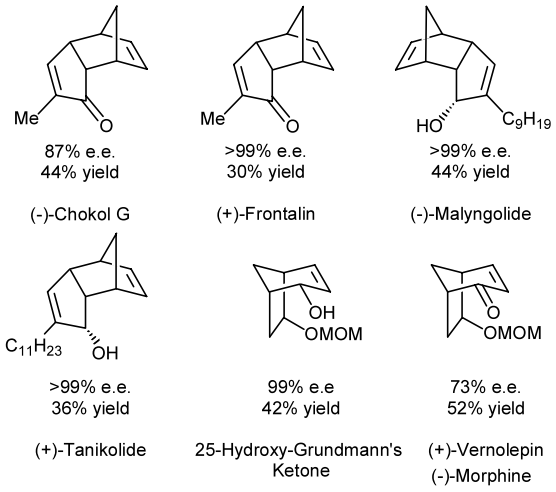
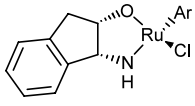


Figure 12. Synthons resolved for natural product synthesis via enantioselective oxidation using **47** or **48**.

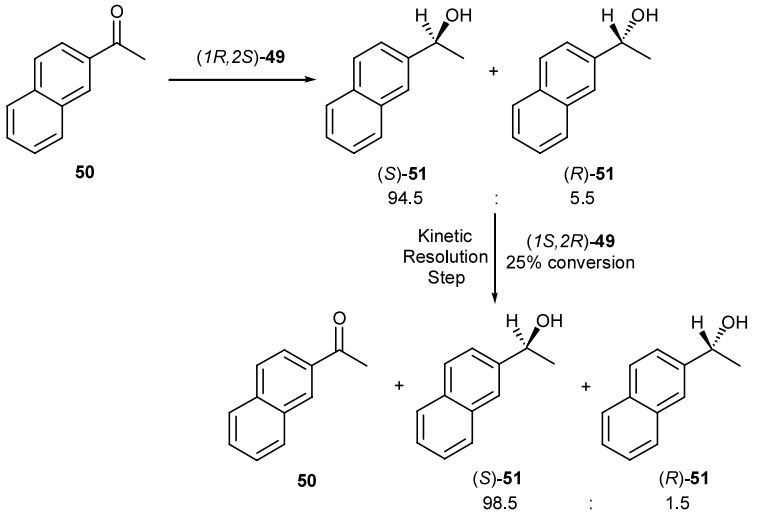
alcohols. For example, reduction of ketone **50** with catalyst (1*R*,2*S*)-**49** in the presence of excess 2-propan-2-ol afforded alcohol (*S*)-**51** in 89% e.e., which was then oxidised with the antipode of catalyst (1*S*,2*R*)-**49** in the presence of excess acetone enabling recovery of (*S*)-**51** in an enhanced 97% e.e. at 25% conversion (Scheme 14).



Ar =η^6-*p*-cymene
(*1R,2S*)-**49**

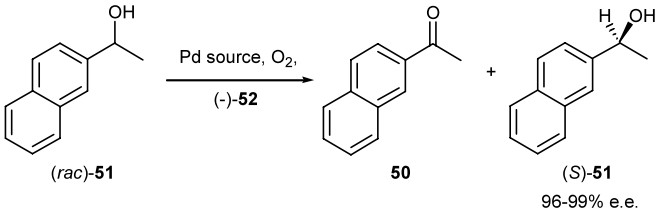
Figure 13.

In 2001, Sigman et al. and Stoltz et al. independently reported a Pd(II)-catalysed oxidative kinetic resolution of a combined total of nine different secondary racemic aryl alcohols using (−)-sparteine **52** (Fig. 14) as a chiral ligand



Scheme 14. Kinetic resolution of scalemic secondary alcohol **51** catalysed by (1*S*,2*R*)-**49**.

and molecular oxygen as the terminal oxidant (Scheme 15).[63,64] In a representative example, Sigman et al. used $Pd(OAc)_2$ as a palladium source, which gave unreacted alcohol (*S*)-**51** in 96% e.e.,[63] whilst Stoltz et al. found that the alternative use of $Pd(nbd)Cl_2$ resulted in the e.e. of the recovered alcohol (*S*)-**51** being increased to 99%.[64] This methodology has recently been exploited for the synthesis of (*S*)-3-phenyl-3-hydroxypropyl tosylate in 95% e.e., which was used in the synthesis of the chiral drugs (*R*)-tomoxetine and (*S*)-fluoxetine.[65] Interestingly, O'Brien et al. have recently reported the use of an alternative chiral diamine (+)-**53** [derived from (−)-cystine] (Fig. 15) as a (+)-sparteine surrogate for the oxidative kinetic resolution of indan-1-ol which afforded indanone **55** and recovered (*R*)-**54** in 80% e.e. (Scheme 16), albeit with inferior stereocontrol to that observed for sparteine (−)-**52** which afforded (*S*)-**54** in 98% e.e.[66]



Scheme 15. Kinetic resolution of secondary alcohols via Pd(II)-catalysed oxidation.

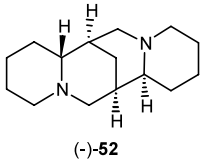
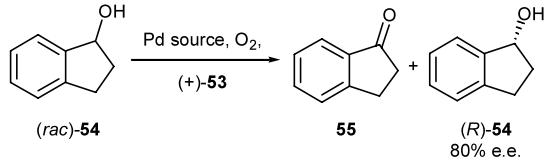


Figure 14.



Scheme 16. Pd(II)-catalysed kinetic resolution of indan-1-ol with diamine (+)-**53**.

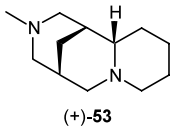


Figure 15.

Studies into the mechanism of this class of oxidative resolution were disclosed in 2002 by Sigman et al.[67] who found that the Pd[(−)-sparteine]Cl_2 complex was ineffective as a catalyst without excess (−)-sparteine acting as an exogenous base to control both the reactivity and selectivity of the catalytic process. This discovery implied that the reaction proceeds via a base-promoted pathway, in which a palladium (*S*)-alkoxide is formed stereoselectively, followed by hydride elimination to afford the corresponding ketone (Fig. 16). The excess (−)-sparteine then acts as a base to deprotonate the bound alcohol thus facilitating the catalytic cycle, with stoichiometric O_2 acting as the terminal oxidant.

An interesting approach to the kinetic resolution of *tert*-cyclobutanols has been described involving Pd(0) mediated C–C bond cleavage of cyclobutanols (*rac*)-**57a–d** in the presence of chiral ferrocenyl ligand (*R*,*S*)-**56** (Fig. 17) with moderate to good enantioselectivities.[68] The

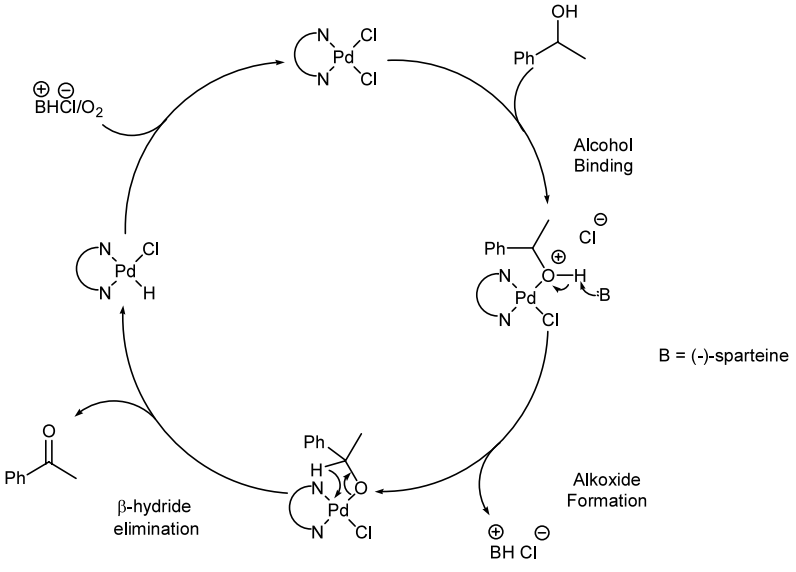
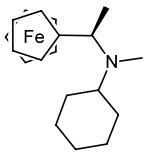


Figure 16. Proposed catalytic cycle for the oxidation of secondary alcohols catalysed by a Pd(II) complex.



(*R*,*S*)-**56**

Figure 17.

range of *tert*-cyclobutanols (*rac*)-**57a–d** that were resolved to afford ring opened ketones **58a–d** are described in Scheme 17, whilst the mechanism by which this resolution is proposed to proceed is described in Fig. 18.

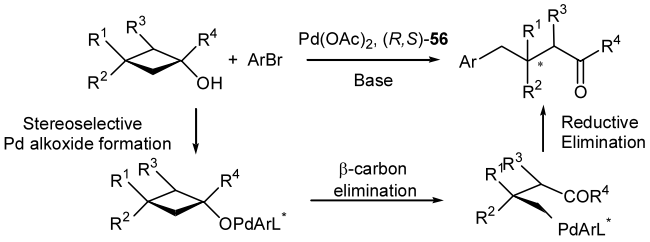
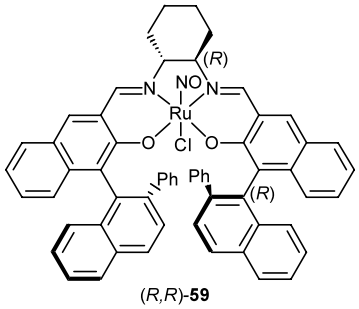


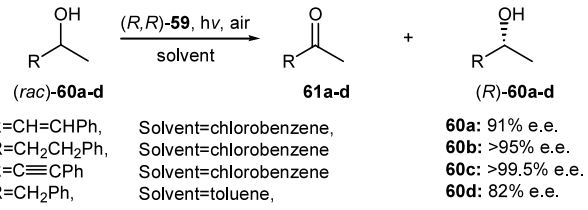
Figure 18. Proposed mechanism for the Pd-mediated resolution of (*rac*)-**57a–d**.

An alternative approach to O_2-mediated oxidative resolution has been disclosed by Katsuki et al. who employed chiral (nitroso)–salen–Ru complexes for the stereoselective oxidation of a range of secondary alcohols under photolytic conditions. Thus, photolysis of solutions of alcohols (*rac*)-**60a–d** in aromatic solvents, in the presence of catalyst (*R*,*R*)-**59** (Fig. 19) under aerobic conditions, resulted in efficient kinetic resolution to afford ketones **61a–d** and recovered alcohols (*R*)-**60a–d** in 82 to >99% e.e. (Scheme 18).[69]



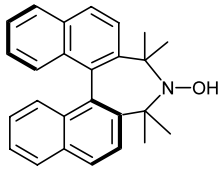
(*R*,*R*)-**59**

Figure 19.



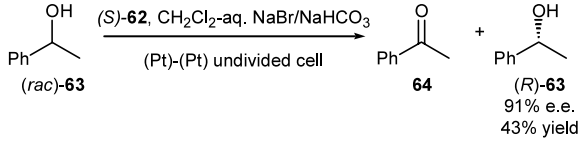
Scheme 18. Kinetic resolution of secondary alcohols (*rac*)-**60a–d** catalysed by (*R*,*R*)-**59**.

Building on previous work employing chiral nitroxyl radicals for enantioselective oxidation,[70] Tanaka et al. reported the kinetic resolution of six secondary racemic arylalcohols via electrochemical oxidation with *s* values ranging from 5.3 to 20.[71] This approach involved electro-oxidation in the presence of a catalytic amount of an enantiomerically pure binaphthyl tertiary *N*-hydroxylamine (*S*)-**62** (Fig. 20) which was performed using a simple undivided cell under constant current.[72] For example, electro-oxidation of 1-phenyl-1-ethanol (*rac*)-**63** proceeded to give acetophenone **64** in 57% yield and unreacted alcohol (*R*)-**63** in 91% e.e. and 43% yield (Scheme 19).



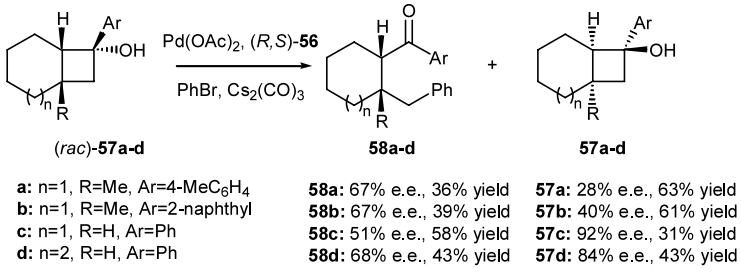
(*S*)-**62**

Figure 20.



Scheme 19. Kinetic resolution of (*rac*)-**63** via electro-oxidation in the presence of catalyst (*S*)-**62**.

The oxidative catalytic cycle proposed for this kinetic resolution is described in Figure 21, in which catalyst (*S*)-**62** is oxidised electrochemically to afford **65**, which then preferentially reacts with one enantiomer of 1-phenyl-1-ethanol (*S*)-**63** to afford adduct **66**, that then decomposes via a cyclic transition state regenerating **62**, thus affording acetophenone **64** and recovered phenylethan-1-ol (*R*)-**63**.



The absolute stereochemistry of the product ketones **58a-d** and recovered alcohols **57a-d** in these reactions were not determined

Scheme 17. Palladium-catalysed kinetic resolution of (*rac*)-*tert*-cyclobutanols **57a–d**.

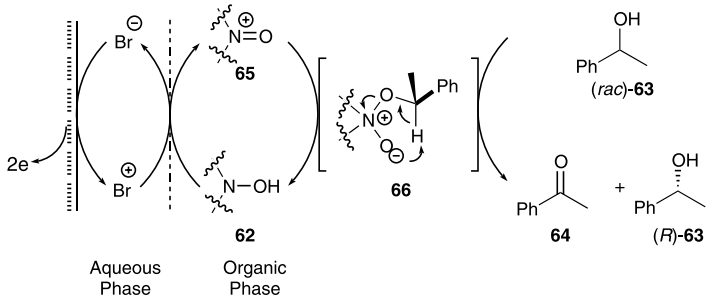
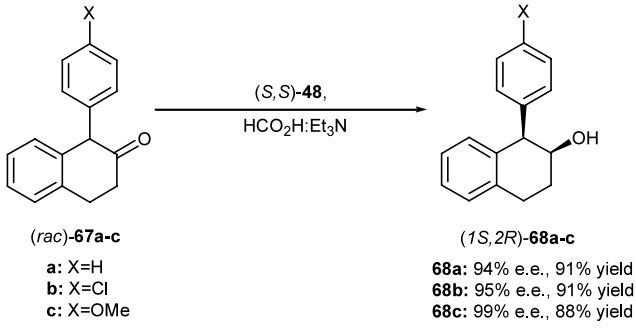


Figure 21. The electro-oxidative cycle for the kinetic resolution of (*rac*)-**63**.

The use of an alternative dipeptide derived oxidation catalyst containing a nitroxyl-containing α-amino acid 2,2,6-tetramethylpiperidine-1-oxyl-4-amino-4-carboxylic acid, and a β-turn inducing L-α-methyl-valine substituent, have also afforded limited success for this type of oxidative resolution, with the best results affording recovered phenylethan-1-ol (*S*)-**63** in 75% e.e.[73]

4. Kinetic resolution via enantioselective reduction of racemic ketones

Racemic ketones that contain configurationally labile α-stereogenic centres often undergo efficient dynamic kinetic resolution (DKR) when they are reduced using Noyori's asymmetric transfer hydrogenation catalysts.[74] For example, a series of 1-aryl-2-tetralones (*rac*)-**67a–c** have recently been subjected to DKR using a RuTsDPEN hydrogenation catalyst (*S*,*S*)-**48** to afford a small library of the corresponding alcohols (1*S*,2*R*)-**68a–c** containing two stereogenic centres in >93% e.e. and >87% yield (Scheme 20).[75]



Scheme 20. DKR of cyclic ketones (*rac*)-**67a–c** via transfer hydrogenation using (*S*,*S*)-**48**.

