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Current applications of kinetic resolution in the asymmetric synthesis of substituted pyrrolidines

Sian S. Berry and Simon Jones *

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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.

1. 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 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

Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield, S3 7HF, UK. E-mail: simon.jones@sheffield.ac.uk

Sian Berry

Sian Berry was born in London, UK in 1995. Sian received her undergraduate degree from the University of Sheffield, completing her final year project in 2018 working on the asymmetric reduction of α-imino esters under the supervision of Professor Simon Jones. She began her Ph. D. studies in the same year in Prof Jones' laboratory on the asymmetric synthesis of amino acids via trichlorosilane mediated reductions.

Simon Jones

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

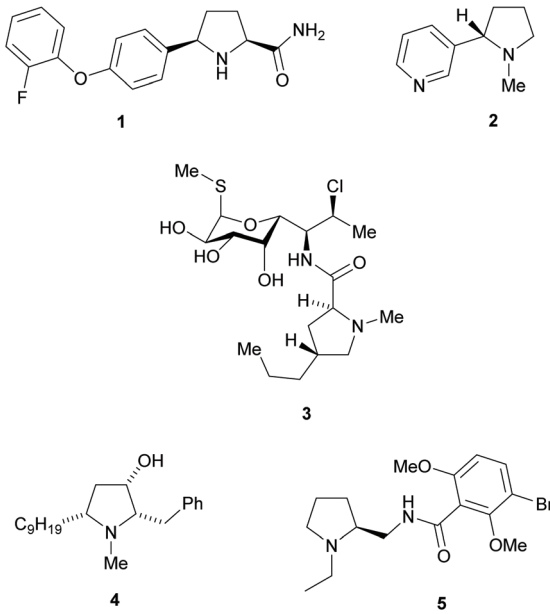
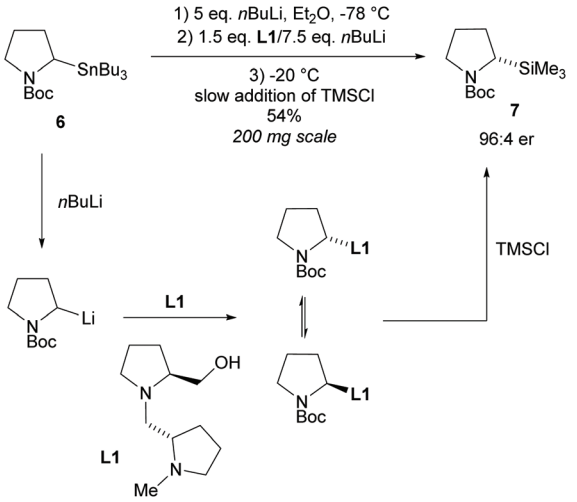


Fig. 1 Pyrrolidine containing natural products and pharmaceuticals, Vixotrigine **1**, Nicotine **2**, Clindamycin **3**, (+)-Preussin **4** and Remoxipride **5**.

by the substitution of their respective parent pyrrolidines framework.

