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Chiral substituted pyrrolidines are key elements in various biologically active molecules and are therefore valuable synthetic targets. One traditional method towards enantiomerically pure compounds is the application of kinetic resolution. In this review, current KR methodology used in the synthesis of substituted pyrrolidines is surveyed, including enzymatic methods, cycloadditions and reduction of ketones.

Current applications of kinetic resolution in the

asymmetric synthesis of substituted pyrrolidines

Introduction

Pyrrolidines are present in many pharmaceuticals and natural products (Fig. 1).¹⁻⁴ The combination of a structural scaffold that has defined shape, together with functional groups that allow for further diversification leading to arrays of products, makes them a popular target for synthesis. Current synthetic routes to construct these systems are numerous and varied, including cycloaddition and cyclization reactions, metal catalysed C–H activations, and reductions of enamines, alkenes, and various carbonyl compounds, to name but a few.⁵⁻¹⁰ A prominent strategy that exists amongst these methods is the use of kinetic resolution (KR) derived protocols. The use of these in synthetic chemistry have been long documented and can offer significant advantages in strategies where asymmetric

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synthetic techniques cannot be employed because of poor substrate compatibility or lack of appropriate methodology. In simplistic terms, KR involves the resolution of a racemic mixture employing a chemical transformation that differentiates between the two enantiomers of substrate based on differences in relative reaction rates of each enantiomer. Thus, in traditional KR, one enantiomer is transformed to a different product, leaving one enantiomer untouched. This immediately brings challenges of separating the transformed product from the starting material and also limits the maximum yield to 50% unless recycling protocols can be introduced. Innovations in this strategy that include dynamic kinetic resolution (DKR) and parallel kinetic resolution (PKR) variants that offer increased yield over traditional processes by circumventing the need for separation and/or loss of starting material (Scheme 1).11-14

In this review, the current KR methods involved in the asymmetric synthesis of pyrrolidines are reviewed categories



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Professor Jones obtained his BSc Chemistry from Southampton University and Ph.D. from University of Wales, Cardiff. He worked in postdoctoral positions at Arizona State University and at the Dyson Perrins Laboratory, University of Oxford, before starting his first academic position at the University of Newcastle upon Tyne. He moved to the University of Sheffield in 2003, where he is now Professor of Chemistry. His research inter-

ests lie in asymmetric organic synthesis and in construction of biological probes.

Fig. 1 Pyrrolidine containing natural products and pharmaceuticals, Vixotrigine 1, Nicotine 2, Clindamycin 3, (+)-Preussin 4 and Remoxipride 5.

by the substitution of their respective parent pyrrolidines framework.

2. Monosubstituted pyrrolidines

In 1994, Beak *et al.*, reported on the asymmetric deprotonation of *N*-Boc-pyrrolidines *via* lithiation/substitution employing (–)-sparteine and *sec*-butyllithium (*s*BuLi), providing access to 2-substituted-*N*-*tert*-butylcarbonyl-pyrrolidines (*N*-Boc). ¹⁵ It was noted that upon warming the enantioselectivity decreased

Scheme 2 Dynamic kinetic resolution of $N ext{-Boc}$ pyrrolidine 6 reported by Coldham et al.

suggesting racemization of the organolithium species at higher temperatures. ¹⁶ From this, Coldham and co-workers developed a dynamic kinetic resolution (DKR) employing chiral diamine ligand **L1** (Scheme 2). ^{17,18} Transmetalation of stannane **6** with excess nBuLi, addition of chiral ligand **L1** with nBuLi, followed by slow addition of trimethylsilyl chloride (TMSCl) at -20 °C formed 2-substituted-pyrrolidine 7 in a moderate 54% yield but with good enantioselectivity of 92% ee.

The opposite enantiomer of pyrrolidine 7 was obtained in a similar yield and enantioselectivity through the use of the diastereoisomer of diamine L1. Many methods involving lithiation of *N*-protected-pyrrolidines operate via dynamic thermodynamic resolution (DTR) with asymmetric deprotonation and so will not be discussed here.^{7,19–22}

Scheme 1 Examples of kinetic resolutions in pyrrolidine synthesis.

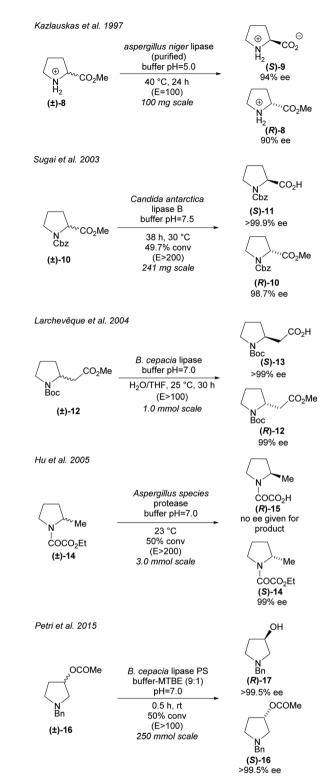
Biocatalytic methods for the kinetic resolution of racemic pyrrolidines provide easy access to enantiomerically enriched pyrrolidines under mild conditions; often performing to high degrees of selectivity at mild temperatures and pH under atmospheric pressure.²³ Unfortunately, the high selectivity comes with a loss of substrate diversity, with many of the enzymes only performing well with one or two pyrrolidine substrates.