In 2002, Noyori et al. introduced a new type of highly efficient chiral Ru–binaphthyl complex (*S*,*R*,*R*)-**69** (Fig. 22) for the kinetic resolution of ketones under non-alkaline conditions, that enables easily racemisable ketones such as 2-isopropylcyclohexanone (*rac*)-**70** to be efficiently resolved to afford unreacted ketone (*S*)-**70** in 91% e.e., and *syn*-alcohol (1*R*,2*R*)-**71** in 85% e.e. at 53% conversion (Scheme 21).[76]

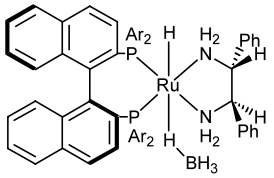
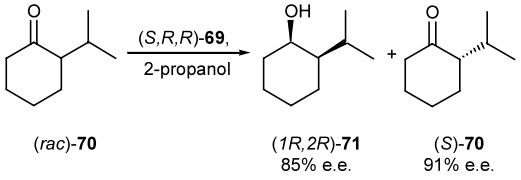
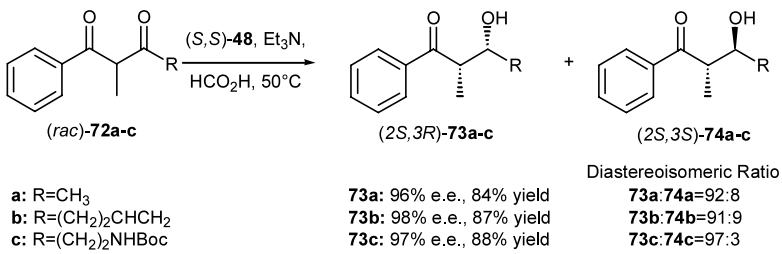


Figure 22.

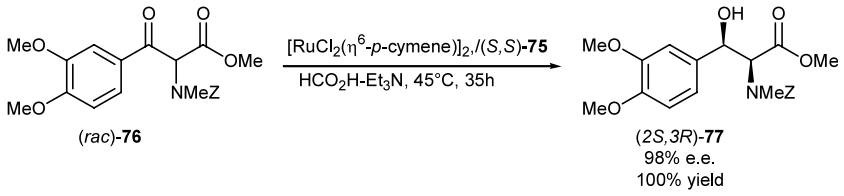


Scheme 21. DKR of 2-isopropylcyclohexanone (*rac*)-**70** using Ru-complex (*S*,*R*,*R*)-**69**.

Noyori's original asymmetric Rh-catalysed hydrogenation catalysts continue to be popular for the dynamic kinetic resolution of β-dicarbonyl compounds in high e.e.,[77] where Cossy et al. have recently extended the use of this methodology to the kinetic resolution of racemic 2-alkyl-1,3-diketones.[78] They found that treatment of diketones (*rac*)-**72a–c** with (*S*,*S*)-**48** in the presence of formic acid and triethylamine resulted in a mixture of alcohols *syn*-(2*S*,3*R*)-**73a–c** and *anti*-(2*S*,3*S*)-**74a–c**, with the major *syn*-alcohols (2*S*,3*R*)-**73a–c** being formed as the major diastereoisomer in good enantiomeric excess in all cases (Scheme 22).



Scheme 22. DKR of β-diketones (*rac*)-**72a–c** via transfer hydrogenation.



Scheme 23. DKR of α-amido-β-keto acid (*rac*)-**76** via transfer hydrogenation.

Wagner et al. have attempted to improve the performance of Noyori's catalytic system by the introduction of a more electron-withdrawing trifluorosulfonyl group into the chiral ligand design.[79] It was found that when ligand (*S*,*S*)-**75** (Fig. 23) was employed in place of (*S*,*S*)-**48** for the DKR of *threo*-β-hydroxy α-amido acid (*rac*)-**76**, that the e.e. of (2*S*,3*R*)-**77** was improved from 94 to 98%, whilst the yield was improved from 80 to 100%, and the reaction time decreased from 72 to 35 h (Scheme 23).

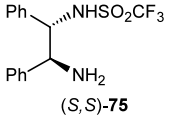
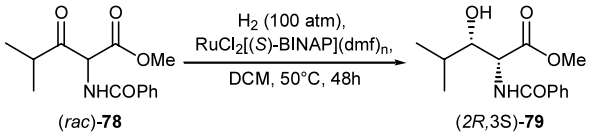


Figure 23.

In 2001, Hamada et al. also described an efficient synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-**3**-hydroxyleucines via DKR using $RuCl_2$[(*S*)-BINAP](dmf)$_n$-catalysed hydrogenation.[80,81] The DKR of β-keto-α-amido acid ester (*rac*)-**78** was performed at 50°C in DCM under 100 atmospheres of H_2, resulting in the 3-hydroxy-leucine derivative (2*R*,3*S*)-**79** being formed in 99% e.e. and 100% yield, which is a key structural motif within a number of naturally occurring cyclic depsipeptides (Scheme 24).



Scheme 24. DKR of α-amido-β-keto-ester (*rac*)-**78** via hydrogenation.

In 2000, Genêt et al. reported the highly stereoselective synthesis of the functionalised hexahydroazepine core of (−)-Balanol (a protein kinase C inhibitor) through DKR of a racemic α-amido-β-keto ester using a Ru(II)-catalysed hydrogenation reaction.[82] Thus, the reduction of α-amido-β-keto ester (*rac*)-**81** with 1 mol% Ru complex of MeO-BIPHEP (*R*)-**80** (Fig. 24) at 50°C in DCM for 96 h afforded (2*S*,3*R*)-**82** in 94% e.e. and 93% d.e., in an overall yield of 80% (Scheme 25).

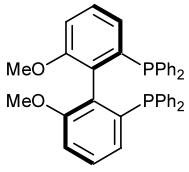
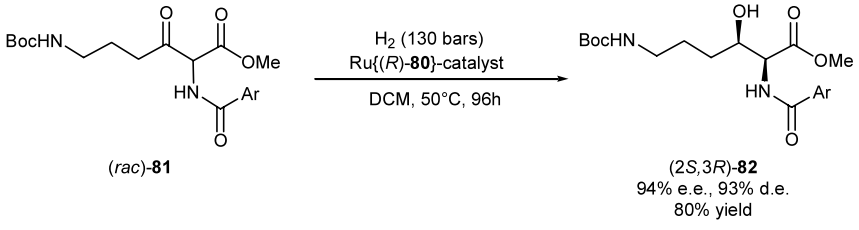
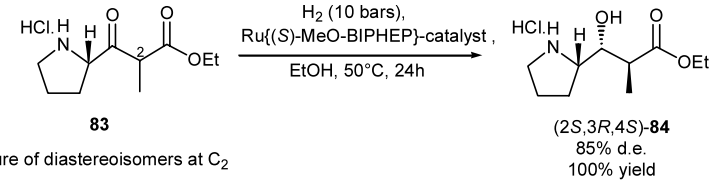


Figure 24.

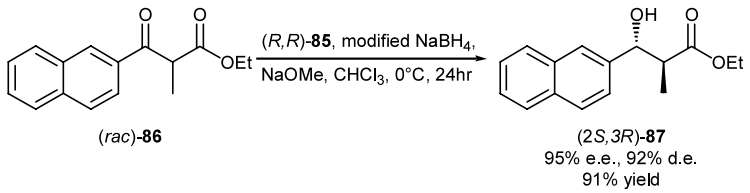
The use of the same Ru-catalyst for the synthesis of *iso*-Dolaproine via DKR was also described in which hydrogenation of a diastereoisomeric mixture of proline derived γ-amino-β-keto esters **83** with 1 mol% of Ru[MeO-BIPHEP (*S*)-**80**] at 10 bar H_2 at 50°C for 24 h afforded β-hydroxy ester (2*S*,3*R*,4*S*)-**84** in quantitative yield in 85% d.e. (Scheme 26).[83]



Scheme 25. DKR of α-amido-β-keto ester (*rac*)-**81** via hydrogenation.



Scheme 26. DKR of diastereoisomeric mixture of proline derived γ-amino β-keto ester **83**.



Scheme 27. DKR of (*rac*)-**86** via enantioselective borohydride reduction using (*R*,*R*)-**85**.

In 2002, Yamada et al. reported a DKR protocol based on enantioselective borohydride mediated reduction of β-keto esters catalysed by chiral β-ketoiminato Co(II) complexes (*R*,*R*)-**85**. For example,[84] borohydride reduction of 2-methyl-3-(2-naphthyl)-3-oxopropionic acid ethyl ester (*rac*)-**86** in the presence of 4 mol% of (*R*,*R*)-**85** (Fig. 25) at 0°C afforded β-hydroxy-ester (2*S*,3*R*)-**87** in 95% e.e., 92% d.e., and in 91% yield (Scheme 27).

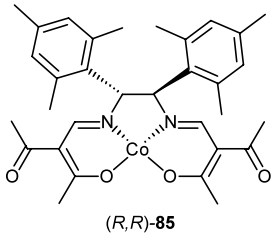
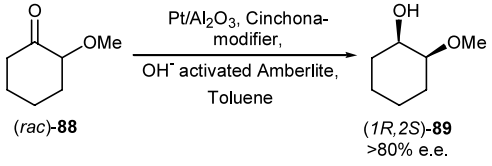


Figure 25.

Studer et al. have also reported that heterogeneous *Cinchona*-modified Pt/Al_2O_3 catalysts can be employed for the reductive kinetic resolution of a range of racemic α-keto ethers in good to excellent e.e. at conversions of less than 50%. This approach was extended to the dynamic kinetic resolution of 2-methoxycyclohexanone (*rac*)-**88**, in the presence of basic ion exchange resins as a solid supported base to facilitate efficient racemisation, to afford *syn*-α-methoxy alcohol (1*R*,2*S*)-**89** in >80% e.e. at 95% conversion (Scheme 28).[85]



Scheme 28. DKR of 2-methoxycyclohexanone (*rac*)-**88** with Cinchona-modified Pt/Al_2O_3.

The use of oxazaborolidine-catalysed asymmetric reductions[86] for kinetic resolutions is an increasingly popular approach; however, the majority of reports to date have employed stoichiometric amounts of catalyst for efficient resolution.[87] In 2001, Kagan et al. described lengthy optimisation studies into the use of this class of catalyst for the kinetic resolution of 4-acetyl[2.2]paracyclophane (*rac*)-**91**, with the best enantioselectivities being observed when 15 mol% of chiral oxazaborolidine (*S*)-**90** (Fig. 26) and 0.6 equiv. of borane were employed for resolution to afford recovered (*S*)-**91** in 98% e.e. and alcohols (*R*,*R*)-**92** and (*R*,*S*)-**93** in 89% e.e. and >99% e.e., respectively (Scheme 29).[88]

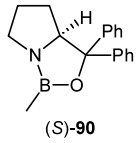
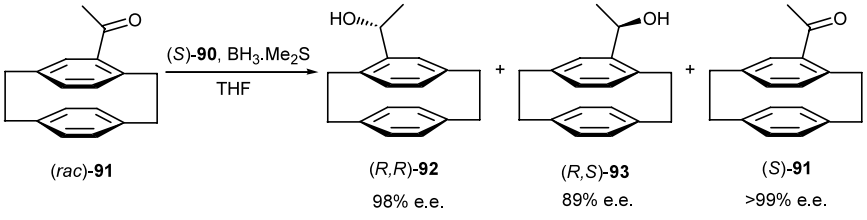


Figure 26.

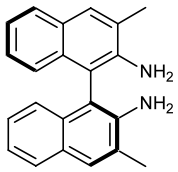
4.1. Kinetic resolution via asymmetric hydrogenation of alkenes

Mikami et al. have employed the use of their ingenious 'chiral poisoning' approach[89] to devise an efficient protocol for the kinetic resolution of racemic allylic alcohols using *racemic* $RuCl_2$[XylBINAP](dmf)$_n$ as catalyst. They found that addition of 0.5 equiv. of 3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine (DM-DABN) (*S*)-**94** (Fig. 27) to racemic $RuCl_2$[XylBINAP](dmf)$_n$ resulted in enantioselective complexation of the (*S*)-$RuCl_2$-[XylBINAP] enantiomer, thus enabling free uncomplexed (*R*)-$RuCl_2$[XylBINAP] to catalyse the kinetic resolution of 2-cyclohexen-1-ol (*rac*)-**95** with an *s* value



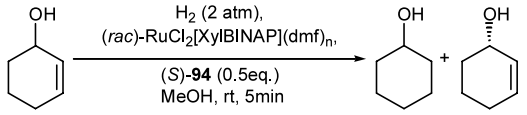
Scheme 29. Kinetic resolution of 4-acetylparacyclophane (*rac*)-**91** using oxazaborolidine (*S*)-**90**.

of 102, affording cyclohexanol **96** and recovered allylic alcohol (*S*)-**95** in 100% e.e. at 53% conversion (Scheme 30).[90]



(*S*)-**94**

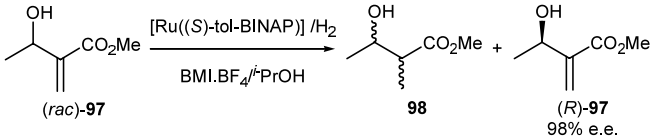
Figure 27.



(*rac*)-**95** **96** (*S*)-**95** 100% e.e.

Scheme 30. Kinetic resolution of (*rac*)-**95** via stereoselective complexation of one enantiomer of (*rac*)-$RuCl_2$[(*S*)-BINAP](dmf)$_n$ using (*S*)-**94**.

In 2001, Dupont et al. reported the influence of hydrogen pressure on the directed asymmetric hydrogenation of methyl-3-hydroxy-2-methylenebutanoate (*rac*)-**97** catalysed by $[RuCl_2$-(*S*)-tolyl-BINAP$]_2 \cdot NEt_3$ using the ionic liquid ^{n}butyl-methylimidazolium tetrafluoroborate (BMI·BF_4) as solvent under various conditions.[91] It was found that the best kinetic resolution was obtained at a pressure of 40 atmospheres of hydrogen affording β-hydroxy ester **98**, with unreacted substrate (*R*)-**97** being recovered in 98% e.e. and 29% yield (Scheme 31). It was found that k_{rel} for this resolution was influenced considerably by hydrogen pressure, with a significant drop to 85% e.e. being observed for (*R*)-**97** at higher pressure (50 atmospheres).

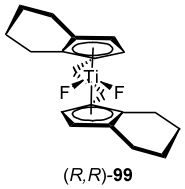


(*rac*)-**97** **98** (*R*)-**97** 98% e.e. 29% yield

Scheme 31. Kinetic resolution of methyl 3-hydroxy-2-methylenebutanoate (*rac*)-**97** via asymmetric hydrogenation.

4.2. Catalytic hydrosilylation or hydroboration strategies for kinetic resolution

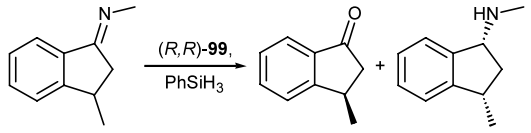
In 2000, Buchwald and Yun described the efficient kinetic resolution of *N*-methyl imines of 3-substituted indanones and 4-substituted tetralones via hydrosilylation with chiral titanocene catalyst, (EBTHI)TiF_2 (*R*,*R*)-**99** (Fig. 28).[92] Hydrosilylation of the *N*-methyl imine of 3-substituted indanones (*rac*)-**100** was carried out employing 1 mol% of catalyst (*R*,*R*)-**99**, which was complete after 2 h at 0°C giving at ~50% conversion



(*R*,*R*)-**99**

Figure 28.

recovered ketone (*R*)-**101** with 93% e.e. (after hydrolysis of unreacted starting material) with the major amine product (1*R*,3*S*)-**102** being obtained in 83% e.e. in high d.e. (Scheme 32). It was found that lowering the reaction temperature increased the *s* value of the resolution at the expense of the reaction rate; thus decreasing the e.e. of recovered ketone (*R*)-**101**, whilst increasing the e.e. of the product amine (1*R*,3*S*)-**102**.

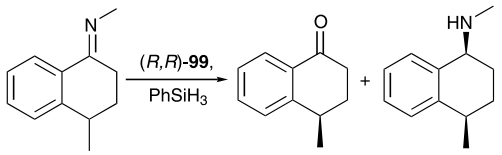


(*rac*)-**100** (*R*)-**101** 93% e.e. (*1R,3S*)-**102** 83% e.e

Scheme 32. Kinetic resolution of *N*-methyl imine (*rac*)-**100** with (*R*,*R*)-**99**.