2. Monosubstituted pyrrolidines

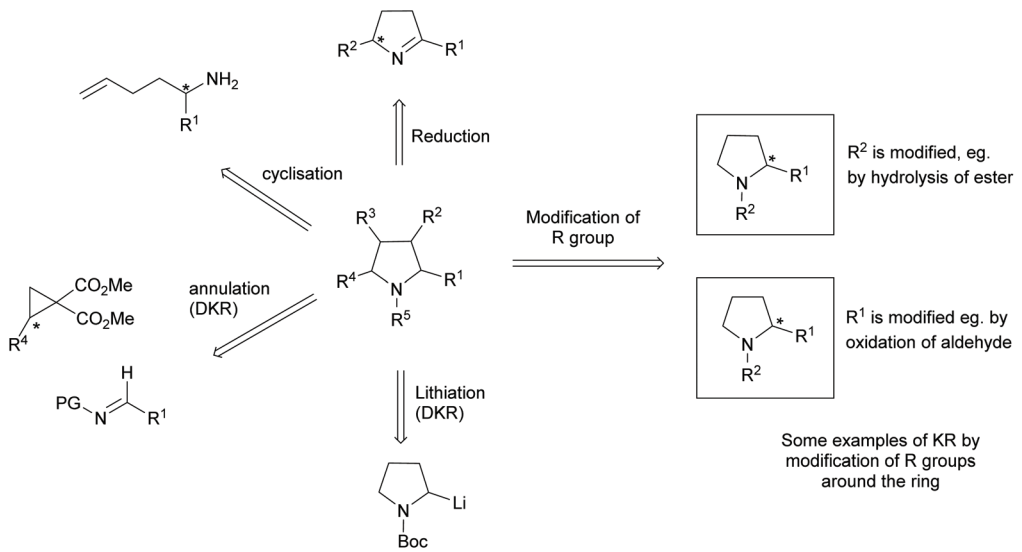
In 1994, Beak *et al.*, reported on the asymmetric deprotonation of *N*-Boc-pyrrolidines *via* lithiation/substitution employing (−)-sparteine and *sec*-butyllithium (*s*BuLi), providing access to 2-substituted-*N*-*tert*-butylcarbonyl-pyrrolidines (*N*-Boc).[15] It was noted that upon warming the enantioselectivity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



Scheme 2 Dynamic kinetic resolution of *N*-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 *n*BuLi, addition of chiral ligand **L1** with *n*BuLi, 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.

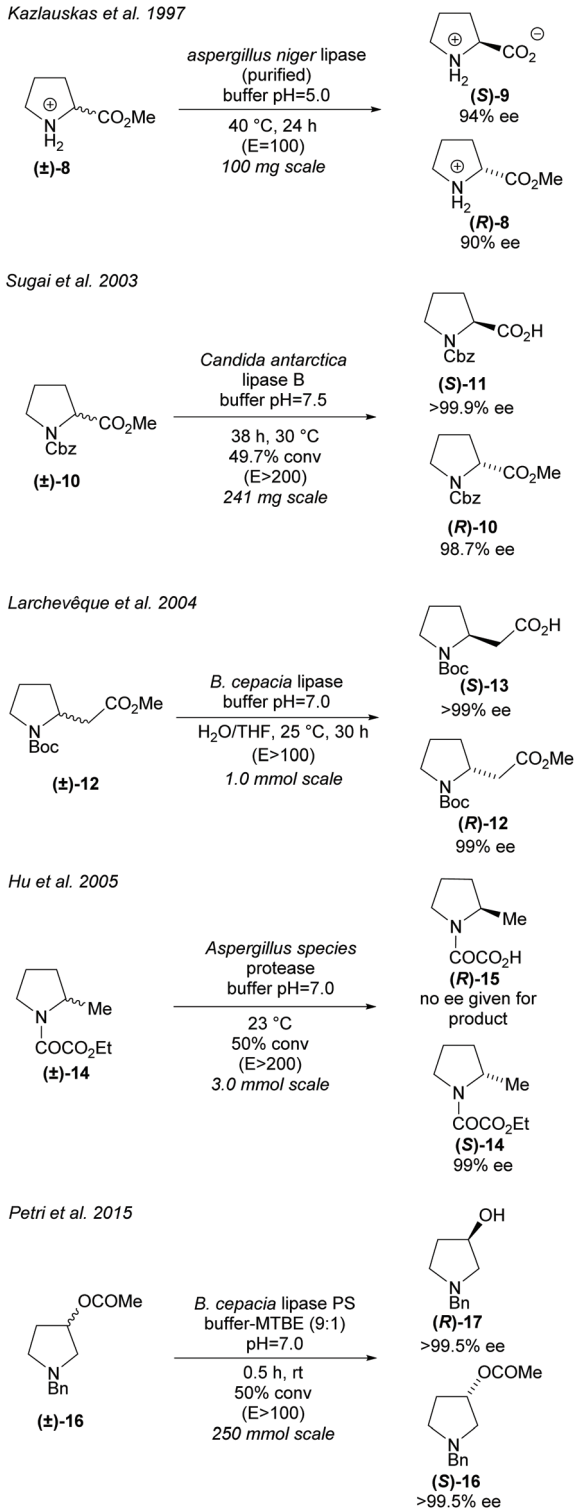
Biocatalytic methods for the kinetic resolution of racemic pyrrolidines provide easy access to enantiomerically enriched pyrrolidines under mild conditions; often performing to high degrees of selectivity at mild temperatures and pH under atmospheric pressure.[23] Unfortunately, the high selectivity 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 (±)-**16** obtaining 3-hydroxypyrrolidine (***R***)-**17** in excellent enantioselectivity.[28]