Hydrolases can be utilised in the hydrolysis of esters closely attached to the pyrrolidine ring (Scheme 3). Racemic proline derivatives were resolved by both Kazlauskas et al. and Sugai et al. employing Aspergillus niger lipase (ANL) and Candida antarctica lipase B (CAL-B) repectively. 24,25 Good selectivity was obtained by Kazlauskas for the unprotected amino acid (S)-9 with the noted requirement of purified ANL due to lower selectivity when using the crude enzyme. Sugai obtained excellent enantioselectivity for the N-benzylacetyl amino acid (R)-11. Changing the protecting group to N-benzyloxycarbonyl (Cbz) afforded similarly good results, however, no reactivity was observed with an N-carbamoyl protected amino ester. In 2004, Larchevêque et al. resolved β-amino esters using B. cepacia lipase, obtaining the best results with N-Boc protected pyrrolidine 12.26 Alternative pyrrolidines, including a *N*-benzylacetyl protected β -amino ester, were attempted, however, very poor selectivity was observed. In 2005, Hu et al. resolved 2-methyl-pyrrolidine 14 via hydrolysis of the oxalamic ester using a protease obtained from Aspergillus species.²⁷ Excellent enantioselectivity was obtained for the remaining oxalamic ester. Two pyrrolidines containing aromatic substituents at the 2-position were also resolved, obtaining good enantioselectivities. In 2015, Petri et al. used phosphatidylserine (PS) from B. cepacia to resolve 3-substituted pyrrolidine (\pm)-16 obtaining 3-hydroxypyrrolidine (R)-17 in excellent enantioselectivity.28

Alternatively, hydrolyses can be used in organic solvents to promote asymmetric acetylation of racemic alcohols (Scheme 4). Use of organic solvents allows for easier extraction of products when compared to hydrolysis methods conducted in buffers. Resolution of 3-hydroxy-pyrrolidines were conducted by Mochida *et al.* and Ueda *et al.* employing Amano lipases P and PS-IM (immobilised), respectfully. ^{29,30} Mochida's acetylation of racemic 3-hydroxy-pyrrolidine (±)-18 achieved excellent enantioselectivity for both the acetylated product (*R*)-19 and the remaining starting material (*S*)-18. Similarly, excellent enantioselectivities were obtained by Ueda for the returned starting material (*S*)-20, however, lower enantioselectivity was obtained for the acetylated pyrrolidine (*R*)-21.

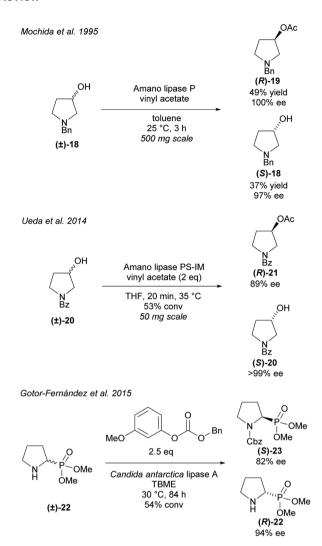
Resolution of racemic cyclic aminophosphonate (±)-22 was conducted by Gotor-Fernández *et al.* employing *Candida antarctica* lipase type A (CAL-A) obtaining good enantioselectivities for both the benzyl carbamate product (*S*)-23 and the returned starting material (*R*)-22.³¹

All methods involving enzymatic resolution of racemic pyrrolidines discussed so far have a theoretical maximum yield of 50% for the enantiopure product and returned starting material. In 2011, Bäckvall *et al.* employed lipase PS-IM in the

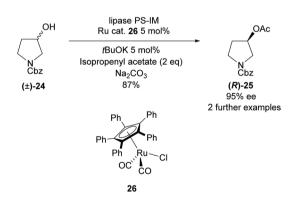


Scheme 3 Hydrolysis of various monosubstituted pyrrolidines.

acetylation of 3-hydroxy-pyrrolidine (±)-24 with a ruthenium catalyst to racemise the starting material (Scheme 5).³² The racemisation catalysis allows dynamic kinetic resolution allowing for significantly higher yields than traditionally available with enzymatic methodologies. They obtained a good yield of



Scheme 4 Acetylation of various monosubstituted pyrrolidines.



Scheme 5 Acetylation of racemic alcohol 24 involving ruthenium catalysed racemisation.

87% with excellent enantioselectivity of 95% for N-Cbz protected pyrrolidine (R)-25.

Protection of amines *via* enzymatic transesterification has been significantly less investigated. One common problem

associated with this method is the higher nucleophilicity of the amine compared to the commonly acetylated alcohols. In 1999, Wong *et al.* attempted to overcome this problem by employing less reactive dibenzyl carbonate as the protecting group source using the lipase CAL to catalyse the reaction (Scheme 6).³³ Unfortunately, the *N*-protected pyrrolidine was obtained in a poor 19% yield with only moderate enantioselectivity. This was the only example provided.

In 2007, Klempier *et al.* employed nitrilase NIT-106 in the synthesis of β -amino acid **30** (Scheme 7). Thirliase catalysed hydrolysis of racemic 3-nitrile-pyrroline (±)-29 afforded the β -amino acid **30** in a good 42% yield at 44% conversion with a good enantioselectivity of 76% ee. Higher conversions at longer reaction times afforded the amide by-product **31**. The stereochemistry of the remaining starting material nitrile or either of the products was not reported.

An alternative functional group transformation is to utilize ω-transaminases to resolve racemic amines by converting one enantiomer of the amine to a ketone. In 2008, Bornscheuer *et al.* employed a ω-transaminase from *Alcaligenes denitrificans* (Ade-TA) to resolve 3-amino-*N*-Boc-pyrrolidine (±)-32 (Scheme 8).³⁵ Excellent enantioselectivity was obtained for the remaining starting material with a moderate 39% yield at 50% conversion. Use of the carbamate protecting group (Boc)

Scheme 6 Enzyme catalysed amine protection by Wong et al.

Scheme 7 Enzyme catalysed hydrolysis of nitrile pyrrolidine 29 reported by Klempier *et al.*

Scheme 8 Conversion of amine to ketone employing ω -transaminase Ade-TA reported by Bornscheuer *et al.*

improved the efficiency and selectivity of the reaction when compared to the unprotected and amide (benzyl) protected substrates.

Modification of functional groups attached to pyrrolidine rings can be achieved using redox methods. In 2008, Onomura and co-workers investigated the electrochemical oxidation of aminoalcohols and aminoaldehydes (Scheme 9).³⁶ Racemic 2-substituted-pyrrolines were resolved employing a copper catalyst with (*R*,*R*)-Ph-BOX as the chiral ligand. Oxidation of the aminoaldehyde (±)-34 achieved a moderate 43% yield in good enantioselectivity however, the recovered starting aldehyde was obtained in a poor 27% ee. The oxidation of aminoalcohol (±)-36 was less successful, obtaining lower enantioselectivities and significantly lower yields for the ester product. Very poor enantioselectivity was obtained for the recovered amino alcohol (*S*)-36.