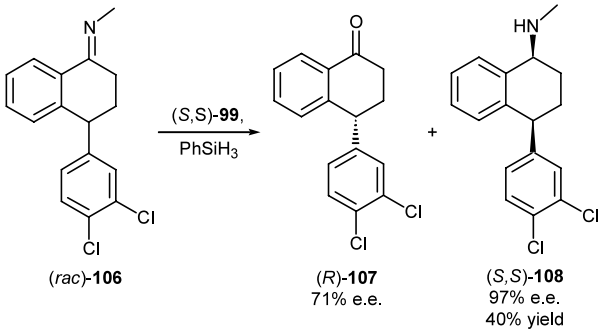
The resolution of racemic *N*-methyl 4-substituted tetralones was also investigated and found to afford better results with *s* values ranging from 18 to 78 at room temperature. For example, the resolution of tetralone (*rac*)-**103** occurred with an *s* value of 60.8, giving recovered ketone (*R*)-**104** in 99% e.e., and the major diastereoisomeric amine (1*R*,4*S*)-**105** in 93% e.e. (Scheme 33).

This approach has been utilised for the asymmetric synthesis of a range of chiral amine products including sertraline [(+)-*cis*-1-methylamino-4-(3,4-dichlorophenyl) tetralin] (*S*,*S*)-**108**, an antidepressant sold by Pfizer under the name of Zoloft as a competitive inhibitor of synaptosomal serotonin uptake. Using this method, sertraline precursor (*rac*)-**106** was exposed to a catalytic quantity (2.5 mol%) of (*S*,*S*)-**99** using $PhSiH_3$ as a stoichiometric reductant to afford sertraline (*S*,*S*)-**108** in 97% e.e. and 40% yield, whilst ketone (*R*)-**107** was recovered in 71% e.e. (Scheme 34).[93]



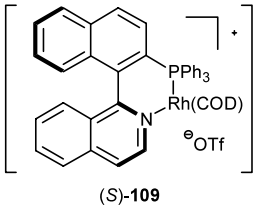
(*rac*)-**103** (*R*)-**104** 99% e.e. (1*R,4S*)-**105** 93% e.e.

Scheme 33. Kinetic resolution of *N*-methyl imine (*rac*)-**103** with (*R*,*R*)-**99**.



Scheme 34. Synthesis of sertraline (*S*,*S*)-**108** via kinetic resolution of (*rac*)-**106**.

Brown et al. have reported an alternative formal asymmetric synthesis of sertraline based on the use of QUINAP–Rh complex (*S*)-**109** (Fig. 29) for the stereoselective hydroboration of 1-aryl-dihydronaphthalene (*rac*)-**110** to afford alcohol (1*S*,4*R*)-**111** and the recovered unreacted 1-aryl-dihydronaphthalene (*S*)-**110** in 98% e.e. and 78% yield. Subsequent hydroamination of (*S*)-**110** using (*S*)-**109** resulted in Sertraline (*S*,*S*)-**108** being formed as the minor diastereoisomer in a 29:71 *cis*:*trans* isomeric mixture containing amine (1*R*,4*S*)-**112** as the major diastereoisomer (Scheme 35).[94]



(*S*)-**109**

Figure 29.

5. Kinetic resolution using chiral acylation catalysts

The development of methodology for the resolution of secondary alcohols using chiral acylation catalysts continues to be a popular theme amongst the synthetic community.[95] Building on their original work using chiral phosphines such as (*S*,*S*)-**113**, Vedejs et al. have reported on the development of a second generation chiral phosphine acyl transfer catalyst (1*R*,2*R*,4*S*,5*S*)-**114** (Fig. 30) which was shown to resolve 1-(*o*-methylphenyl)ethanol (*rac*)-**115** to afford unreacted alcohol (*S*)-**115** in 98% e.e., and ester (*R*)-**116** in 95% e.e. at 51% conversion (Scheme 36).[96] The scope of this type of phosphine catalyst was subsequently demonstrated for the kinetic resolution of a small library of twelve allylic alcohols (*rac*)-**117a–d**, typically affording isobutyryl esters (*R*)-**118a–d** and unreacted alcohols (*S*)-**117a–d** in satisfactory to excellent e.e. (Scheme 37).[97]

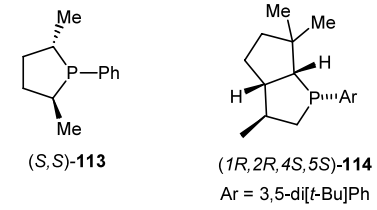
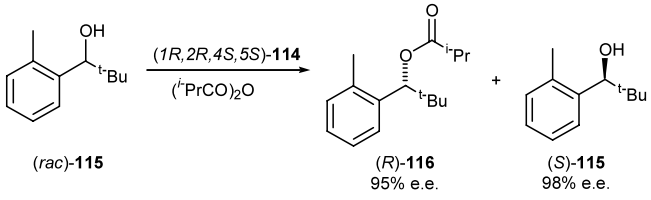
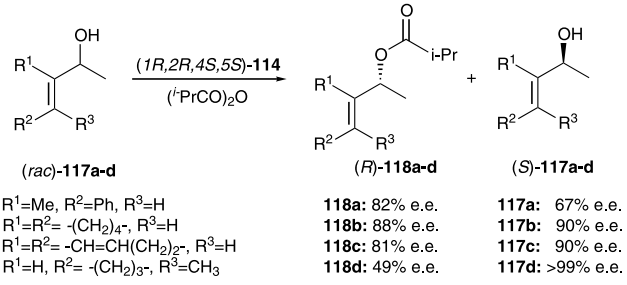


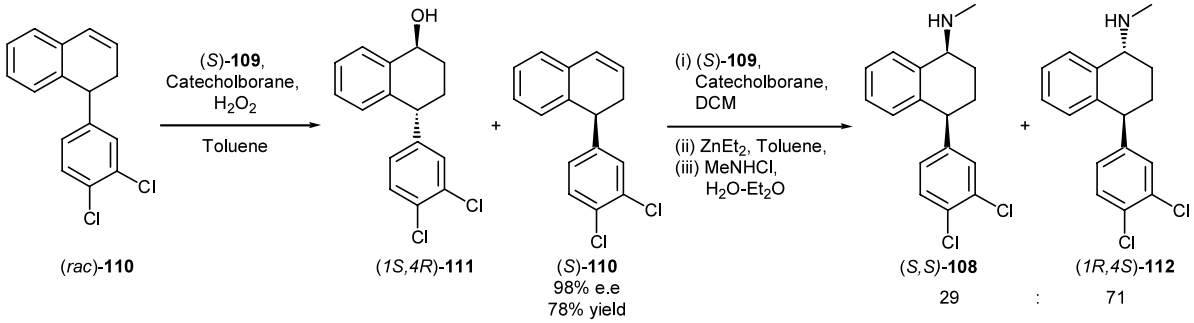
Figure 30.



Scheme 36. Kinetic resolution of (*rac*)-**115** with *i*butyric anhydride and **114**.



Scheme 37. Kinetic resolution of allylic alcohols (*rac*)-**117a–d** with isobutyric anhydride and **114**.



Scheme 35. Synthesis of Sertraline (*S*,*S*)-**108** via asymmetric hydroboration using (*S*)-**109**.

The versatile ferrocene derived acyl transfer catalysts (−)-**119** and (−)-**120** (Fig. 31) described by Fu et al. remain one of the most effective systems for the kinetic resolution of a wide range of racemic arylalkylcarbinols, including phenylethanol (*rac*)-**63** which gave ester (*R*)-**121** in 90% e.e., and unreacted alcohol (*S*)-**63** in 99% e.e. (Scheme 38).[98] These catalyst systems have recently been employed for the resolution of a series of racemic allylic alcohols to afford a wide range of structurally diverse chiral allylic alcohols such as (*R*)-**117a** in >90% e.e.[99]

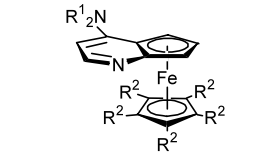
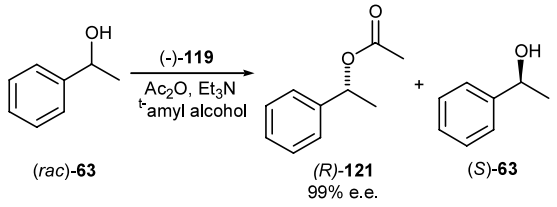


Figure 31.



Scheme 38. Kinetic resolution of (*rac*)-**63** with acetic anhydride and catalyst (−)-**119**.

In an important breakthrough, Fu et al. have recently reported that this catalytic system can be extended to the kinetic resolution of a series of secondary arylamines (*rac*)-**122a–e** using *O*-acylated β-naphthyl-azlactone **123** as a stoichiometric carbonyl donor in the presence of catalyst (−)-**120** to afford chiral carbamates (*S*)-**124a–e** and recovered amines (*R*)-**122a–e** with *s* values >12 (Scheme 39).[100]

In 1999, Oriyama et al. reported an alternative method for the kinetic resolution of a wide range of cyclic racemic alcohols,[101] involving treatment with benzoyl chloride in the presence of 0.3 mol% of chiral diamine (*S*)-**125** (Fig. 32). For example, under these conditions benzoate ester (1*S*,2*R*)-**127** was formed in 96% e.e. and 49% yield, whilst the unreacted alcohol (1*R*,2*S*)-**126** was recovered in 95% e.e. and 48% yield (Scheme 40). This system has subsequently been employed for the kinetic resolution of a range of cyclic racemic β-halohydrins to afford the corresponding benzoate esters and recovered alcohols in fair to excellent e.e.[102]

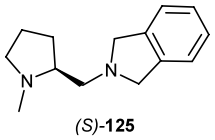
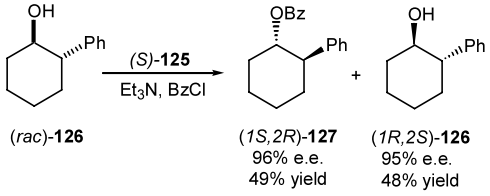


Figure 32.



Scheme 40. Catalytic asymmetric benzoylation of (*rac*)-**126** using (*S*)-**125**.

This type of proline based diamine has also been immobilised onto poly(ethylene glycol) (PEG) supports and used as recyclable acylation catalysts for the kinetic resolution of a range of racemic secondary alcohols with *s* values similar to those obtained using the soluble catalyst (*S*)-**125**.[103] This class of acyl transfer catalyst has also been attached to soluble polymer supports with *J*anda*J*el supported catalyst **128** (Fig. 33) affording benzoate ester (1*S*,2*R*)-**127** in 96% e.e. and recovered unreacted alcohol (1*R*,2*S*)-**126** in 85% e.e.

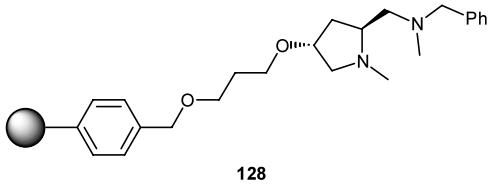
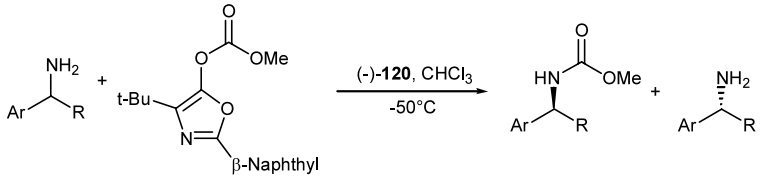
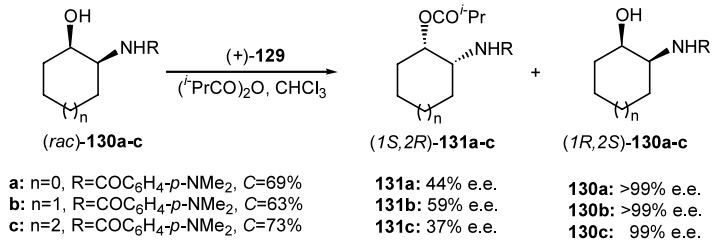


Figure 33.

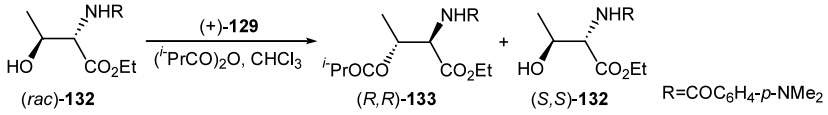


122a: Ar=Ph, R=Me, *s*=12
122b: Ar=α-naphthyl, R=Me, *s*=27
122c: Ar=*o*-tol, R=Me, *s*=16
122d: Ar=*m*-MeO-C_6H_4, R=Me, *s*=22
122e: Ar=Ph, R=Et, *s*=16

Scheme 39. Kinetic resolutions of (*rac*)-amines **122a–e** catalysed by (−)-**120**.



Scheme 41. Kinetic resolution of (*rac*)-**130a–c** catalysed by (+)-**129**.



Scheme 42. Kinetic resolution of acyclic α-amido-β-hydroxy ester (*rac*)-**132** with (+)-**129**.

Another class of chiral dimethylaminopyridine like catalyst (+)-**129** (Fig. 34) has been reported for the kinetic resolution of cyclic *N*-acyl-β-amino alcohols (*rac*)-**130a–c** that selectively afforded esters (1*S*,2*R*)-**131a–c** as major products and (1*R*,2*S*)-**130a–c** in very high e.e. (Scheme 41).[104] Thus, at relatively high conversions, excellent enantioselectivities were obtained for recovered five-, six- and seven-membered *cis*-*N*-acyl-β-amino alcohols (1*R*,2*S*)-**130a–c**, respectively. Although the selectivity observed for acyclic β-amino alcohols was generally poor, *anti*-β-amino alcohol (*rac*)-**132** was shown to be enantioselectively acylated to afford ester (*R*,*R*)-**133**, enabling *N*-acyl-β-amino alcohol (*S*,*S*)-**132** to be recovered in 93% e.e. at 70% conversion (Scheme 42).[105]

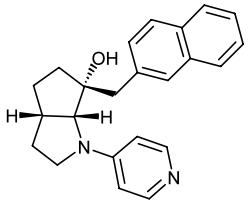
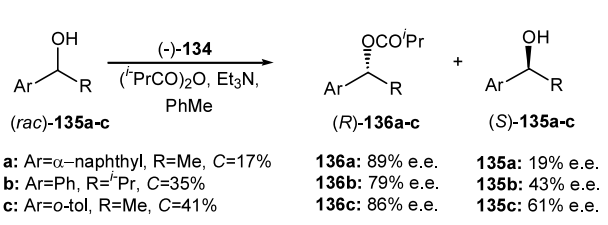


Figure 34.

Spivey et al. have continued to explore the use of their axially chiral analogues of 4-(dimethylaminopyridine),[106] with atropisomeric biaryl diamine (−)-**134** (Fig. 35) having proved the most successful catalyst for the resolution of aryl-alcohols (*rac*)-**135a–c** to date, affording esters (*R*)-**136a–c** in moderate to good e.e. at low conversion



Scheme 43. Kinetic resolution of aryl-alcohols (*rac*)-**135a–c** catalysed by (−)-**134**.

(Scheme 43).[107] The use of C_2-symmetric analogues of 4-(pyrrolidino)-pyridine (*R*,*R*)-**137** for related kinetic resolutions proved less successful however (Fig. 36).[108]

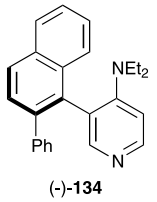


Figure 35.

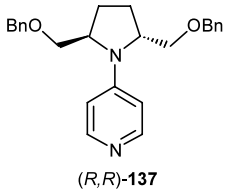


Figure 36.

Jeong et al. have reported a new tertiary amine based nucleophilic DMAP analogue (−)-**138** (Fig. 37) that gives good to excellent results for the resolution of racemic alkylarylcarbinols.[109] It was found that the *s* values for this catalyst increased as the steric bulk of the alkyl group of the alcohol substrate increased, with the best result being obtained for acylation of racemic *trans*-2-phenylcyclohexanol (Table 3, entry 6) which proceeded with $s = 21$ giving recovered (1*S*,2*R*)-alcohol in 99% e.e. and the (1*R*,2*S*)-ester product in 62% e.e.