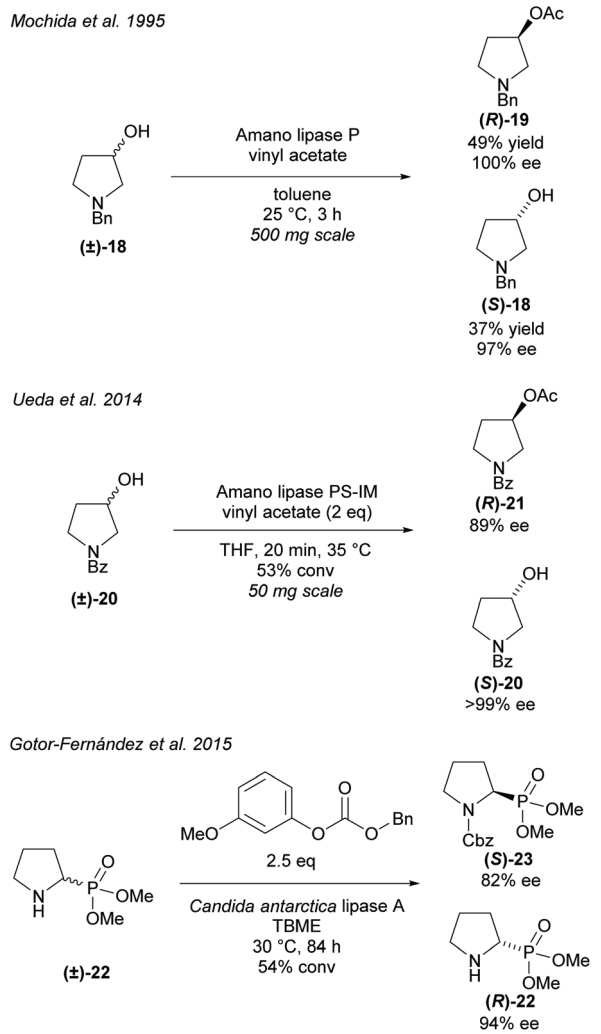
Alternatively, hydrolyses can be used in organic solvents to promote asymmetric acetylation of racemic alcohols (Scheme 4). Use of organic solvents allows for easier extraction of products when compared to hydrolysis methods conducted in buffers. Resolution of 3-hydroxy-pyrrolidines were conducted by 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]

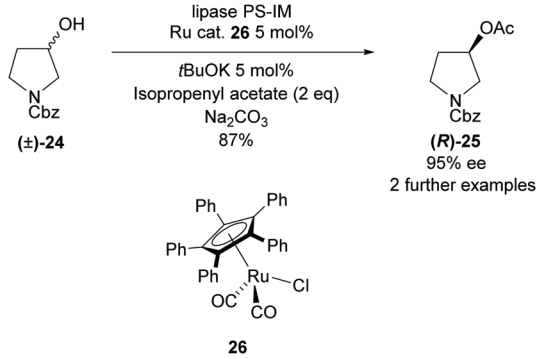
All methods involving enzymatic resolution of racemic pyrrolidines discussed so far have a theoretical maximum yield of 50% for the enantiopure product and returned starting material. In 2011, Bäckvall *et al.* employed lipase PS-IM in the acetylation of 3-hydroxy-pyrrolidine (±)-**24** with a ruthenium 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 3 Hydrolysis of various monosubstituted pyrrolidines.



Scheme 4 Acetylation of various monosubstituted pyrrolidines.