Monosubstituted pyrrolidine Dolaproine (Dap) is a key unit of Dolastatin 10, a marine natural product belonging to a family of antineoplastic peptides (Scheme 10).³⁷ Genet and co-workers developed a ruthenium catalysed hydrogenation via dynamic kinetic resolution of β-keto-esters derived from (S)-Boc-proline as a route to access Dolaproine and its isomers. 38-40 Initial work produced Boc-(2S,3R)-iso-Dap in good diastereoselectivity and excellent yield for the DKR of pyrrolidine salt 40 (Scheme 10).³⁸ Ru[(R)-MeO-BIPHEP]₂ was employed to access Boc-(2R,3S)-iso-Dap however, a mixture of diastereoisomers (2R,3S)-42, (2S,3R)-42 and (2S,3S)-42 was obtained with 71:24:5 dr.39 Recrystallisation effectively removed one diastereoisomer, and subsequent functionalisation allowed for separation of the remaining diastereoisomers via chromatography on silica gel. Harsher reaction conditions by an increase in pressure from 10 bar to 100 bar and longer reaction times were employed to afford (2S,3S)-42 in 87% de from Boc-protected pyrrolidine 41. Changing the chiral ligand to (S)-SYNPHOS allowed for access to (2R,3R)-42, the isomer required for the synthesis of Dolastatin 10.40 A mixture of four diastereoisomers was obtained with moderate 59:33:5:4 dr. Separation by chromatography on silica gel afforded an inseparable mixture of (2R,3R)-42 and (2S,3R)-42 in 2:1 dr.

Methylation of the mixture and separation by chromatography on silica gel afforded pure O-methylated-(2R,3R)-43 which was used in the total synthesis of Dolastatin 10.

In 2011, Ohkuma *et al.* employed a similar method, synthesising 2- and 3-monosubstituted pyrrolidines from racemic pyrrolidines containing a ketone (Scheme 11).⁴¹

A ruthenium catalyst **48** was employed in the hydrogenation, obtaining *syn*-3-substituted pyrrolidine **45** in moderate diastereoselectivity and excellent enantioselectivity and *anti*-2-substituted pyrrolidine **47** in excellent diastereoselectivity and good enantioselectivity.

3. Disubstituted pyrrolidines

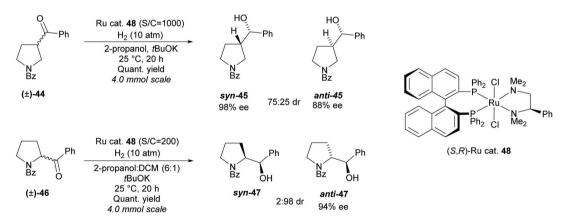
Reduction of racemic disubstituted cyclic imines provides access to disubstituted pyrrolidines. In 1994, Buchwald and co-workers developed a resolution of disubstituted cyclic imines via titanocene catalysed asymmetric reduction (Scheme 12).42,43 2,5-Disubstituted pyrrolidines were afforded as single diastereoisomers in excellent enantioselectivity and moderate yields with the recovered imines also obtained in excellent enantioselectivities. 2,3-Disubstituted pyrrolidine 45 was obtained in good diastereoselectivity with excellent enantioselectivity observed for both cis- and trans-isomers. Good enantioselectivity for the remaining cyclic imine was obtained from the crude reaction mixture at 50% conversion, however, due to racemisation on deactivated silica gel during purification, the remaining cyclic imine was not isolated. The 2,4-disubstituted pyrrolidine 46 was obtained in lower diastereoselectivity but with similarly excellent enantioselectivity. The enantioselectivities for the recovered imine for both the 2,3- and 2,4-pyrrolidines was significantly lower than observed with the 2,5-pyrrolidines.

Monosubstituted nitrile pyrrolidine **49** is a key intermediate in the synthesis of PF-00951966, a fluoroquinolone based broad-spectrum antibiotic discovered at Pfizer. In 2012, Lall and co-workers reported the synthesis of nitrile pyrrolidine **49** *via* a modified Noyori asymmetric hydrogenation of racemic disubstituted β-keto-γ-lactam (±)-**47** (Scheme 13).

Scheme 9 Electrochemical oxidation reported by Onomura et al.

Scheme 10 Synthesis of Dolaproine reported by Genet et al.

59:33:5:4 dr



N-Boc-Dap

Scheme 11 Ruthenium catalysed hydrogenation involving DKR reported by Ohkuma et al.

diastereoselectivity and enantioselectivity was obtained after recrystallisation affording (S,S)-lactam 48 in a good yield. Further functional group manipulations including reduction of the lactam afforded nitrile pyrrolidine 49 in 11 steps. This method of dynamic kinetic resolution using ruthenium cata-

lysts was developed by Noyori *et al.* and first expanded to the reduction of β -keto- γ -lactams by Hattori *et al.* during the synthesis of 2-[*N*-imidoylpyrrolidinyl]carbapenems. ^{45,46}

In 2013, Magnus *et al.* at Eli Lilly employed a similar method of hydrogenation of racemic β -keto- γ -lactam (\pm)-51 in

Scheme 12 Reduction of disubstituted cyclic imines reported by Buchwald et al.

Scheme 13 Synthesis of nitrile pyrrolidine 49 reported by Lall et al.

the synthesis of a pyrrolidine-based serotonin norepinephrine reuptake inhibitor 53 (Scheme 14).⁴⁷ Good yields and selectivities were obtained for the β-hydroxy-γ-lactam 52. Further modifications obtained the pyrrolidine-based inhibitor in 7 steps.

More recently, Xie et al. employed an iridium catalyst in the asymmetric hydrogenation of racemic β-keto-γ-lactams (Scheme 15).48 They obtained excellent yields and selectivities across the 12 examples. From β-hydroxy-γ-lactam 54, diamine 55, a key intermediate in the synthesis of fluoroquinolone antibiotic Premafloxacin 56, was synthesised in 6 steps.