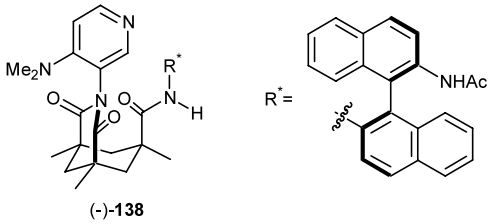


Figure 37.

Table 3. Kinetic resolution of racemic secondary alcohols with catalyst (−)-**138**

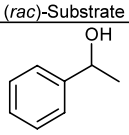
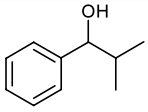
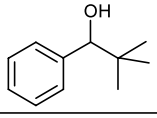
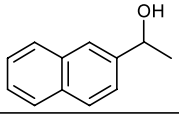
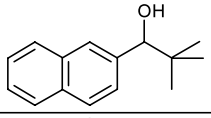
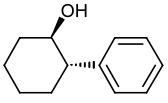
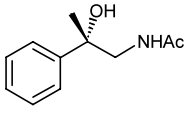
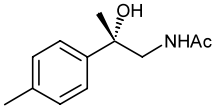
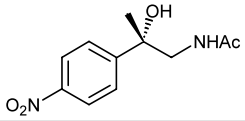
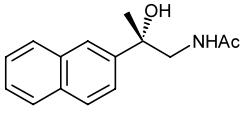
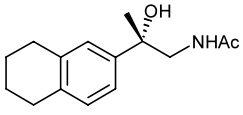
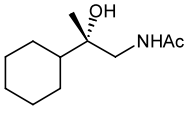
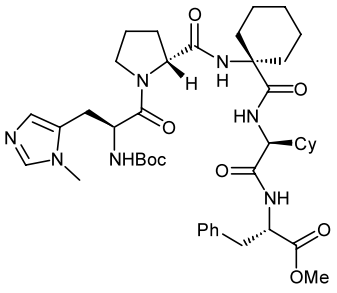
Entry	(*rac*)-Substrate	*C*/%	e.e./%		*s*
			(*S*)-Alcohol	(*R*)-Ester	
1		70	79	34	4.4
2		77	99	31	8.1
3		59	90	64	13.3
4		72	98	38	8.3
5		63	95	57	12.4
6	 (*trans*)	62	99 (*1S,2R*)	62 (*1R,2S*)	21.0

Table 4. Kinetic resolution of racemic *N*-acyl-1,2-aminoalcohols using Ac_2O and peptide catalyst **139**

Entry	(*rac*)-Substrate	Temp/°C]	Conv./%	k_{rel}
1		4	47	20
		-23	37	40
2		4	52	22
		-23	48	>50
3		4	54	15
		-23	40	32
4		4	47	14
		-23	35	40
5		4	51	20
		-23	38	39
6		4	51	9
		-23	35	19

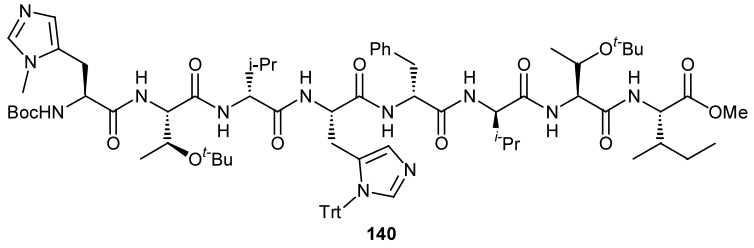


139

Figure 38.

Miller et al. have employed an alternative biomimetic approach to the identification of enantioselective *O*-acylation catalysts based on β-turn peptide fragments with defined secondary structures that contain nucleophilic *N*-alkyl-imidazole residues.[110] Initial work was directed towards the kinetic resolution of racemic *N*-acyl-1,2-aminoalcohols (Table 4) (to afford recovered (*S*)-alcohols) which were chosen due to their ability to hydrogen bond to a chiral peptide catalyst **139** (Fig. 38) that contained a D-Pro residue known to induce β-turns into peptide backbones.[111] Subsequent application of the full power of combinatorial synthesis for the preparation of 1st and 2nd generation libraries that contained over 100,000 and 600 peptide catalysts, respectively, resulted in the identification of octapeptide **140** (Fig. 39) that catalysed the resolution of more conventional secondary alcohol substrates in excellent e.e. (Table 5).[112]

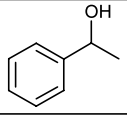
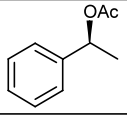
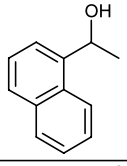
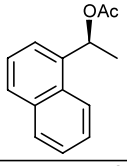
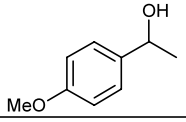
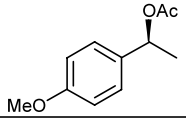
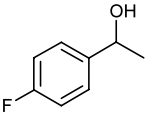
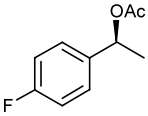
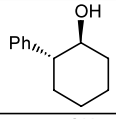
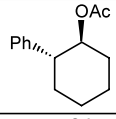
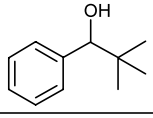
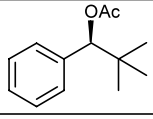
The potential use of this combinatorial approach for catalyst design was demonstrated in the asymmetric synthesis of (−)-Mitosane **143**, where an *N*-methyl-Histidine containing peptide **141** (Fig. 40) was isolated as the most active enantioselective catalyst from a library of 152 members for the resolution of allylic alcohol (*rac*)-**142** (Scheme 44).[113] The mechanism of this class of peptidic acyl transfer catalyst is currently under investigation using a novel approach that employs peptidic isosteres as mechanistic probes.[114]

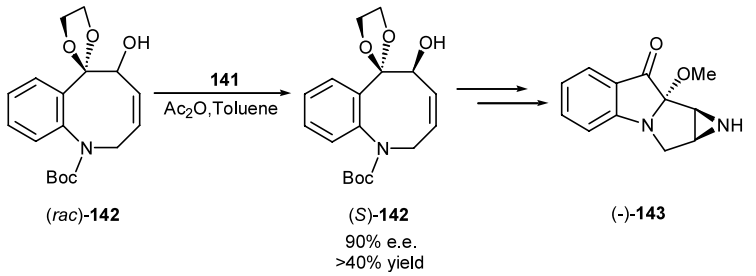


140

Figure 39.

Table 5. Kinetic resolutions catalysed by peptide **140** and Ac_2O

Entry	(*rac*)-Substrate	Acylated Product	k_{rel}
1			20
2			>50
3			16
4			11
5			>50
6			30



Scheme 44. Synthesis of (–)-Mitosane **143** via kinetic resolution of (*rac*)-**142**.

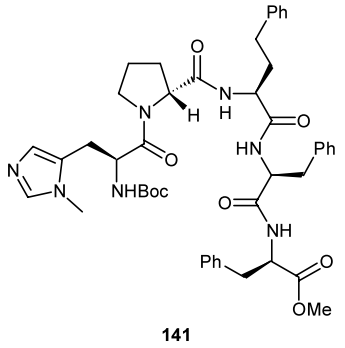


Figure 40.

The use of catalytic Lewis acids for the kinetic resolution of racemic alcohols has been less well explored, however a recent report has described on the potential of chiral yttrium–salen complex (*S*,*S*)-**144** (Fig. 41) for enantioselective acyl transfer.[115] The *s* values (1.50–4.81) obtained using these catalysts for resolution of a typical range of benchmark secondary alcohols **145a–e** are currently inferior to those obtained using chiral nucleophilic catalysts however, with the best results being obtained for indan-1-ol (*rac*)-**145c** which afforded recovered alcohol (*R*)-**145c** in 91% e.e. at 76% conversion (Table 6).

The development of a novel method for mono-benzylation of vicinal diols using dimethyltin dichloride and aqueous potassium carbonate that is proposed to proceed via an stannylene acetal intermediate has been exploited for the partial kinetic resolution of a range of 1-aryl-1,2-diols (*rac*)-**147a–e**. Thus, mono-benzoyl esters (*S*)-**148a–e** were obtained in moderate e.e. using

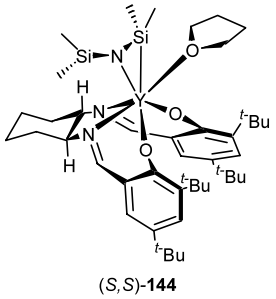
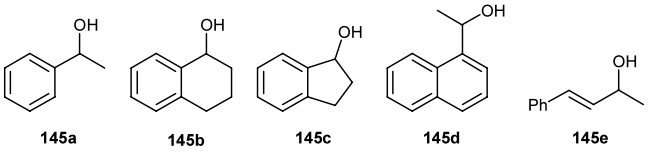


Figure 41.

Table 6. Kinetic resolution of secondary alcohols (*rac*)-**145a–e** catalysed by (*S*,*S*)-**144** via acylation with isopropenyl acetate



Alcohol	*C* (%)	E.e. (%) recovered alcohol
145a	65	23 (*S*)
145b	39	14 (*R*)
145c	76	91 (*R*)
145d	61	36 (*S*)
145e	42	13 (*S*)

dibromobinaphthylstannepin (*S*)-**146** (Fig. 42) as a chiral catalyst (Scheme 45).[116]

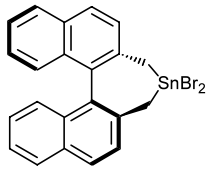
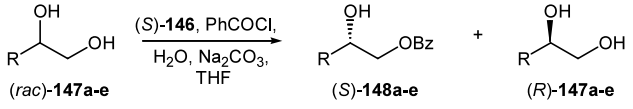


Figure 42.



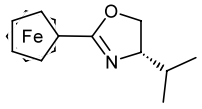
a: R=Ph
b: R=β-naphthyl
c: R=α-naphthyl
d: R=$CH_3(CH_2)_9$-
e: R=C_2H_5-

148a: 86% e.e., 38% yield
148b: 64% e.e., 25% yield
148c: 72% e.e., 41% yield
148d: 59% e.e., 35% yield
148e: 44% e.e., 35% yield

Scheme 45. Kinetic resolution of (*rac*)-**147a–e** catalysed by dibromobinaphthylstannepin (*S*)-**146**.

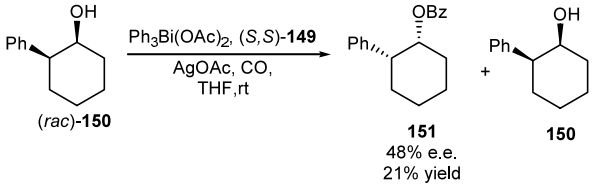
Uemura et al. have reported an alternative Pd(0) mediated carbonylation strategy for the kinetic resolution of racemic secondary alcohols involving treatment with carbon monoxide, $Ph_3Bi(OAc)_2$, AgOAc,

and a catalytic amount of $PdCl_2$ in the presence of homochiral oxazolinylferrocenyl phosphine ligand (*S*,*S*)-**149** (Fig. 43).[117] The enantioselectivity obtained in these type of resolutions were generally unsatisfactory however, with the best results to date being obtained for the resolution of *cis*-1-phenyl-hexan-2-ol (*rac*)-**150** to afford benzoate ester *cis*-**151** in 48% e.e. (Scheme 46).



(*S*,*S*)-**149**

Figure 43.



(*rac*)-**150**

151
48% e.e.
21% yield

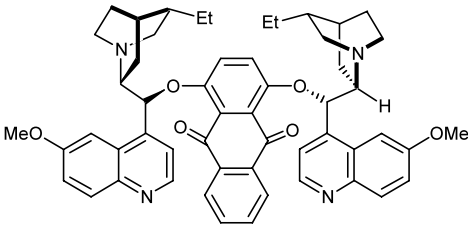
150

Absolute Configuration not specified

Scheme 46. Kinetic resolution of *cis*-1-phenyl-hexan-2-ol (*rac*)-**150**.

6. Kinetic resolution via alcoholysis of racemic carbonyl derivatives

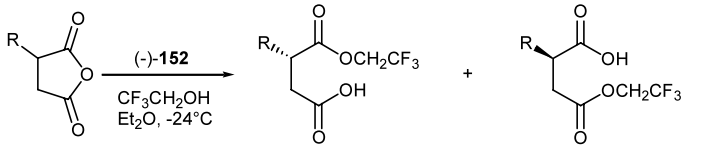
Deng et al. have recently published a series of important papers on the use of modified cinchona alkaloid catalysts for the kinetic resolution of racemic succinic anhydrides, 5-substituted-1,3-dioxolane-2,4-diones, and *N*-carbamoyl-α-aminoacid-*N*-carboxyanhydrides.



(-)-**152**

Figure 44.

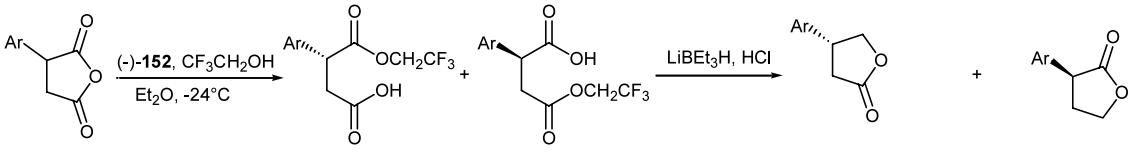
Building on their original work on the desymmetrisation of (*meso*)-cyclic anhydrides,[118] they reported that cinchona catalyst $(DHQD)_2AQN$ (–)-**152** (Fig. 44) could be employed as a catalyst for the parallel kinetic resolution of 2-alkyl succinic anhydrides (*rac*)-**153a–d** using trifluoroethanol (10 equiv.) as a nucleophile.[119] They found that the (*S*)-**153a–d** enantiomers of these 2-alkyl-succinic anhydrides were stereoselectively transformed into the corresponding trifluoroethyl 3-alkyl-succinates (*S*)-**154a–d**, whilst their (*R*)-**153a–d** enantiomers were converted into the corresponding trifluoroethyl 2-alkyl-succinates (*R*)-**155a–d**, affording easily separable regioisomeric products in excellent e.e. (Scheme 47). This methodology was extended to the kinetic resolution of 2-aryl-succinates (*rac*)-**156a–c** containing both electron-rich or electron-poor aryl substituents, enabling the synthetically useful lactones (*R*)-**159a–c** (via (*R*)-**157a–c**) and (*S*)-**160a–c** (via (*S*)-**158a–c**) to be obtained (Scheme 48). This approach clearly demonstrates the power of the strategy of parallel kinetic resolution for asymmetric



(*rac*)-**153a-d** (*S*)-**154a-d** (*R*)-**155a-d**

a: R=Me	**154a:** 93% e.e., 36% yield	**155a:** 80% e.e., 41% yield
b: R=Et	**154b:** 91% e.e., 38% yield	**155b:** 70% e.e., 50% yield
c: R=^{n}-C_8H_{17}	**154c:** 98% e.e., 38% yield	**155c:** 66% e.e., 41% yield
d: R=-$CH_2CH{=}CH_2$	**154d:** 96% e.e., 40% yield	**155d:** 82% e.e., 49% yield

Scheme 47. $(DHQD)_2AQN$ (–)-**152**-catalysed parallel kinetic resolution of (*rac*)-**153a–d**.