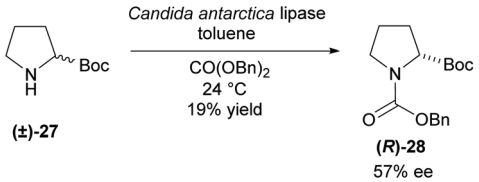
Scheme 5 Acetylation of racemic alcohol **24** involving ruthenium catalysed racemisation.

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

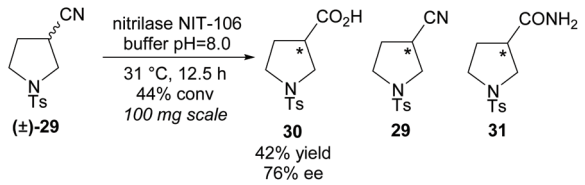
Protection of amines *via* enzymatic transesterification has been significantly less investigated. One common problem associated with this method is the higher nucleophilicity of the amine compared to the commonly acetylated alcohols. In 1999, Wong *et al.* attempted to overcome this problem by employing 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).[34] Nitrilase 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.

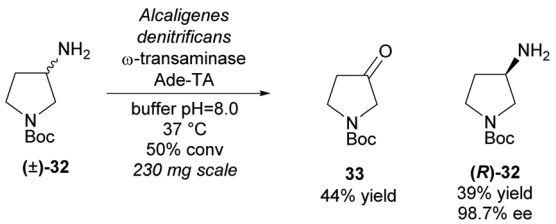
An alternative functional group transformation is to utilize ω-transaminases to resolve racemic amines by converting one enantiomer of the amine to a ketone. In 2008, Bornscheuer *et al.* employed a ω-transaminase from *Alcaligenes denitrificans* (Ade-TA) to resolve 3-amino-*N*-Boc-pyrrolidine (±)-**32** (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-(2*S*,3*R*)-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-(2*R*,3*S*)-iso-Dap however, a mixture of diastereoisomers (2*R*,3*S*)-**42**, (2*S*,3*R*)-**42** and (2*S*,3*S*)-**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 (2*S*,3*S*)-**42** in 87% de from Boc-protected pyrrolidine **41**. Changing the chiral ligand to (*S*)-SYNPHOS allowed for access to (2*R*,3*R*)-**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 (2*R*,3*R*)-**42** and (2*S*,3*R*)-**42** in 2 : 1 dr.

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

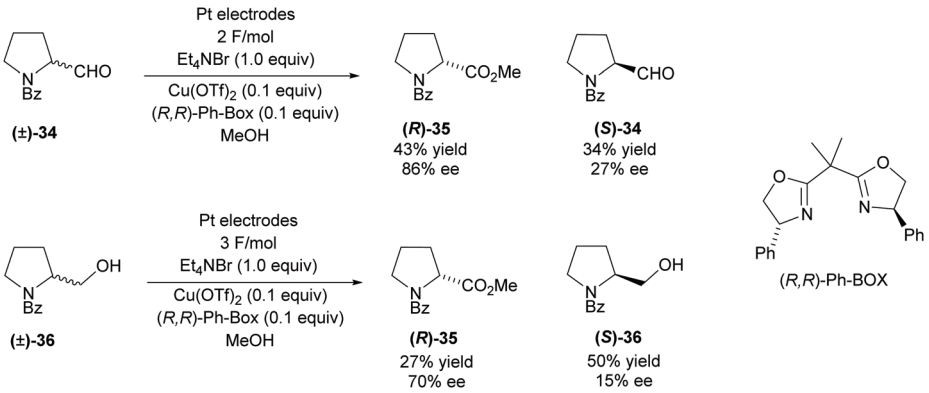
In 2011, Ohkuma *et al.* employed a similar method, synthesising 2- and 3-monosubstituted pyrrolidines from racemic pyrrolidines containing a ketone (Scheme 11).[41]

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.