Various methods of intramolecular cyclisation have been employed in the synthesis of disubstituted pyrrolidines. The resolution of racemic α -substituted-1-aminopent-4-enes *via* the asymmetric hydroamination of aminoalkenes was developed by Hultzsch et al. employing rare earth metal catalysts with

various binaphtholate ligands (Scheme 16). 49-54 Initial investigations employed binaphtholate catalyst 57 in the cyclisation affording a 2,5-disubstituted pyrrolidine in moderate diastereoselectivity and poor enantioselectivity. 49 Building on this result, more sterically demanding binaphtholate ligands were developed incorporating 3,3'-bis(triarylsilyl) groups. In most cases, the highest enantioselectivities were observed using yttrium catalyst 59, with the exception of the α-phenylaminoalkene which obtained a higher selectivity for the recovered starting material employing a lutetium catalyst. 51 In many cases, the enantioselectivity was only reported for the recovered aminoalkenes after the kinetic resolution. The same group also attempted the resolution of β- and γ-substituted-1aminopent-4-enes, obtaining 2,4- and 2,3-disubstituted pyrrolidines respectfully.⁵² 2,4-Disubstituted pyrrolidine 60 was obtained in poor diastereoselectivity with no enantioselectivi-

Scheme 14 Synthesis of serotonin norepinephrine reuptake inhibitor 53 reported by Magnus et al.

Scheme 15 Synthesis of premafloxacin via iridium catalysed hydrogenation reported by Xie et al.

ties for either isomer reported. Poor enantioselectivity was observed for the recovered starting aminoalkene **60**. Moderate enantioselectivity was reported for the recovered aminoalkene **62** however no diastereoselectivity or enantioselectivity was reported for the 2,3-disubstituted pyrrolidine **63**.

In 2009, Gracza *et al.* reported the Pd catalysed carbonylative bicyclisation of *N*-protected 1-aminopent-4-ene-3-ols as a route to synthesize bicyclic pyrrolidines (Scheme 17).⁵⁵

They obtained the Cbz protected pyrrolidine **65** in a poor yield at a low conversion with good enantioselectivity. The yield could be improved with the use of *p*-toluenesulfonyl as the protecting group compared to carboxybenzyl however the enantioselectivity decreased to 60% ee.

(–)-Supinidine, a pyrrolizidine alkaloid, can be synthesised from disubstituted pyrrolidine **70**. In 1991, Takahata and coworkers employed the Katsuki–Sharpless asymmetric epoxidation in the kinetic resolution of racemic N-protected 1-aminopent-4-ene-3-ol **67**, a method the group developed to access chiral urethanes (Scheme 18). ^{56–58} Disubstituted pyrrolidine **70** was obtained with good enantioselectivity and was subsequently used in the synthesis of (–)-supinidine in 12 further steps.

Cyclisation employing dynamic kinetic resolution within the aza-Cope rearrangement was developed by Overman *et al.*

(Scheme 19).⁵⁹ *N*-Protected bicyclic pyrrolidine 73 was obtained in a good 89% yield over two steps in an excellent 99% ee. Hydrolysis of the formaldiminium ion after the aza-Cope rearrangement using standard methods failed to form the desired product and so dimedone was employed.⁶⁰

The dynamic kinetic resolution of racemic disubstituted pyrrolidine (±)-74 within an enantioselective Morita-Baylis-Hillman (MBH) cyclisation was investigated by Zakarian *et al.* (Scheme 20).⁶¹ When employing non-racemic pyrrolidine 74, significant racemisation was observed at temperatures above –30 °C during the MBH cyclisation. They suggested this occurred through acid-catalysed isomerisation of the cyclic iminium ion, however, the exact route of epimerisation is not currently known. After screening a series of chiral sufides, they obtainedbicyclic 75 in good enantioselectivity but poor yield. Further work is required to improve yields and make this a viable route.

As with the monosubstituted pyrrolidines, enzymes are a popular technique to synthesise disubstituted pyrrolidines from racemic pyrrolidines in a highly selective way. The same issues of the limits of diversity while retaining selectivity are still prevalent. Akai *et al.* employed CAL-B in the esterification of racemic *N*-oxide (±)-76, which then underwent an intramolecular Diels–Alder reaction affording pyrrolidine 77

enantioselectivities reported

Scheme 16 Asymmetric hydroamination of aminoalkenes reported by Hultzsch et al.

Scheme 17 Carbonylative cyclisation reported by Gracza et al.

(Scheme 21). 62,63 In two further steps they synthesised (–)-rosmarinecine, a component of several pyrrolizidine alkaloids. This method is the shortest reported total synthesis for (–)-rosmarinecine, achieving a 15% yield over 4 steps. Previous methods include synthesis from a furanose derivative, obtain-

ing a higher yield of 18% but in 10 total steps, and intramolecular cycloaddition methods, obtaining the same 15% yield but in 8 steps. 64-67 N-Oxide 76 was shown to partially racemise and so the group attempted to develop a DKR. Higher yields could be obtained with a slight decrease in enantioselectivity, however the enantioselectivity was higher than that that would be obtained if no racemization were occurring.

Hydrolysis of esters closely attached to the pyrrolidine ring in disubstituted pyrrolidines is again a popular technique (Scheme 22). In 1996, Kawanami et al. employed PS to resolve racemic 2,5-diacetyl pyrrolidine trans-(±)-79 affording the monoacetyl pyrrolidine 80 in moderate enantioselectivity with the returned diacetyl 79 in excellent enantioselectivity. 68 In 2007, Correia et al. hydrolysed racemic 3,4-disubstituted pyrrolidine trans-(±)-81 employing PS-AK obtaining excellent enantioselectivity for both the hydroxy product and remaining starting material.⁶⁹ They used several different aromatic substituents obtaining excellent enantioselectivities for all examples. Faigl et al. has since used a similar method synthesizing the

Scheme 18 Synthesis of (-)-supinidine via Katsuki-Sharpless asymmetric epoxidation reported by Takahata et al.

Scheme 19 aza-Cope rearrangement reported by Overman et al.