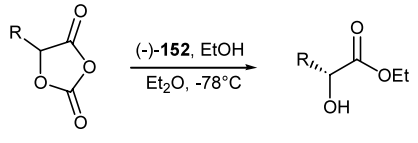
(*rac*)-**156a-c** (*R*)-**157a-c** (*S*)-**158a-c** (*R*)-**159a-c** (*S*)-**160a-c**

a: Ar=Ph	**157a:** 95% e.e.	**158a:** 87% e.e.,	**159a:** 95% e.e., 44% yield	**160a:** 82% e.e., 32% yield
b: Ar=3-C_6H_4	**157b:** 96% e.e.	**158b:** 83% e.e.,	**159b:** 95% e.e., 45% yield	**160b:** 83% e.e., 30% yield
c: Ar=4-ClC_6H_4	**157c:** 96% e.e.	**158c:** 76% e.e.,	**159c:** 96% e.e., 44% yield	**160c:** 63% e.e., 29% yield

Scheme 48. Asymmetric synthesis of β-aryl-lactones (*R*)-**159a–c** and α-aryl-γ-lactones (*S*)-**160a–c** via PKR of (*rac*)-**156a–c**.

synthesis, with the authors commenting that '*a conventional kinetic resolution of a selectivity factor of at least 112 would be required to obtain lactone* ***159c*** *from racemic anhydride* (*rac*)-***156c*** *with the same e.e. and yield afforded by the parallel kinetic resolution processes*.'[120]

This methodology was further applied to the dynamic kinetic resolution of 5-aryl-1,3-dioxolane-2,4-diones (*rac*)-**161a–e** to afford α-hydroxy acids (*R*)-**162a–e** in >90% e.e. and >65% yield. The catalytic cinchona alkaloid catalyst (–)-**152** in these reactions was proposed to serve a dual function by facilitating efficient in situ racemisation of (*rac*)-**161a–e**, as well as acting as an efficient catalyst for alcoholytic kinetic resolution (Scheme 49). Related racemic 5-alkyl-1,3-dioxolane-2,4-diones did not undergo dynamic kinetic resolution under these conditions, presumably due to the reduced acidity of the α-proton at the C-5 stereocentre, however efficient kinetic resolutions were still observed in these cases with *s*-values >49.[121]



Scheme 49. DKR of 5-aryl-1,3-dioxolane-2,4-diones (*rac*)-**161a–e**.

A third report on the use of $(DHQD)_2AQN$ (–)-**152** for the kinetic resolution of *N*-urethane-α-amino acid-*N*-carboxyanhydrides (UNCAs) (*rac*)-**163a–f** using methanol (0.5 equiv.) as a nucleophile at temperatures <–60°C was equally impressive, affording either enantiomer of the *N*-carbamoyl-α-amino acid in high e.e. Thus, UNCAs (*rac*)-**163a–f** that contained α-alkyl, α-benzyl, or α-aryl substituents were resolved in high e.e. using catalyst (–)-**152**, to afford *N*-carbamoyl-α-amino esters (*R*)-**164a–f**, and recovered UNCAs (*S*)-**163a–f** with *s* values ranging from 23 to 170. The recovered UNCAs (*S*)-**163a–f** were easily deprotected to their parent (*S*)-*N*-carbamoyl-α-amino acids **165a–f** via mild aqueous hydrolysis (Scheme 50). A general base-catalysed mechanism was proposed to explain the high stereoselectivities in these resolutions, in which coordination of the incipient alcohol nucleophile to a nitrogen atom of a dihydroquinidyl group of the catalyst results in a chiral complex that could efficiently discriminate between the two enantiomers of the racemic UNCAs as depicted in Figure 45.[122]

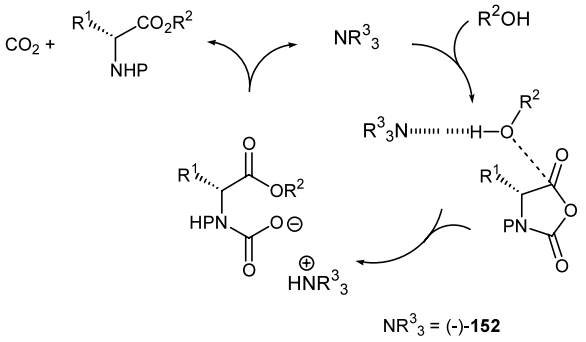
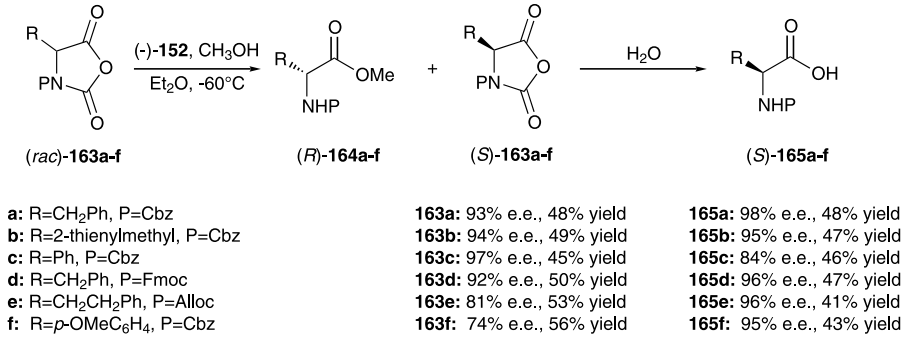
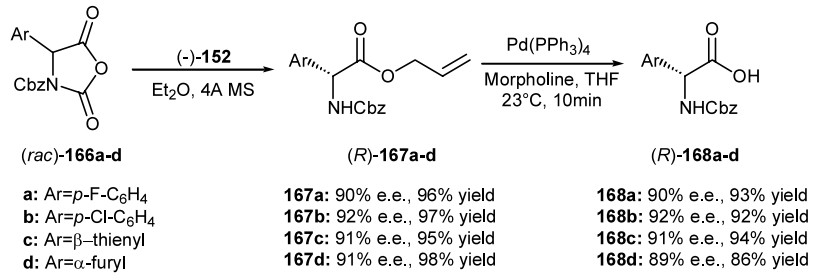


Figure 45. General base catalysis for (–)-**152**-catalysed alcoholysis of the (*R*)-enantiomer of UNCAs **163a–f**.

Subsequent investigations into the resolution of α-aryl-UNCAs (*rac*)-**166a–d** revealed that raising the temperature of the reaction mixture to 23°C, and substituting allyl alcohol for methanol as nucleophile, resulted in an efficient dynamic kinetic resolution at room temperature, thus affording a wide range of *N*-carbamoyl-α-aryl-α-amino esters including (*R*)-**167a–d** in >90% e.e. and >94% yield which were easily deprotected to their *N*-carbamoyl-α-amino acids (*R*)-**168a–d** under mild conditions (Scheme 51).[123]



Scheme 50. Kinetic resolutions of UNCAs (*rac*)-**163a–f** via (–)-**152**-catalysed alcoholysis.



Scheme 51. DKR of 5-aryl-UNCAs (*rac*)-**166a–d** catalysed by (–)-**152**.

7. Resolution via palladium-catalysed allylic substitution reactions

There continues to be considerable interest in the development of methodology based on palladium-catalysed dynamic kinetic resolution of allylic acetates/carbonates/epoxides using a wide range of nucleophiles.[124] Recent reports in this area may be conveniently divided into those that apply existing chiral phosphine ligands to new substrates or transformations, and those directed towards the development of new classes of chiral ligand. Trost et al. have published detailed full experimental details on the use of their bis-phosphine ligand (*R*,*R*)-**169** (Fig. 46) for the dynamic kinetic resolution (or dynamic kinetic asymmetric transformation) of allylic mono-epoxide (*rac*)-**170** using phthalimide **171** as a nucleophile to afford (*R*)-**172** which was used for the asymmetric synthesis of the drugs vigabatrin (*R*)-**173** and ethambutol (*S*,*S*)-**174** (Scheme 52).[125] The alternative use of either enantiomer of ligand **175** (Fig. 47) to control the addition of benzoic acid, or the sodium salt of phenylsulfonylnitromethane to (*rac*)-**176** was also described thus enabling the preparation of (+)-**177** and **179**, as synthons for the synthesis of the aminocyclitol fragment of Hygromycin A **178**, and (–)-Cyclophellitol **180**, respectively (Scheme 53).[126]

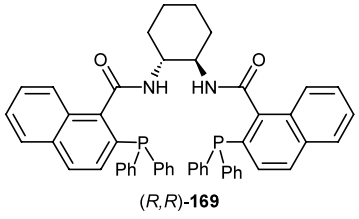


Figure 46.

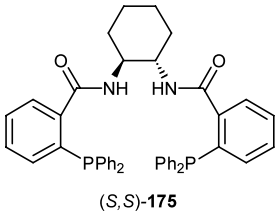
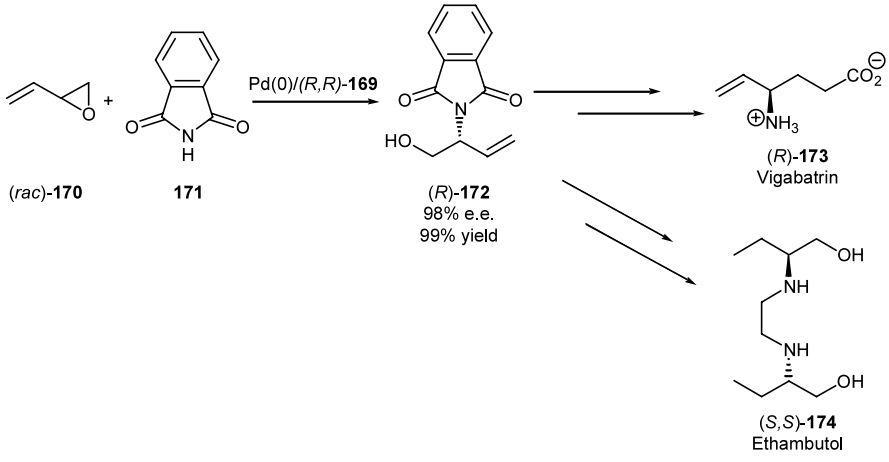
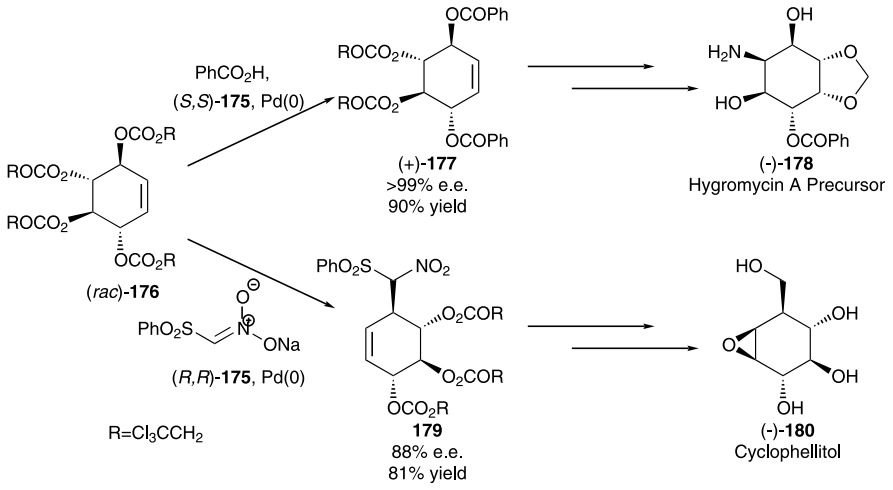


Figure 47.



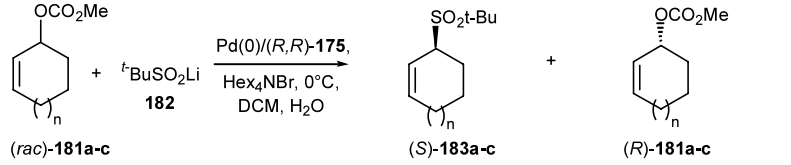
Scheme 52. Synthesis of Vigabatrin (*R*)-**173** and Ethambutol (*S*,*S*)-**174** via DKR.



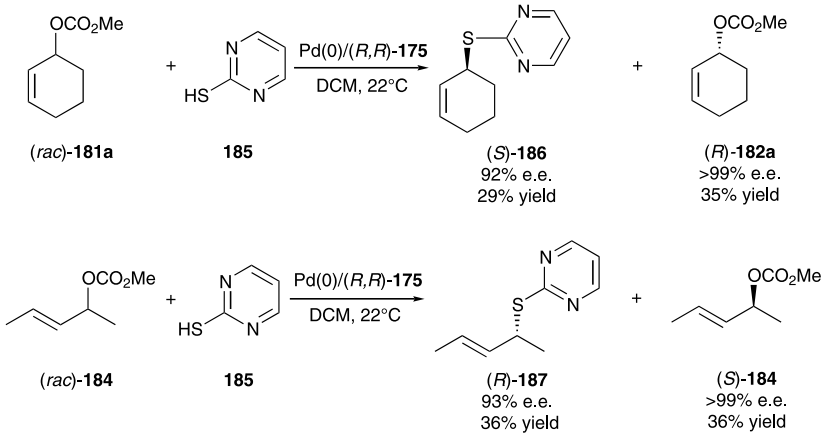
Scheme 53. Synthesis of Hygromycin A precursor **178** and (–)-Cyclophellitol **180** via DKR.

Building on their previous work on the Pd-catalysed asymmetric synthesis of allylic *S*-derivatives via kinetic resolution,[127] Gais et al. have reported the use of ligand (*R*,*R*)-**175** for the efficient kinetic resolution of both cyclic and acyclic carbonates (*rac*)-**181a**–**c** and (*rac*)-**184** using lithium *tert*-butyl sulfinate **182** (Scheme 54) or thiol **185** as nucleophiles affording allylic sulfones (*S*)-**183a**–**c** and allylic sulfides (*R*)-**186** and (*S*)-**187**, respectively with $s > 40$ (Scheme 55).[128]

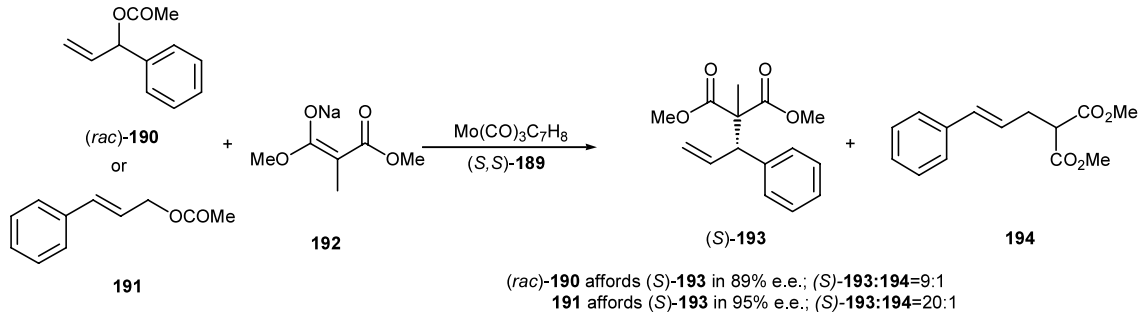
In a novel approach to the identification of new chiral ligands for asymmetric catalysis, Lloyd-Jones et al.



Scheme 54. Pd(0)-catalysed kinetic resolution of carbonates (*rac*)-**181a**–**c** with lithium *t*butyl sulfinate.

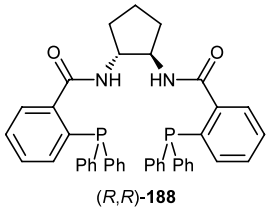


Scheme 55. Pd(0)-catalysed kinetic resolution of carbonates (*rac*)-**181a** and (*rac*)-**184** with thiol **185**.



Scheme 56. DKR of allylic carbonates (*rac*)-**190** and **191** via Mo allylic substitution.

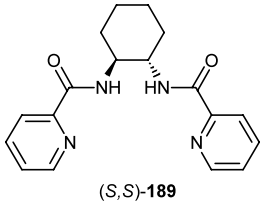
have introduced the concept of screening catalysts derived from racemic ligands against scalemic substrates under pseudo zero order conditions. Thus, by monitoring the change in enantiomeric excess of a scalemic sample of cyclohexenyl acetate in palladium-catalysed allylic alkylation reactions using racemic bis-phosphine ligands over time, they were able to identify that the Trost-like ligand (*rac*)-**188** was an excellent prospective ligand for this class of kinetic resolution. Subsequent preparation of (*R*,*R*)-**188** (Fig. 48) in enantiomerically pure form, and its use as a chiral ligand for the palladium-catalysed resolution of racemic cyclohexenyl acetate, resulted in an *s* value >100 which is the highest value reported to date for this class of resolution.[129]



(*R*,*R*)-**188**

Figure 48.