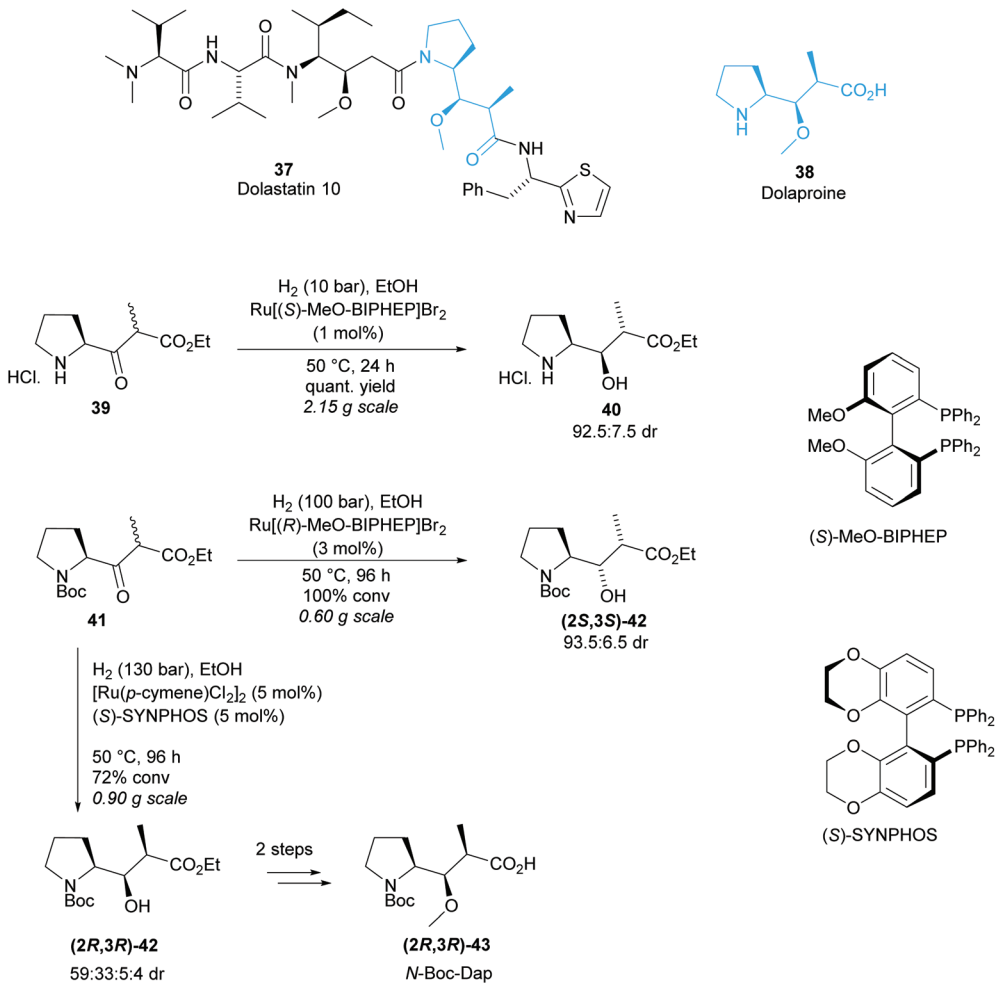
3. Disubstituted pyrrolidines

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.

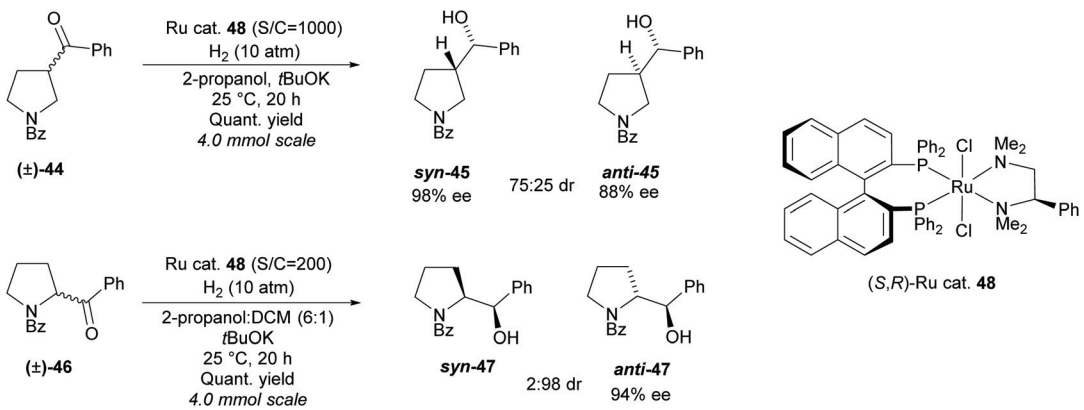
Monosubstituted nitrile pyrrolidine **49** is a key intermediate in the synthesis of PF-00951966, a fluoroquinolone based broad-spectrum antibiotic discovered at Pfizer. In 2012, Lall and co-workers reported the synthesis of nitrile pyrrolidine **49** *via* a modified Noyori asymmetric hydrogenation of racemic disubstituted β-keto-γ-lactam **(±)-47** (Scheme 13).[44] Excellent