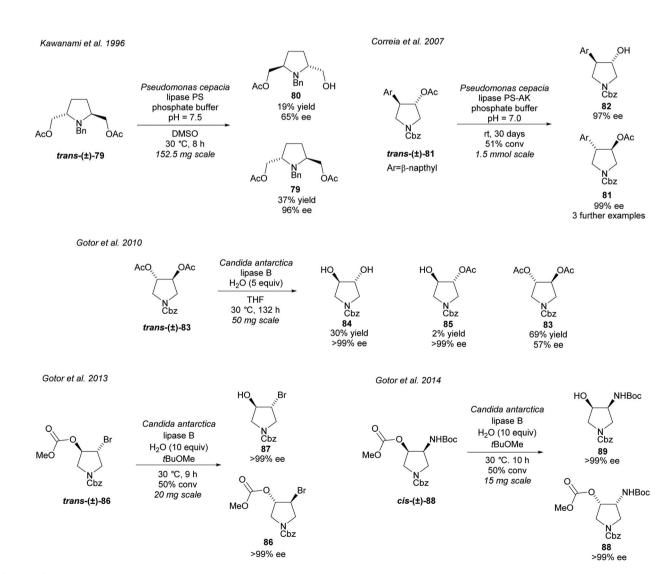
Scheme 20 DKR of disubstituted pyrrolidine 74 reported by Zakarian

phenyl substituted analogue.⁷⁰ CAL-B has been employed by Gotor *et al.* in the hydrolysis of 3,4-diacetylated pyrrolidine *trans*-(±)-83, brominated pyrrolidine *trans*-(±)-86, and amino pyrrolidine *cis*-(±)-88.⁷¹⁻⁷³ Hydrolysis of racemic diacetate *trans*-(±)-83 afforded the dihydroxy-pyrrolidine 84 and the monoacetylated pyrrolidine 85 in excellent enantioselectivities, however, the returned diacetylated pyrrolidine 83 was obtained in significantly lower enantioselectivity.⁷¹ Improved enantioselectivity for diacetate 83 could be obtained with longer reaction times with a small decrease in enantioselectivity for the dihydroxy product. Bromohydrin 87 was obtained in excellent enantioselectivity after the hydrolysis of racemic methoxymethyl pyrrolidine *trans*-(±)-86.⁷² Similarly excellent enantioselectivity was obtained for *cis*-3-amino-4-hydroxy-pyrroldine 89 and its returned starting methoxymethyl pyrrolidine 88.⁷³

In 2005, Aggarwal and co-workers employed hydrolyses from *Candida lipolytica* and *Rhizomucor meihei* to resolve the *cis*- and *trans*-2,5-disubstituted pyrrolidine **90**, respectively (Scheme 23).⁷⁴ Excellent enantioselectivities were obtained for the returned esters with no reports of the enantioselectivities of the acid products.

Transesterification of alcohols attached to a pyrrolidine ring promoted by lipases is another popular use of enzymes in the synthesis of disubstituted pyrrolidines (Scheme 24). In 1994, Sibi et al. acetylated racemic 2,5-disubstituted-dihydroxy pyrrolidine trans-(±)-92 employing PS lipase, affording the diacetate product 79 and the returned dihydroxy pyrrolidine 92 in excellent enantioselectivities.⁷⁵ Poor enantioselectivity was obtained for the monoacetylated product 80. Kawanami et al. developed a method to obtain the monoacetylated pyrrolidine 93 in excellent enantioselectivity employing the same enzyme, with good a enantioselectivity also reported for the diacetylated product.⁷⁶ Further work was conducted by the same group investigating the substituents of the aryl group of the N-protecting group, concluding that 3,5-dimethylbenzyl affords the best enantioselectivities.⁷⁷ Kamal et al. employed lipases PS-C (lipase immobilized on ceramic particles) and PS-D (lipase immobilized on diatomaceous earth) in the

Scheme 21 Synthesis of (–)-rosmarinecine via enzyme catalysed KR reported by Akai et al.



Scheme 22 Hydrolysis of various disubstituted pyrrolidines.

Candida lipolytica esterase pH = 7.0NaCl_(aq) (0.1 M) rt. 70 h cis-90 trans-91 35.2% conv 90 86% of theoretical yield 7:3 cis/trans >99% ee Rhizomucor miehei lipase pH = 7.0CO₂Me NaCl_(aq) (0.1 M) rt 43 h trans-90 74% conv cis-91 52% of theoretical vield 99.6% ee

Scheme 23 Resolution of disubstituted pyrrolidine 90 via enzyme catalysed hydrolysis reported by Aggarwal et al.

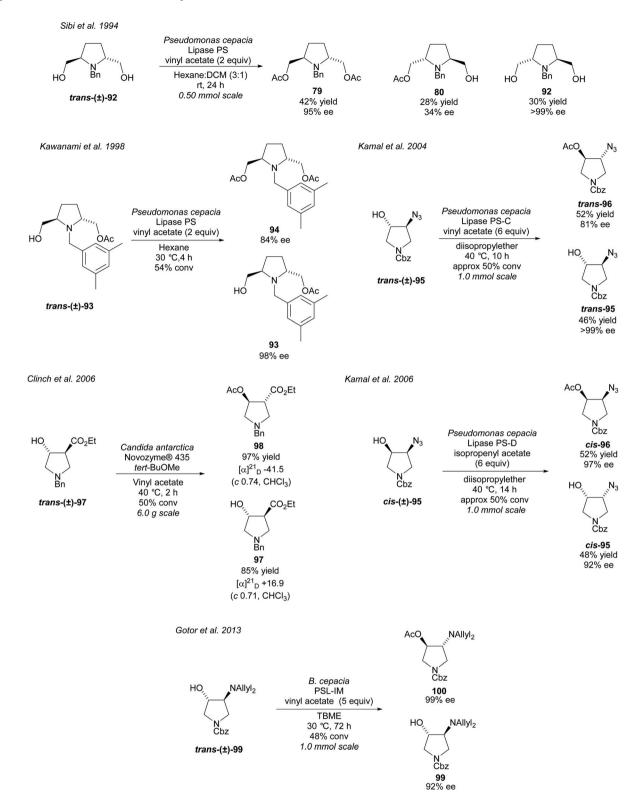
resolution of transand cis-azido pyrrolidines 95, respectively. 78,79 Good to excellent enantioselectivities were obtained for both the returned alcohols and the acetylated products. In 2006, Clinch et al. employed Novozyme® 435 (an immobilized form of CAL-B) in the resolution of 3,4-disubstituted pyrrolidine trans-(±)-97 obtaining good to excellent yields of 85% and 97% for the product ester 98 and remaining alcohol 97, respectively.80 These yields are presumed to be on the basis of a 50% maximum yield of either compound. This method was used by Whelligan et al. during the synthesis of new aza-nucleoside mimics, obtaining optical rotations in line with those reported by Clinch et al., however, they obtained lower yields of 83% and 75% for the remaining alcohol and product ester respectively.81 In 2013, Gotor et al. resolved trans-3,4-disubstituted pyrrolidine trans-(±)-99 using the lipase PLS-IM (immobilised) affording the acetylated product 100 and the returned alcohol 99 in good to excellent enantioselectivities.82 Acetylation of the unprotected primary amine was also attempted employing CAL-B although only moderate enantioselectivities were obtained for the returned free amine and monoacetylated product.