From a practical perspective the process group at Merck have described a detailed mechanistic investigation into the alternative use of molybdenum-catalysed asymmetric allylic alkylation reactions using (bis)-picolinamide (*S*,*S*)-**189** (Fig. 49) as a ligand to induce enatioselectivity.[130] Thus, they have shown that the molybdenum-catalysed allylic alkylation of branched carbonate (*rac*)-**190** or unbranched carbonate **191** with a malonate nucleophile **192** results in efficient dynamic kinetic asymmetric transformation with a significant chiral memory effect,[131] to

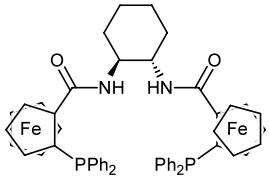


(*S*,*S*)-**189**

Figure 49.

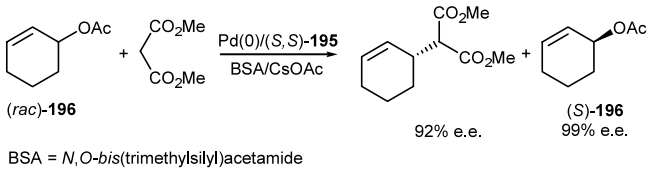
afford the desired branched product (*S*)-**193** in good yields and e.e., with excellent selectivity over unbranched alkylation product **194** in both cases (Scheme 56).[132]

In 2000, Zhang et al. reported the development of a new phosphinoferrocenyl ligand (*S*,*S*)-**195** (Fig. 50) which was successfully employed for alkylation of 2-cyclohexenyl acetate (*rac*)-**196** via treatment with dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and CsOAc.[133] This approach afforded the unreacted enantiomer (*S*)-**196** in 99% e.e. at 54% conversion (Scheme 57).



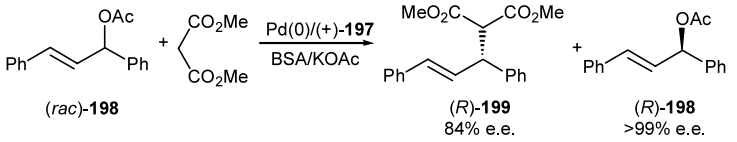
(*S*,*S*)-**195**

Figure 50.



Scheme 57. Kinetic resolution of 2-cyclohexenyl acetate (*rac*)-**182a** via Pd(0) allylic substitution.

Reetz et al. have described the use of a chiral helical diphosphine 2,15-bis-(diphenylphosphino)-hexahelicene (+)-**197** (Fig. 51) as a ligand in palladium-catalysed kinetic resolution of 1,3-diphenylpropenylacetate (*rac*)-**198** using dimethyl malonate, BSA and a catalytic amount of anhydrous KOAc. A conversion of 81% was observed after 1 h leading to the formation of the allylic substitution product (*R*)-**199** in 84% e.e. and unreacted 1,3-diphenylpropenylacetate (*R*)-**198** in >99% e.e. (Scheme 58).[134]



Scheme 58. Kinetic resolution of 1,3-diphenylpropenylacetate (*rac*)-**198** via Pd(0) allylic substitution.

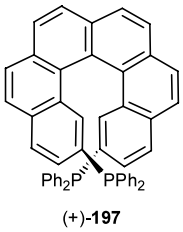


Figure 51.

A method related to parallel kinetic resolution is regiodivergent kinetic resolution, in which the enantiomers of a racemic substrate react with a chiral catalyst to afford regioisomeric products.[135] A proof of principle of this RKR approach was demonstrated for the palladium-catalysed allylic substitution of a mixture of all four possible stereoisomers of 5-vinyloxazolidinone (*rac*)-**201** and (*rac*)-**202** with phthalimide.[136] In this case the racemic mixture of diastereoisomers was treated with a Pd(0)-DIOP-(*R*,*R*)-**200** (Fig. 52) catalyst and phthalimide to afford (via diastereoisomeric Pd–allyl complexes **203** and **204**) a 1:1.2 mixture of vicinal diamine (*R*,*R*)-**205** (52% e.e., 33% yield) and 1,4-diamine (*S*)-**206** (48% e.e., 39% yield), respectively (Scheme 59).

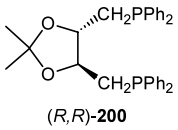
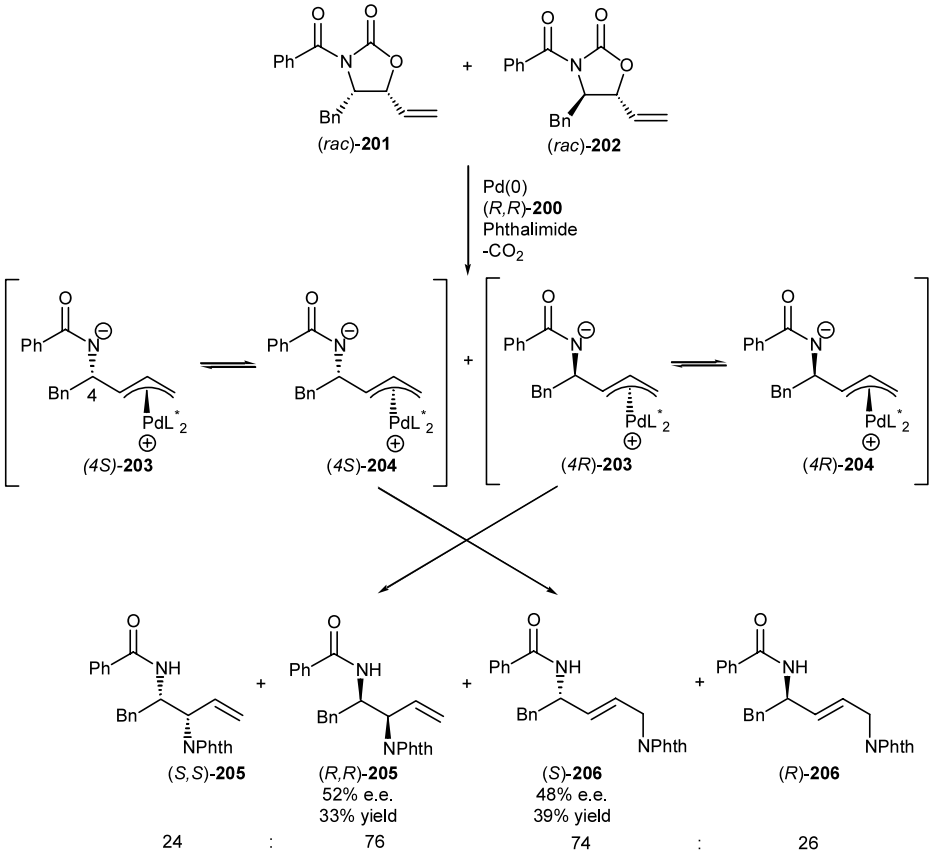
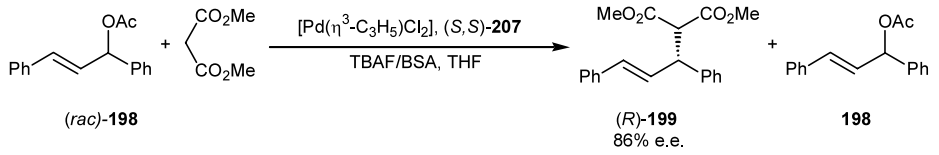


Figure 52.

Alternative types of chiral *P*,*O*-ligands have also been introduced that afford useful levels of stereocontrol for palladium-catalysed allylic substitution reactions. Firstly, Gilbertson et al. have employed combinatorial screening approaches to identify chiral phosphines such as (*S*,*S*)-**207** (Fig. 53) for the efficient kinetic



Scheme 59. Regiodivergent kinetic resolution of oxazolidin-2-ones (*rac*)-**201** and (*rac*)-**202**.



Scheme 60. Pd(0)-mediated kinetic resolution of (*rac*)-**198** using ligand (*S*,*S*)-**207**.

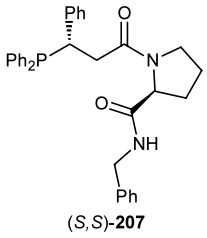


Figure 53.

resolution of allylic acetate (*rac*)-**198** to afford (*R*)-**199** in 86% e.e. at 45% conversion (Scheme 60).[137] Alternatively, a palladium complex derived from 3-(diphenylphosphino)butanoic acid (*S*)-**208** (Fig. 54) has been employed for the transformation of *cis*-alkenediol diacetate (*meso*)-**209** to afford mono-acetate (1*R*,4*S*)-**210** in 92% e.e. and 41% yield.[138] In this approach, initial desymmetrisation of (*meso*)-**209** to afford (1*R*,4*S*)-**210** and (1*S*,4*R*)-**210** is followed by a subsequent kinetic resolution step in which (1*S*,4*R*)-**210** is stereoselectively converted into the bis-alkylated product (1*R*,4*R*)-**211** (Scheme 61).[139]

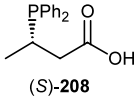


Figure 54.

8. Transition metal-mediated carbon–carbon bond forming reactions

The use of ruthenium and molybdenum catalysts for ring closing metathesis (RCM) is now a well established strategy for the construction of a wide range of compounds that contain small, medium and large ring systems.[140] The development of asymmetric variants of these catalysts has enabled stereoselective RCM reactions to be developed, using either kinetic resolution, or enantioselective desymmetrisation strategies.[141] In 1996, Grubbs et al. reported the first example of an RCM mediated kinetic resolutions using chiral molybdenum alkylidene biphenyl-complex (*R*,*R*)-**212** (Fig. 55) as a catalyst for the resolution of racemic dienes in moderate to good e.e.[142] In their best example, treatment of diene (*rac*)-**213** with 2.0 mol% of (*R*,*R*)-**212** at 25°C resulted in stereoselective cyclisation to afford allylic acetate (*R*)-**214**, enabling recovery of unreacted starting material (*S*)-**213** (10%) in 84% e.e. at 90% conversion (Scheme 62).

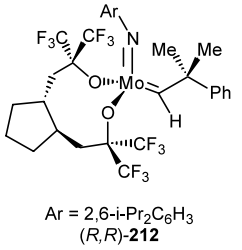
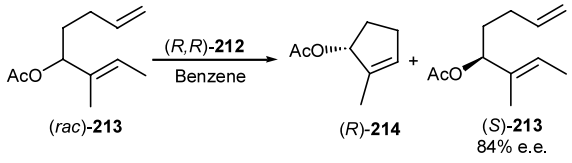
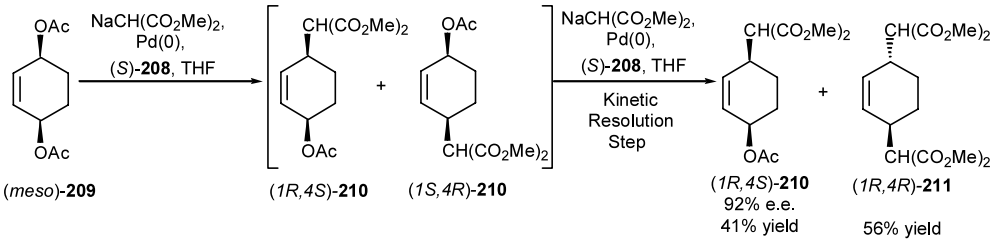


Figure 55.



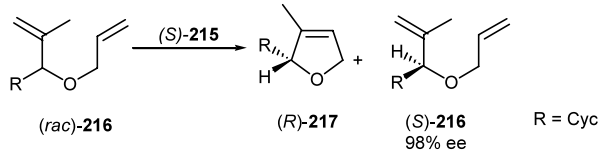
Scheme 62. Kinetic resolution using RCM catalysed by (*R*,*R*)-**212**.

Hexafluoro-MoTBEC catalyst (*R*,*R*)-**212** generally afforded only moderate levels of enantiodiscrimination for these type of kinetic resolutions however, and consequently Hoveyda et al. reported on a new improved Mo–biphen catalyst (*S*)-**215** (Fig. 56) for the catalytic resolution of a range of racemic allylic ethers.[143] In a typical reaction, treatment of allylic ether (*rac*)-**216** with 5 mol% of catalyst (*S*)-**215** in



Scheme 61. Sequential Pd(0)-mediated kinetic resolution of (*rac*)-**210** using ligand (*S*)-**208**.

toluene at −25°C gave dihydrofuran (*R*)-**217**, enabling recovery of unreacted (*S*)-**216** in 98% e.e. at 62% conversion (Scheme 63). Importantly, a recyclable polymer supported version of catalyst (*S*)-**215** has recently been reported that provides excellent selectivity for this type of kinetic resolution.[144]



Scheme 63. RCM kinetic resolution of an allylic ether (*rac*)-**216** catalysed by complex (*S*)-**215**.

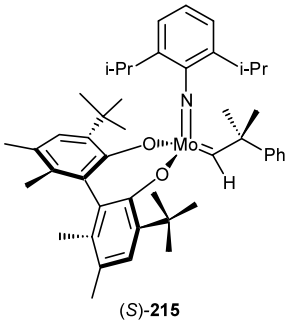
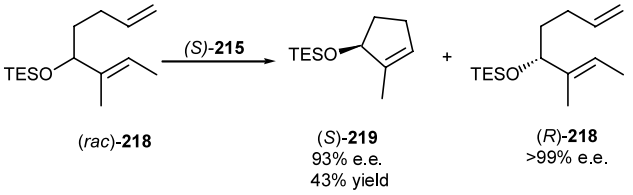


Figure 56.

Similar to Grubbs original work, Hoveyda et al. also described the use of catalyst (*S*)-**215** for RCM-catalysed kinetic resolution of racemic 1,6-dienes containing allylic alkoxy or allylic siloxy groups. For example, treatment of allylic triethylsilylether (*rac*)-**218** with catalyst (*S*)-**215** resulted in formation of TMS protected cyclopent-2-enol (*S*)-**219** in 93% e.e. and 43% yield, whilst unreacted (*R*)-**218** was recovered in >99% e.e. (Scheme 64).[145]



Scheme 64. Kinetic resolution of an acyclic diene (*rac*)-**218** catalysed by complex (*S*)-**215**.

RCM-catalysed kinetic resolution of structurally related racemic 1,7-dienes using (*S*)-**215** was ineffective however, and was best carried out using a new second generation Mo-BINOL catalyst (*R*)-**220** that gave outstanding selectivities for a range of racemic *O*-silyl-allylic ethers.[146] Interestingly, subsequent introduction of a third generation catalyst (*R*)-**221** (Fig. 57), that combines the structural features of both biphen-**215** and BINOL-**220**, has resulted in a robust catalyst that demonstrates an equally good reactivity profile for the resolution of both 1,6-dienes (*rac*)-**222** and 1,7-dienes (*rac*)-**223** (Table 7).[147]

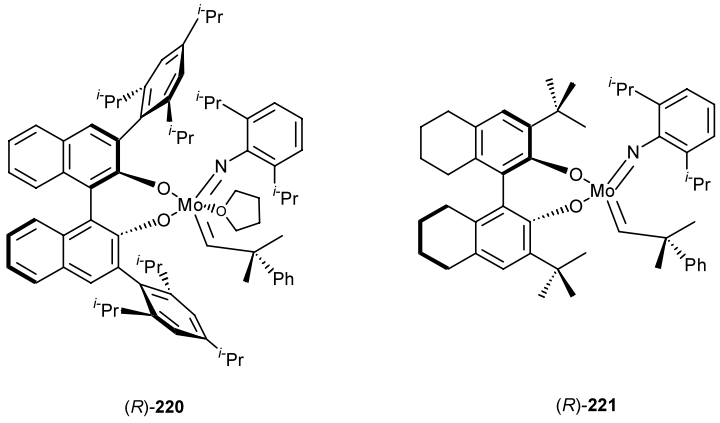
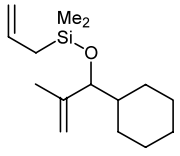
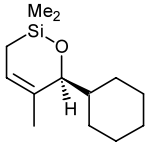
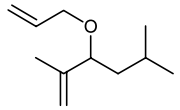
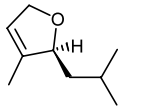
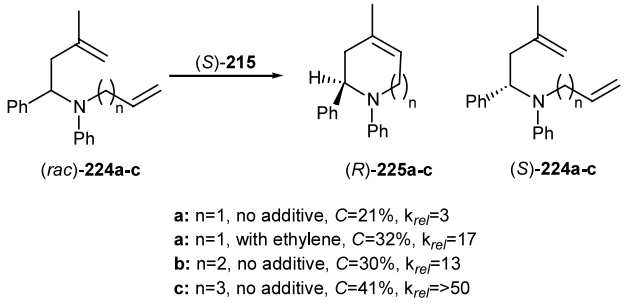


Figure 57.