Scheme 9 Electrochemical oxidation reported by Onomura *et al.*



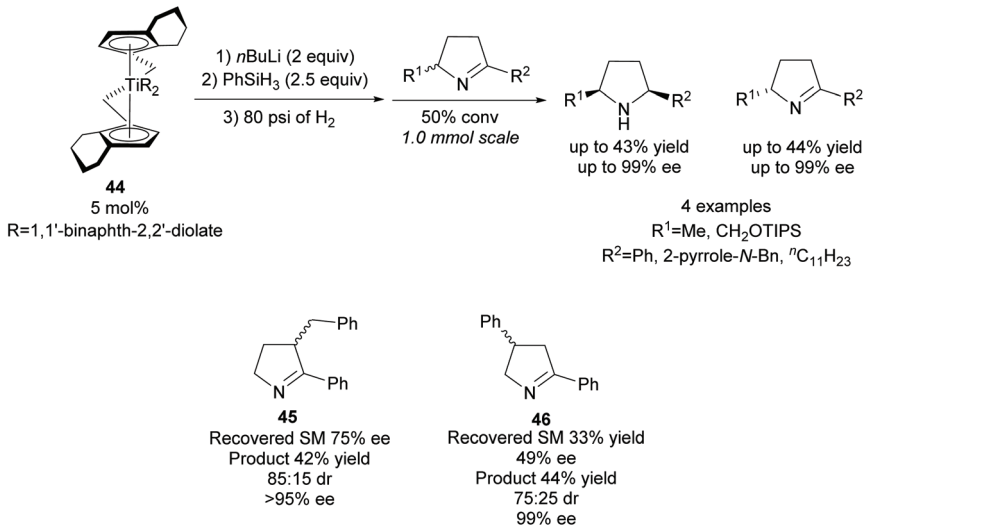
Scheme 10 Synthesis of Dolaproine reported by Genet *et al.*



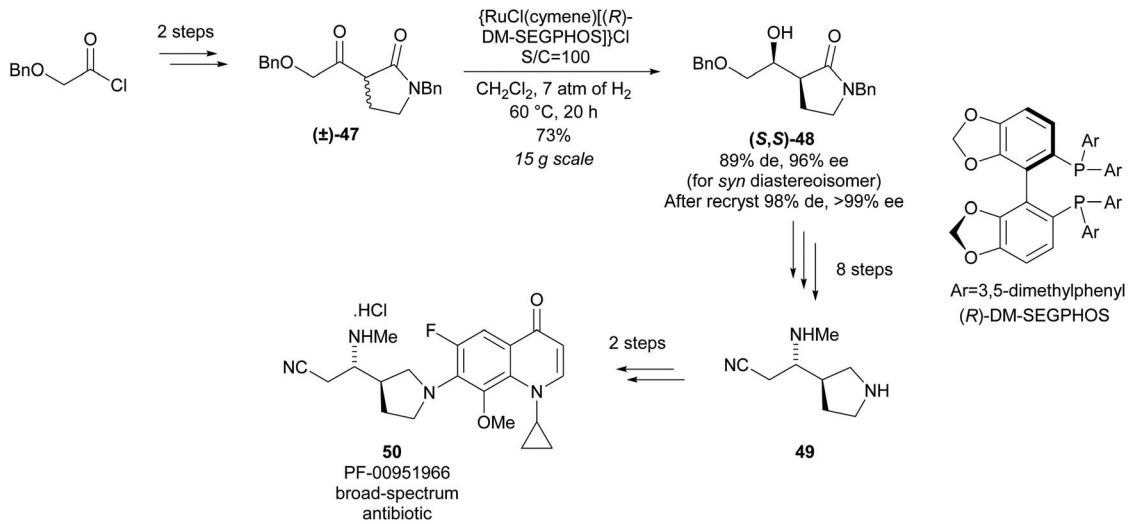
Scheme 11 Ruthenium catalysed hydrogenation involving DKR reported by Ohkuma *et al.*