Pyrrolidine based precursors to nitric oxide synthase inhibitors have been synthesised by Gotor and co-workers via enzyme catalysed esterification of racemic 3,4-disubstituted pyrrolidines (Scheme 25).83 The highest selectivities were observed during the resolution of trans-disubstituted pyrrolidine trans-(±)-101 employing CAL-A (IMMCALA-T2-150) obtaining the returned alcohol 102 in optically pure form. A pyridine regioisomer was also investigated, as both cis- and transisomers, affording lower enantioselectivities for the returned alcohols of both diastereoisomers. Hydrolysis of acetylated pyrrolidine 102 was also investigated however significantly lower enantioselectivities were obtained for both the returned acetylated pyridine and alcohol product. C-H Activation of racemic monosubstituted N-Boc pyrrolidines employing the rhodium catalysed decomposition of methyl aryldiazoacetates was reported by Davies et al. as a method to provide access to β-amino acid derivatives (Scheme 26).84,85 Excellent enantioselectivities and diastereoselectivities were obtained, exhibiting control over three stereogenic centres in the final disubstituted pyrrolidine. Limited substrate scope was investigated with variation only occurring at the 2-position in the racemic pyrrolidine with the exception of the kinetic resolution of pyrrolidine cis-(\pm)-105. Brigaud et al. employed phenyl magnesium bromide to selectively consume one diastereoisomer of a diastereomeric mixture of oxazolopyrrolidine rac-107 (Scheme 27). ⁸⁶ As the rate of addition to (S)-107 was faster than the addition to (R)-107, but less selective, (S)-107 could effectively be destroyed leaving (R)-oxazolopyrrolidine 107 to be recovered in excellent diastereoselectivity and good yield. (R,R)-Disubstituted pyrrolidine 108 was also obtained in excellent diastereoselectivity.

4. Trisubstituted pyrrolidines

Trisubstituted pyrrolidines have been accessed *via* an organocatalysed aza-Henry/aza-Michael cascade reaction by Huang *et al.* (Scheme 28).⁸⁷ The reversable aza-Henry step provided a modest 2:1 ratio of *trans*: *cis* 109 and in the subsequent aza-Michael cyclisation only the trans isomer reacted to form trisubstituted pyrrolidine 110. Using *rac-trans*-aza-Henry product 109 in an independent reaction provided pyrrolidine 110 in a moderate 50% ee and good 80% yield suggesting a moderately selective DKR. Good to excellent enantioselectivities and yield were observed across the 17 examples during the optimised cascade reaction employing modified cinchona alkaloid catalyst 111.

Imino-*C*-disaccharide precursors featuring a trisubstituted pyrrolidine subunit were synthesised by Cardona and coworkers (Scheme 29). S8,89 A partial kinetic resolution of racemic five-membered ring nitrone (±)-cis-112 was achieved in a 1,3-diploar cycloaddition with isolevoglucosenone 114. Moderate enantioselectivity was obtained for the recovered nitrone. They adapted this method, employing both levoglucosenone 115 and its isomer 114, to achieve a parallel kinetic resolution (PKR) obtaining two distinct products in moderate to good yields. PKRs have the advantage of reacting both enantiomers at the same or similar rates to two different, separable products. Unlike simple KRs, the 1:1 ratio of the starting enantiomers is maintained throughout the reaction leading to higher enantioselectivities and higher yields.



Scheme 24 Enzyme mediated transesterification of various disubstituted pyrrolidines.

The 1,3-dipolar cycloaddition of α ,β-unsaturated δ - and γ -lactones to racemic nitrone *cis*-(±)-112 was investigated by Chmielewski *et al.* (Scheme 30). 90 δ -Lactone 117 exhibited good yields with excellent diastereoselectivity, obtaining *exo*-

cycloaddition product **118** exclusively, with (3R,4S)-nitrone **112** recovered in good enantioselectivity. δ -Lactones **119** and **120** achieved similarly good results, however, in the cycloaddition of γ -lactone **121** to racemic nitrone cis-(\pm)-**112** both the exo and

Scheme 25 Nitric oxide synthase inhibitors synthesised by Gotor et al. via enzyme catalysed acetylation.

Scheme 26 C-H activation of N-Boc pyrrolidines reported by Davies et al.

Scheme 27 Phenyl magnesium bromide employed to consume one diastereoisomer reported by Brigaud et al.

Scheme 28 aza-Henry/aza-Michael cascade reaction reported by Huang et al.

Cardona et al. 2003

Scheme 29 PKR method employing levoglucosenone and isolevoglucosenone reported by Cardona et al.

Scheme 30 1,3-dipolar cycloaddition of racemic nitrone 112 to various lactones reported by Chmielewski et al.

endo products were formed. In this case, the mismatched (3R,4S)-nitrone reacts, forming the endo product.