Table 7. Mo-catalysed kinetic resolutions via RCM

Substrate	Product	Catalyst	*CI*/%	Dimer/%	k_{rel}
 **222**	 *ent* for (*S*)-**215**	(*S*)-**215**	54	47	<2.0
		(*R*)-**220**	60	8	>25
		(*R*)-**221**	65	45	>25
 **223**	 *ent* for (*S*)-**215**	(*S*)-**215**	59	<2	11
		(*R*)-**220**	44	<2	<2.0
		(*R*)-**221**	58	<2	23

Finally, the use of biphen catalyst (*S*)-**215** has been extended to the kinetic resolution of unsaturated amines (*rac*)-**224a–c** containing 1,6-, 1,7- and 1,8-diene functionality for the synthesis of medium-ring unsaturated *N*-aryl amines (*R*)-**225a–c**, including an impressive stereoselective synthesis of (*R*)-**225c** ($n=3$) containing an eight-membered azocine skeleton (Scheme 65). These RCM reactions were carried out under essentially solvent free conditions, and in certain cases required the presence of one atmosphere of ethylene to ensure reversible Mo–alkylidene formation to ensure efficient enantiodiscrimination.[148]



Scheme 65. Kinetic resolution of acyclic amines (*rac*)-**224a–c** via RCM.

Schmalz et al. have reported the stereoselective functionalisation of dichloroarene–$Cr(CO)_3$ complex **227** via a Pd(0)-catalysed carbonylation reaction using Hayashi's PPF–pyrrolidine ligand (*R*,*S*)-**226** (Fig. 58) to control enantioselectivity. Thus, treatment of complex **227** with carbon monoxide, Et_3N, and 2 mol% of catalyst (*R*,*S*)-**226** in methanol resulted in the formation of chloroester (*S*)-**228** in 95% e.e. and 31% yield, as well as a 48% yield of bis-ester **229**. Subsequent investigations revealed that the e.e. of recovered chloroester (*S*)-**228** increased as the reaction proceeded, consistent with a second kinetic resolution step operating to selectively convert the (*R*)-**228** enantiomer to (bis)-ester **229** (Scheme 66).[149]

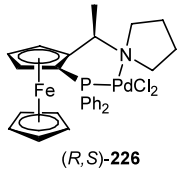
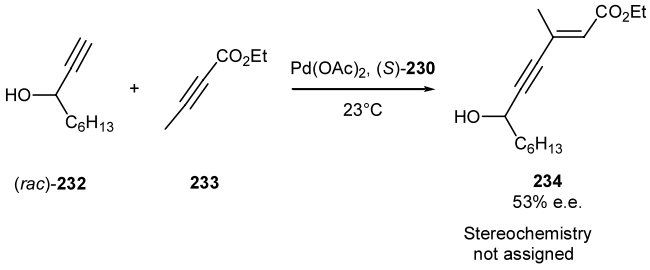


Figure 58.

Pfaltz et al. have disclosed that palladium complexes derived from chiral *P*,*N*-oxazoline ligands are highly efficient catalysts for the coupling of alkynes and alkenes, and have used this methodology for the kinetic resolution of racemic propargylic alcohols.[150] Thus, the use of *P*,*N*-ligand (*S*)-**230** resulted in the cross-coupling of propargylic alcohol (*rac*)-**232** with alkynoate **233** and to form (*E*)-ene-yne **234** in 53% e.e. (Scheme 67). The use of *P*,*N*-ligand (*S*)-**231** (Fig. 59) for the cross-coupling of γ-hydroxyalkynoate (*rac*)-**235** with alkyne **236** resulted in a 1:1 mixture of the regioisomeric butenolides **237** and **238** in 85% e.e. and 25% e.e., respectively (Scheme 68).



Scheme 67. Kinetic resolution of propargylic alcohol (*rac*)-**232**.

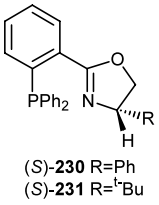
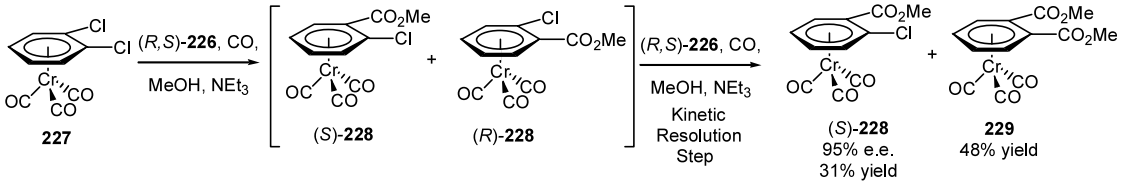
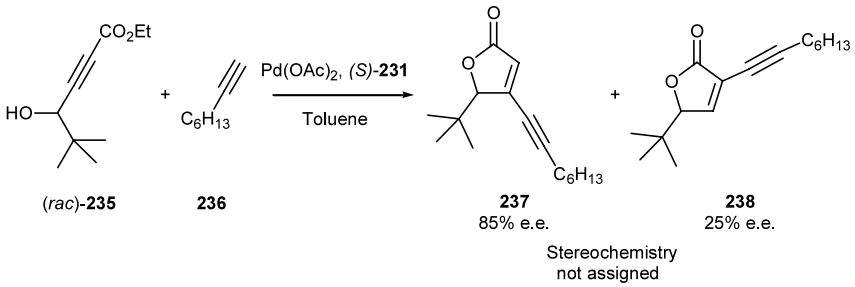


Figure 59.

Fu et al. have applied their recently published methodology[151] employing rhodium-catalysed cyclisation of alkyne–aldehydes to afford cyclopenten-2-ones for the kinetic resolution of racemic 3-methoxy-alkyn-1-als with good stereocontrol.[152] They proposed that the presence of the 3-methoxy substituent within the alkyn-1-al substrate resulted in two-point complexation to the rhodium catalyst to afford a highly ordered transition state that enabled 3-methoxy-alkyn-1-als (*rac*)-**239a–f** to be resolved in $\geq 90\%$ e.e. via enantioselective cyclisation of their (*S*)-enantiomers to afford cyclopent-2-enones (*S*)-**240a–f** (Table 8).

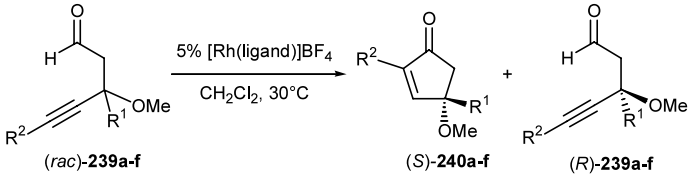


Scheme 66. Stepwise kinetic resolution of scalemic dichloroarene-$Cr(CO)_3$ complex **228** via a Pd(0)-catalysed carbonylation reaction.



Scheme 68. Kinetic resolution of α-hydroxyalkynoate (*rac*)-**235**.

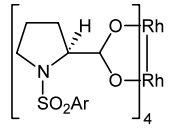
Table 8. Rhodium-catalysed kinetic resolution of 4-alkynals (*rac*)-**239a–f**



Substrate	R^1	R^2	Ligand	*C* (%)	e.e. of (*R*)-**239a–f**	*s*
239a	H	Ph	(*S*,*S*)-^{i}Pr-DUPHOS	56	93	22
239b	H	*o*-Tol	(*S*,*S*)-^{i}Pr-DUPHOS	56	90	19
239c	H	$CH_2CH(CH_3)_2$	(*S*,*S*)-^{i}Pr-DUPHOS	53	93	41
239d	CH_3	Ph	(*R*)-Tol-BINAP	60	99	22
239e	CH_3	*c*-Hex-1-enyl	(*R*)-Tol-BINAP	63	99	18
239f	^{i}Pr	Ph	(*R*)-Tol-BINAP	76	95 (*S*)	5.4

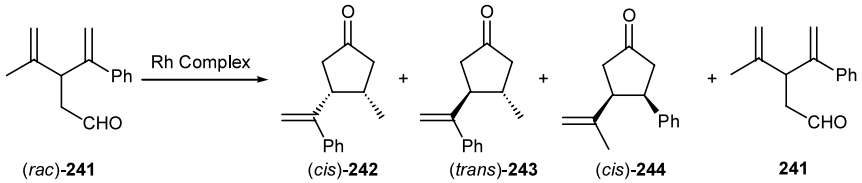
Rhodium-catalysed cyclisations have also been applied to the kinetic resolution of 3,4-disubstituted 4-pentenal (*rac*)-**241** using the cationic Rh[(*S*)-BINAP]ClO_4 complex which gave *trans*-**243** in >95% e.e. and 42% yield, and enantiomerically enriched **241** in 43% yield. The alternative use of neutral complex Rh[(*S*)-BINAP]Cl resulted in stereoselective cyclisation of (*rac*)-**241** to afford *cis*-**242** in >95% e.e. and 19% yield, and *cis*-**244** in >95% e.e. and 21% yield (Scheme 69).[153]

Davies et al. have employed their [Rh_2-DOSP] catalyst (*S*)-**245** (Fig. 60) for highly enantioselective and diastereoselective C–H insertion reactions into *N*-Boc-2-pyrrolidines substituted (*rac*)-**246a–d**, thus enabling the simultaneous control of three stereocentres in high e.e.[154] Reaction of methyl *p*-bromophenyldiazoacetate **247** with *N*-Boc-proline derived esters (*rac*)-**246a**,**b**, or protected alcohols (*rac*)-**246c**,**d**, in the presence of catalyst (*S*)-**245** resulted in the formation of (*trans*)-1,3-disubstituted-pyrrolidines (1*R*,4*S*,5*S*)-**248a–d** in >79% e.e., >78% d.e. and in >30% yield (Scheme 70).



Ar = *p*-($C_{12}H_{25}$)C_6H_4
(*S*)-**245**

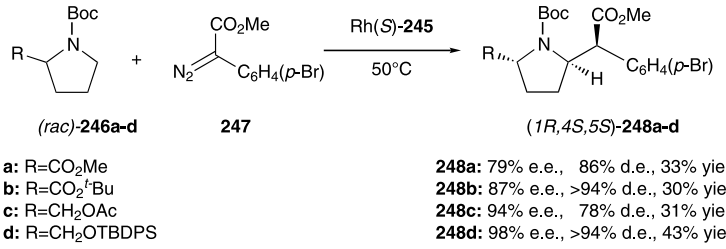
Figure 60.



Rh[(*S*)-BINAP]ClO_4: (*trans*)-**243:** >95% e.e., 42% yield; **241:** 43% yield
Rh[(*S*)-BINAP]Cl: (*cis*)-**242:** >95% e.e., 19% yield; (*cis*)-**244:** >95% e.e., 21% yield

Absolute stereochemistry of major products not assigned

Scheme 69. Kinetic resolution via asymmetric cyclisation of dissymmetric 3,4-disubstituted 4-pentenal (*rac*)-**241**.



Scheme 70. Kinetic resolution via enantioselective C–H insertion into 2-substituted pyrrolidines (*rac*)-**246a–d**.

9. Kinetic resolution via 1,4-conjugate addition[155]

Feringa et al. have continued to explore their original work employing chiral phosphoroamidite ligands[156] to control the stereoselective 1,4-addition of dialkylzinc species to conjugate acceptors, which has previously been reported for the kinetic resolution of 1,3-diene monoepoxides and alkynyl epoxides.[157] Recent developments have shown that enantioselective conjugate addition of 0.5 equiv. of Et_2Zn to methylidenecyclohexene epoxide (*rac*)-**250**, in the presence of catalytic amounts of $Cu(OTf)_2$ and phosphoramidite ligand (*S*,*S*,*S*)-**249** (Fig. 61), resulted in a stereoselective S_N2' reaction to afford allylic alcohol (*S*)-**251** in 88% e.e. and 45% yield (Scheme 71).[158] This methodology was further developed to afford a parallel kinetic resolution strategy, in which the use of excess Et_2Zn in the presence of $Cu(OTf)_2$ and ligand (*R*,*R*,*R*)-**249** resulted in each enantiomer of mono-epoxide (*rac*)-**250** being stereospecifically and quantitatively transformed into allylic alcohol (*R*)-**251** (80% e.e., S_N2'), or homoallylic alcohol (*S*,*S*)-**252** (99% e.e., S_N2), respectively (Scheme 72).[159]

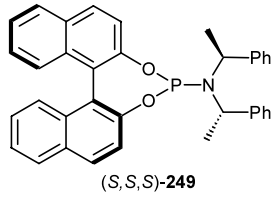
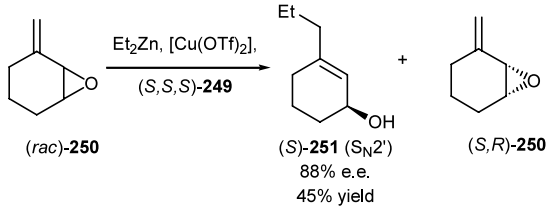
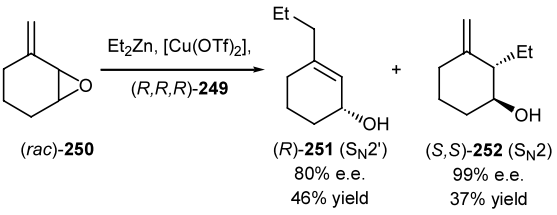


Figure 61.

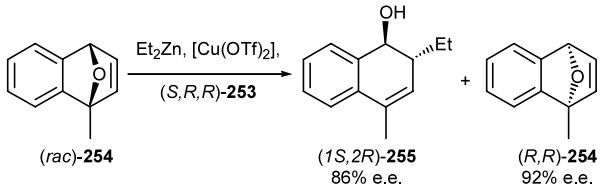


Scheme 71. Kinetic resolution of vinyl epoxide (*rac*)-**250** with (*S*,*S*,*S*)-**249**.

Additionally, they have also demonstrated that an oxabenzonorbornadiene derivative (*rac*)-**254** can be successfully resolved using this type of catalytic conjugate addition approach, with (*S*,*R*,*R*)-**253** (Fig. 62) catalysing the addition of Et_2Zn to afford recovered cyclic ether (*R*,*R*)-**254** in 92% e.e., and (*anti*)-dihydronaphthol (1*S*,2*R*)-**255** in 86% e.e. at 56% conversion (Scheme 73).[160]



Scheme 72. PKR of a vinyl epoxide (*rac*)-**250** with (*R*,*R*,*R*)-**249**.



Scheme 73. Kinetic resolution of oxabenzonorbornadiene derivative (*rac*)-**254**.

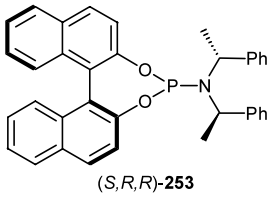
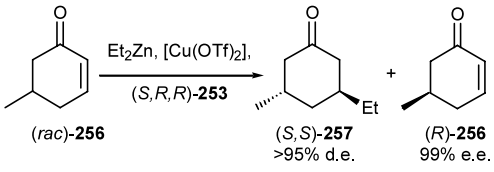


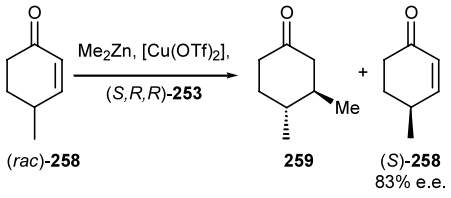
Figure 62.