Use of enzymes in kinetic resolutions are a popular technique again for trisubstituted substrates. Most uses of enzymes in this class of pyrrolidines are aimed at synthesizing intermediates for nucleoside analogues, often for use as enzyme inhibitors. Mason et al. resolved lactone trans-(±)-122 using Novozyme® 435 obtaining the acid product 123 in a moderate yield with excellent enantioselectivity (Scheme 31).91 Similary excellent enantioselectivies were obtained for the recovered starting alcohol 122. From acid 123 in three further steps, they obtained disubstituted pyrrolidine 124 which is a

key intermediate in the synthesis of a number of nucleoside analogues.

In 2008, Gotor et al. resolved bicyclic pyrrolidine (±)-125 employing CAL-A in an enzyme catalysed carbamate formation (Scheme 32).92 Excellent enantioselectivities were obtained for both the carbamate product 126 and the unreacted amino ester 125. In the same year, Mason et al. resolved fluoropyrrolidine (±)-127 via CAL-B catalysed acetylation of an alcohol. 93 Good enantioselectivity was obtained for the unreacted alcohol 127 with moderate yields for both the unreacted alcohol and acetylated product 128. The fluoropyrrolidine was subsequently used to synthesise a phosphorylase enzyme inhibitor.

EtO₂C, OH Novozyme® 435 phophate buffer pH 7.5

27 °C, 5.7 h
$$50 \pm 2\%$$
 conv 346 g scale

trans-(\pm)-122

123

124

key intermediate in the synthesis of nucleoside

Scheme 31 Enzyme catalysed hydrolysis reported by Mason et al.

Scheme 32 Alcohol and amine enzyme mediated protection.

Takabe and co-workers resolved hydroxylactam rac-129 via lipase PS-D catalysed acetylation (Scheme 33).94 Excellent yields and enantioselectivities were obtained for both the acetylated product 130 and unreacted alcohol 129. They developed a method to racemise acetate 130 producing racemic alcohol rac-129, creating a kinetic resolution/racemisation cycle. Through this, they could obtain alcohol 129 in 96% yield with >99% ee after 5 cycles. Alcohol 129 was transformed in 10 steps to polyhydroxylated indolizidine (-)-2-epi-lentiginosine 131, an inhibitor of glycosidases and was afforded in a 16% yield over 13 total steps.

Scheme 33 Synthesis of (-)-2-epi-lentiginosine reported by Takabe et al.

Scheme 34 Fluorination of trisubstituted pyrrolidine rac-132 reported by Juhl et al.

Scheme 35 DKR [3 + 2] annulation of racemic cyclopropanes to aldimines reported by Johnson et al.

CH₂CH₂OTBS

Scheme 36 DKR [3 + 2] annulation of racemic 2-arylaziridines with indoles reported by Chai et al.

Scheme 37 Synthesis of epoxy-pyrrolidines via KR of racemic amidoketone rac-137 reported by Aggarwal et al.

In 2016, Juhl et al. developed a method for accessing 3,4substituted fluoropyrrolidines by fluorination of pyrrolidines employing prolinol and imidazolidinone based organocatalysts to obtain the syn- and anti-fluoropyrrolidines, respectfully. 95 They used this methodology in the resolution of racemic pyrrolidine rac-132, obtaining the anti-fluoropyrrolidine 133 in excellent enantioselectivity with a good yield (Scheme 34).

5. Multisubstituted pyrrolidines

Tetrasubstituted pyrrolidines have been accessed from racemic cyclopropanes via [3 + 2] annulation with aldimines. Initial work in this area achieved a highly diastereoselective reaction employing various vtterbium and scandium-based catalysts. ^{96,97} In 2010, Johnson *et al.* developed a dynamic kinetic resolution variant of this reaction employing magnesium iodide and a chiral pyridine-based ligand (Scheme 35).98 2-Methoxybenzyl was selected as the protecting group, producing excellent enantioselectivities and yields. They obtained good diastereoselectivities with good yields and excellent enantioselectivities across the 11 examples.

In 2015, Chai et al. reported the [3 + 2] annulation of racemic aziridines with indoles employing a copper(1)/BINAP derived catalyst system (Scheme 36).99 The kinetic resolution obtained excellent yields, diastereoselectivities, and enantio-

Scheme 38 1,3-dipolar cycloaddition of azomethine ylides with racemic allenes reported by Gong et al.

selectivities across 25 examples. Under the optimised reaction conditions, 2-arylaziridines containing election donating groups proceeded more rapidly in the reaction than those containing electron withdrawing groups. 2-Alkylaziridines were reported to barely react and so are a limitation for this reaction system.

Epoxy-pyrrolidines have been synthesised via epoxy-annulations of vinyl sulfonium salts with α -amido ketones by Aggarwal and co-workers (Scheme 37). They successfully achieved a kinetic resolution of racemic amido-ketone rac-137 obtaining epoxy-pyrrolidine 139 in a good yield with good diastereoselectivity and enantioselectivity. This was the only KR example reported. One popular technique for the synthesis of multisubstituted pyrrolidines is the 1,3-dipolar cycloaddition of azomethine ylides with various dipolarphiles.⁵

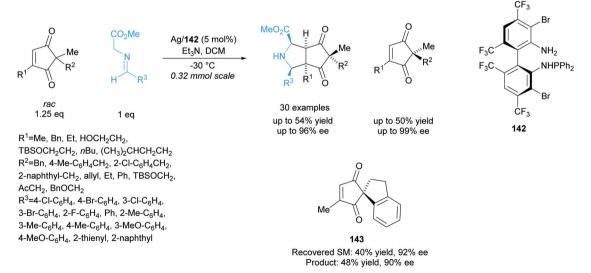
The kinetic resolution of racemic axially chiral allenes during 1,3-dipolar cycloadditions has been investigated by Gong et al. employing a bisphosphoric acid organocatalyst 140 (Scheme 38). 101,102 They obtained excellent yields across 12 examples, affording the 3-methylenepyrrolidines in good

enantioselectivities and the recovered starting allenes in excellent enantioselectivities.

Waldmann et al. resolved racemic tropanes in a copper catalysed 1,3-dipolar cycloaddition reaction with various azomethine ylides aiming to synthesise polycyclic structures containing pyrrolidine and tropane fragments (Scheme 39). 103 A series of azomethine ylides varying the aryl group provided good yields and excellent enantioselectivities for the polycyclic products. In the kinetic resolution of different tropanes under modified reaction conditions, excellent enantioselectivities of up to 99% ee were obtained for the recovered starting tropanes with similarly excellent enantioselectivities obtained for the polycyclic products. They went on to conduct one-pot sequential 1,3-dipolar cycloadditions using chiral ligand 141 in the first cycloaddition and rac-BINAP in the second cycloaddition. Each addition used a different azomethine ylide affording two distinct polycyclic products in excellent enantioselectivities of up to 99% ee and yields up to 49%.

In 2018, Wang and co-workers employed a similar technique to resolve racemic cyclopentenediones producing bicyc-

Scheme 39 1,3-dipolar cycloaddition of azomethine ylides with racemic tropanes reported by Waldmann et al.

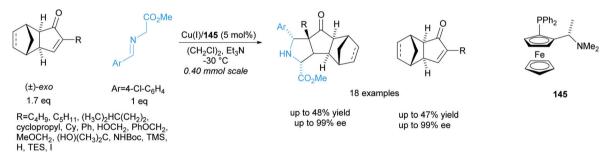


Scheme 40 1,3-dipolar cycloaddition of azomethine ylides with racemic cyclopenenediones reported by Wang et al.

lic pyrrolidines (Scheme 40). 104 Silver catalysis was employed in the 1,3-cycloaddtion reaction between cyclopentenediones and azomethine ylides, achieving excellent enantioselectivities for

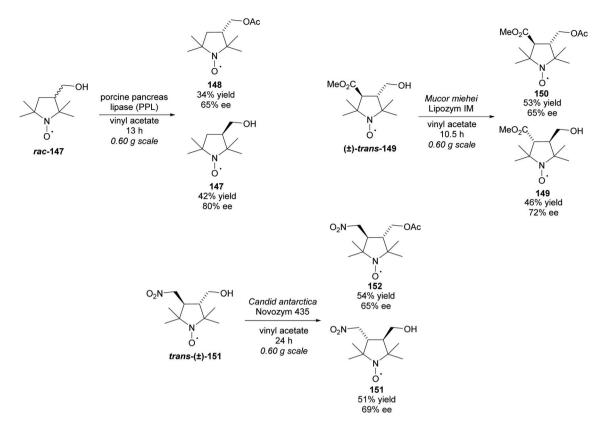
both the recovered starting cyclopentenediones and the bicyclic pyrrolidine products. Good enantioselectivity was also obtained for the spiro-moiety containing cyclopentenedione 143.

Scheme 41 1,3-dipolar cycloaddition of azomethine ylides with racemic alkylidene norcamphors reported by Wang et al.



Scheme 42 1,3-cycloaddition of racemic oxodicyclopentadienes with azomethine ylides reported by Wang et al.

Scheme 43 PKR 1,3-dipolar cycloaddition between MBH adducts and azomethine ylides reported by Xu et al.



Scheme 44 Enzymatic acetylation of various multisubstituted pyrrolidines reported by Hideg et al.

Further work by the group employed biphenyl ligand 142 in the copper catalysed 1,3-dipolar cycloaddition between racemic alkylidene norcamphors and azomethine ylides (Scheme 41). Spirocyclic pyrrolidine products were obtained in good yields with moderate to excellent enantioselectivities. The kinetic resolution of a series of different alkylidene norcamphors achieved good to excellent enantioselectivities for both products and recovered starting materials. Fused norcamphors also exhibited excellent enantioselectivities.

The same group resolved a series of racemic *exo-*3-oxodicy-clopentadienes in a copper catalysed 1,3-cycloaddition reaction with a glycine aldimino ester (Scheme 42). They obtained excellent enantioselectivities for both the recovered *exo-*3-oxodicyclopentadienes and polycyclic pyrrolidine products. One racemic *endo-*3-oxodicyclopentadiene was resolved under the same conditions and achieved excellent enantioselectivities of 95% ee for both recovered starting material and pyrrolidine product.

In 2018, Xu and co-workers developed a parallel kinetic resolution involving a copper catalysed 1,3-dipolar cyclo-addition between racemic Morita-Baylis-Hillman (MBH) adducts *rac-*146 and glycine aldimino esters (Scheme 43). Pyrrolidines containing four stereogenic centres including one all-carbon quaternary were obtained in excellent diastereoselectivities and enantioselectivities. Glutamic acid derivatives were also produced during the reaction and were obtained in similarly excellent enantioselectivities. When MBH adducts

containing aliphatic groups, ethyl or cyclohexyl, were used a significant decrease in enantioselectivity was observed, obtaining enantioselectivities as low as 42% ee for the glutamic acid product.

There are a very limited number of examples of enzymatic resolution of racemic multisubstituted pyrrolidines. Hideg *et al.* preformed acetylations of alcohols on the 3-position of three different pyrrolidines (Scheme 44). These all occurred with moderate enantioselectivities to good enantioselectivities obtained for each of the recovered alcohols and acetylated products.

6. Summary

Application of kinetic resolution remains an important technique to obtain enantiomerically pure substituted pyrrolidines. Enzymatic methodology is heavily relied upon for monosubstituted substrates and is regularly used for disubstituted substrates. The poor substrate diversity obtained through this technique is often outweighed by high selectivity. Whilst these biotransformations offer high selectivity, there is significant future scope in this area to develop better synthetic chemistry routes that are both selective and efficient in delivering the desired products with high diversity and complexity. In contrast, it is also important to note that although enzymes are widely used for some substrate classes, methods involving

annulations and cycloadditions are favoured for heavily substituted substrates, with the added benefit of additional points of diversity. Therefore, there is scope from both the synthetic chemistry and biological chemistry community to identify and develop complementary techniques that can improve the efficiency of these transformations, and at the same time expand the diversity of products that can be obtained using this methodology.

A final point to reflect on as illustrated in this review, is that traditional KR methods are far more commonly used than DKR and PKR methods despite the limit on overall yields, leaving significant scope for the development of new synthetic methodology in this area as well. Strategies and methodologies that embrace these methods offer significant advantages and would significantly enhance the atom efficiency in an area of continuing significant importance.

Conflicts of interest

There are no conflicts to declare.

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