In 2001, Feringa et al. also demonstrated that their copper–BINOL–phosphoramidite complex could also be used for the kinetic resolution of a range of racemic 5-alkyl cyclohex-2-enones via stereoselective 1,4-conjugate addition of a range of different $(R_1)_2Zn$ species (R_1 = Me, Et, ^{i}Pr and ^{n}Bu).[161] For example, treatment of 5-methyl-cyclo-hex-2-en-one (*rac*)-**256** with ligand (*S*,*R*,*R*)-**253**, $[Cu(OTf)_2]$, and diethyl zinc gave the unreacted enantiomer (*R*)-**256** in 99% e.e. and the *syn*-3,5-dialkyl addition product (*S*,*S*)-**257** in >95% d.e. at 53% conversion (Scheme 74). Indeed, the authors report that the stereoselectivities obtained in these transformations rivalled those of enzymatic-catalysed kinetic resolutions

since they '*approach the near perfect situation…as the reaction virtually ceases at 50% conversion in the presence of 1 equiv. of Me_2Zn*'. The resolution of 4-methyl-cyclohex-2-enone (*rac*)-**258** using (*S*,*R*,*R*)-**253** was also reported affording **259** (stereochemistry not assigned), and (*S*)-**258** in 83% e.e. at 55% conversion using Me_2Zn as a nucleophile (Scheme 75).



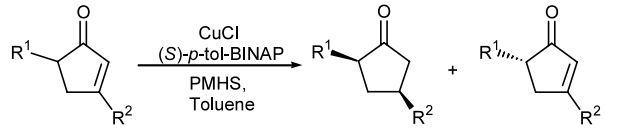
Scheme 74. Kinetic resolution of 5-methyl-2-cyclohex-2-enone (*rac*)-**256**.



Scheme 75. Kinetic resolution of 4-methyl-2-cyclohexanone (*rac*)-**258**.

Independent studies by Krause et al. have also shown that this kinetic resolution protocol also works equally well for racemic 6-*tert*-butyl-cyclohex-2-enone (*rac*)-**260** which on treatment with 0.8 equiv. of Et_2Zn in the presence of ligand (*S*,*R*,*R*)-**253** resulted in conversion of the (*S*)-enantiomer to (*S*,*S*)-**262a** in 89% e.e. and the recovery of (*R*)-**260** in 82% e.e. after 42% consumption. The alternative use of $(n\text{-Bu})_2Zn$ as a nucleophile resulted in formation of (2*R*,5*S*)-**261b** and (2*S*,5*S*)-**262b** in a combined yield of 78%, with (*R*)-**260** being recovered in >99% e.e. (Scheme 76).[162]

Buchwald et al. have employed a different strategy for the dynamic kinetic resolution of cyclic α,β-unsaturated ketones (*rac*)-**263a–g**, employing a chiral copper hydride species derived from CuCl, NaO^{t}Bu and (*S*)-*p*-tol-BINAP, for the catalytic 1,4-conjugate reduction of 3,5-dialkyl cyclopentenones using poly(methylhydrosiloxane) as a stoichiometric reductant.[163] Reduction of α,β-unsaturated ketones (*rac*)-**263a–g** using this chiral Cu–H–BINAP complex occurred with universally high *s* values to afford, affording *syn*-**264a–g** and unreacted chiral ketones **263a–g** in high e.e. (Scheme 77). Addition of NaO*t*-Bu/*t*-BuOH to the reaction media facilitated efficient racemisation at the C_5 stereocentre in situ, resulting in a DKR protocol that gave *syn*-2,5-dialkyl-cyclopentanones **264a–f** in >90% e.e and in high diastereoisomeric excess {<10% yield of *anti*-**265a–f** formed in all cases} (Scheme 78).

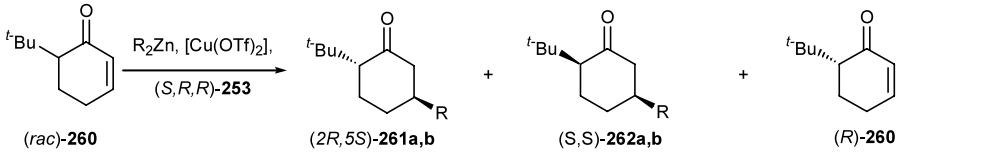


PMHS=polymethylhydrosilane

a: R^1=Me, R^2=$(CH_2)_2$Ph
b: R^1=^{i}Pr, R^2=$(CH_2)_2$Ph
c: R^1=^{t}Bu, R^2=$(CH_2)_2$Ph
d: R^1=$CH_2CO_2{}^t$Bu
e: R^1=Bn, R^2=^{i}Pr
f: R^1=Me, R^2=Ph
g: R^1=^{n}Bu, R^2=$(CH_2)_2$Ph

263a: 95% e.e.
263b: 97% e.e.
263c: 91% e.e.
263d: 95% e.e.
263e: 96% e.e.
263f: 72% e.e.
263g: 90% e.e.

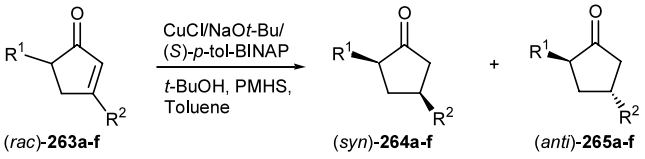
Scheme 77. Kinetic resolution of 3,5-dialkylcyclopent-2-enones (*rac*)-**263a–g**.



a: R = Et
b: R = ^{n}Bu

261b: >99% e.e., 18% yield
262a: 89% e.e., 36% yield
262b: 60% yield
260: 82% e.e., 58% yield
260: >99% e.e., 22% yield

Scheme 76. Kinetic resolution of 6-*tert*-butyl-2-cyclohex-2-en-one (*rac*)-**260**.



a: R^1=Me, R^2=$(CH_2)_2$Ph
b: R^1=^{i}Pr, R^2=$(CH_2)_2$Ph
c: R^1=^{t}Bu, R^2=$(CH_2)_2$Ph
d: R^1=$CH_2CO_2{}^t$Bu, R^2=$(CH_2)_2$Ph
e: R^1=Bn, R^2=^{i}Pr, 93% e.e.
f: R^1=Me, R^2=Ph, 91% e.e.

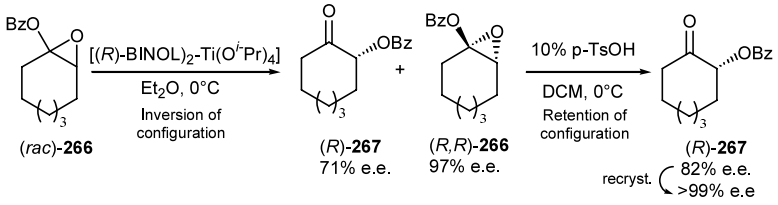
264a: 91% e.e., 82% d.e., 89% yield
264b: 93% e.e., 86% d.e., 94% yield
264c: 94% e.e., 87% d.e., 94% yield
264d: 93% e.e., 80% d.e., 91% yield
264e: 93% e.e., 83% d.e., 95% yield
264f: 91% e.e., 93% d.e., 90% yield

Scheme 78. Dynamic kinetic resolution of 3,5-dialkylcyclopent-2-enones **263a–f**.

10. Lewis acid- or base-catalysed kinetic resolution

In 2002, Shi et al. reported the chiral Lewis acid-catalysed resolution of racemic enol ester epoxides, which converted both enantiomers of (*rac*)-**266** into the same enantiomer of α-benzoyloxy ketone (*R*)-**267** (Scheme 79).[164] This was achieved by resolution of enol ester epoxide (*rac*)-**266** with a catalytic amount of the chiral Lewis acid [(BINOL)$_2$–Ti(O^{i}Pr)$_4$], to yield a mixture of the unreacted epoxide (*R*,*R*)-**266** in 97% e.e. and α-benzoyloxy ketone (*R*)-**267** in 71% e.e. which was formed via intramolecular benzoyl migration with inversion of configuration (Fig. 63, pathway a). This mixture was then treated with a catalytic amount of an achiral protic acid (pTSA) which catalysed the rearrangement of (*R*,*R*)-**266** via intramolecular benzoyl migration with retention of configuration (Fig. 63, pathway b) to afford α-benzoyloxy ketone (*R*)-**267** in an overall 82% e.e., which could be improved to >99% e.e. after recrystallisation.

Tu et al. have reported on a novel strategy for the enantioselective preparation of β-hydroxy ketones (*R*,*R*)-**269a–f** containing quaternary stereogenic centres via rearrangement of racemic tertiary α-hydroxy epoxides (*rac*)-**268a–f** using Ti–[(*R*)-BINOL]$_2$ complexes to catalyse enantioselective semipinacol rearrangements (Scheme 80).[165] The best enantioselectivities were observed for substrates in which the migrating group of the tertiary alcohol substrate was an aryl substituent, with tertiary α-hydroxy epoxides (*S*,*S*)-**268a–f** being recovered in 77–94% e.e. at 60–70% conversion.



Scheme 79. Enantioconvergent kinetic resolution of (*rac*)-**266** to afford the same enantiomer of α-benzoyloxy ketone (*R*)-**267**.

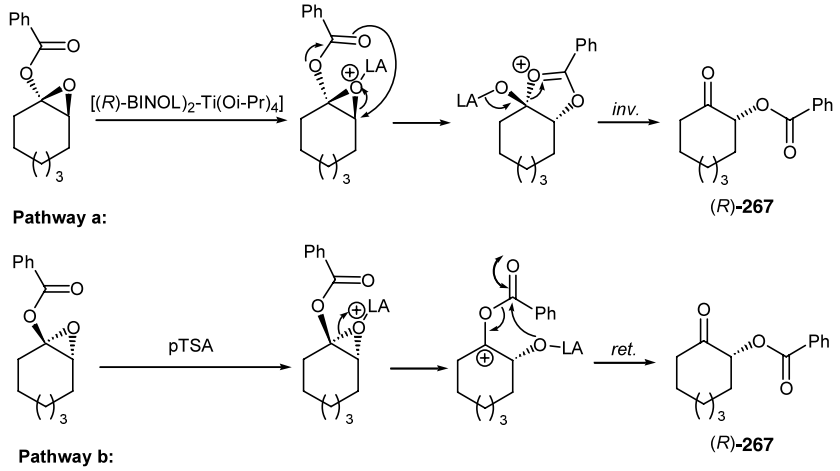
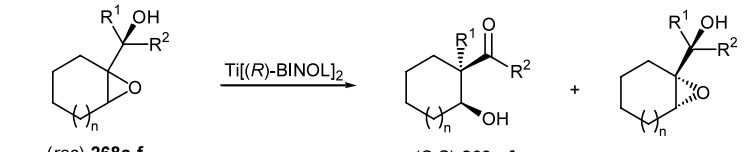


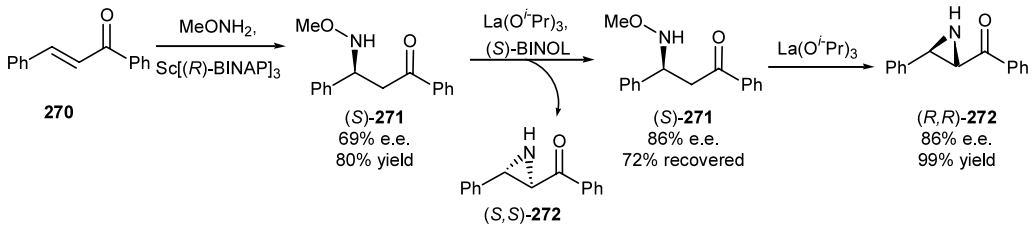
Figure 63. Two pathways for the rearrangement of each enantiomer of enol ester epoxide (*rac*)-**266** to afford (*R*)-**267**.



a: n=0, R^1=R^2=Ph, *C*=62
b: n=1, R^1=R^2=Ph, *C*=63
c: n=1, R^1=Bn, R^2=Ph, *C*=64
d: n=1, R^1=Ph, R^2=Bn, *C*=65
e: n=1, R^1=^{n}Bu, R^2=1-Naphth, *C*=65
f: n=1, R^1=^{n}Bu, R^2=*p*-CF$_3$Ph-, *C*=67

269a: 61% e.e.	**268a:** 90% e.e.
269b: 60% e.e.	**268b:** 94% e.e.
269c: 48% e.e.	**268c:** 82% e.e.
269d: 47% e.e.	**268d:** 80% e.e.
269e: 46% e.e.	**268e:** 79% e.e.
269f: 41% e.e.	**268f:** 77% e.e.

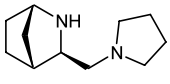
Scheme 80. Kinetic resolution of α-hydroxy epoxides (*rac*)-**268a–f** catalysed by Ti[(*R*)-BINOL]$_2$.



Scheme 81. Three-step enantioselective catalytic conversion of chalcone to afford α-keto aziridine (*R*,*R*)-**272**.

In 2002, Inanaga et al. described the synthesis of an enantiomerically enriched α-keto aziridine (*R*,*R*)-**272** via a protocol involving sequential action of three lanthanoid complexes including (i) Sc[(*R*)-BINAP]$_3$-catalysed Michael addition of *O*-methylhydroxylamine to chalcone **270** to afford β-amino-ester (*S*)-**271** in 69% e.e.; (ii) La-(O^{i}Pr)$_3$–(*S*)-BINOL complex-mediated kinetic resolution of enantioenriched (*S*)-**271** to enhance its e.e. from 69 to 86% e.e. via preferential cyclisation of (*R*)-**271** to afford aziridine (*S*,*S*)-**272**; (iii) La(O^{i}Pr)$_3$-catalysed ring closure of (*S*)-**271** to afford aziridine (*R*,*R*)-**272** in 86% e.e. (Scheme 81).[166]

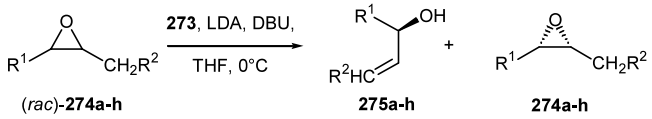
The majority of asymmetric deprotonation reactions reported to date involve protocols that require the use of stoichiometric amounts of chiral bases for efficient asymmetric induction;[167] however, Andersson et al. have recently introduced the use of 5 mol% of enantiopure diamine (1*S*,3*R*,4*S*)-**273** (Fig. 64) as a catalytic ligand for



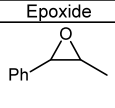
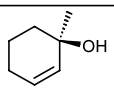
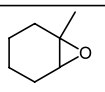
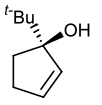
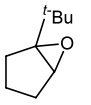
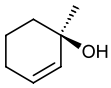
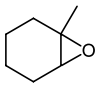
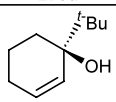
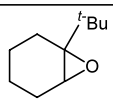
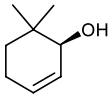
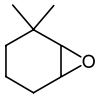
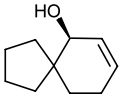
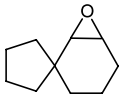
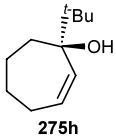
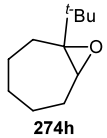
(*1S,3R,4R*)-**273**

Figure 64.

Table 9. Kinetic resolution of (*rac*)-**274a**–**h** via asymmetric deprotonation using a catalytic amount of chiral diamine (1*S*,3*R*,4*S*)-**273**



(*rac*)-**274a-h** **275a-h** **274a-h**

Entry	Product	e.e./%	yield/%	Epoxide	e.e./%	yield/%
1	 **275a**	89	94	 **274a**	85	84
2	 **275b**	63	87	 **274b**	79	94
3	 **275c**	79	34	 **274c**	-	50
4	 **275d**	94	40	 **274d**	87	38
5	 **275e**	99	40	 **274e**	99	36
6	 **275f**	94	43	 **274f**	99	47
7	 **275g**	90	45	 **274g**	93	40
8	 **275h**	94	34	 **274h**	41	51

the desymmetrisation of *meso*-epoxides in the presence of LDA as a stoichiometric base.[168] This methodology has now been extended to the kinetic resolution of both acyclic and cyclic epoxides to afford recovered chiral epoxides **274a**–**h** and chiral allylic alcohols **275a**–**h** with good levels of stereocontrol (Table 9).[169,170]

11. Conclusions

Over 125 reports on catalytic kinetic resolutions using non-enzymatic catalysts have appeared over the last three years based on the use of existing or new catalytic methodology, many of which produce chiral starting materials or products in very high e.e. Strategies such as HKR of racemic terminal epoxides, Sharpless epoxidation of allylic alcohols, and the use of transfer hydrogenation catalysts for oxidative/reductive resolution are now widely used for the preparation of synthons for natural product synthesis, whilst it is clear that the application of new types of stereoselective catalysts will provide new opportunities for kinetic resolution in the near future.

Acknowledgements

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