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 catalysts 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 **(±)-51** in



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

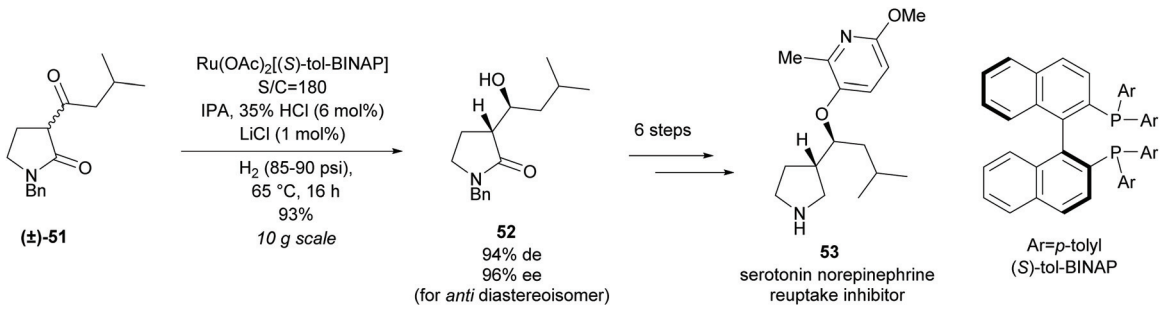


Scheme 13 Synthesis of nitrile pyrrolidine **49** reported by Lall *et al.*

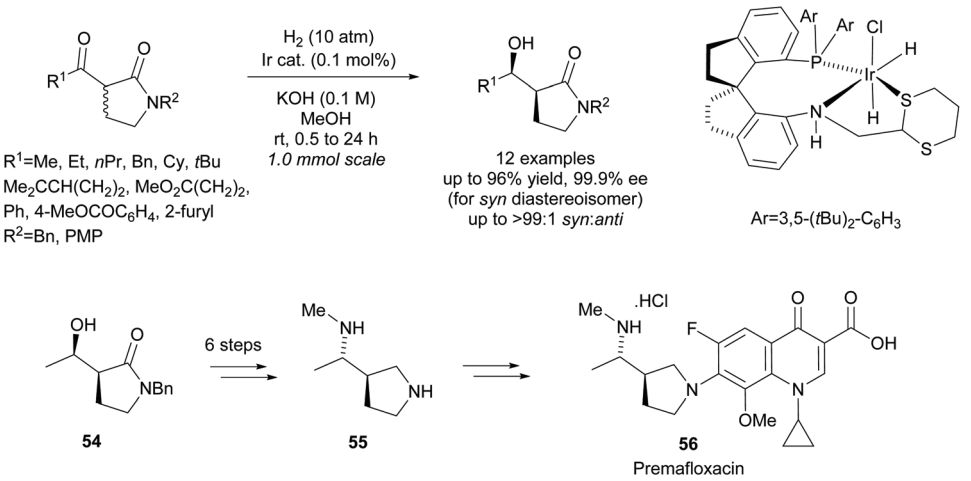
the synthesis of a pyrrolidine-based serotonin norepinephrine reuptake inhibitor **53** (Scheme 14).[47] Good yields and selectivities were obtained for the β-hydroxy-γ-lactam **52**. Further modifications obtained the pyrrolidine-based inhibitor in 7 steps.

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-phenyl-aminoalkene 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-1-aminopent-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]

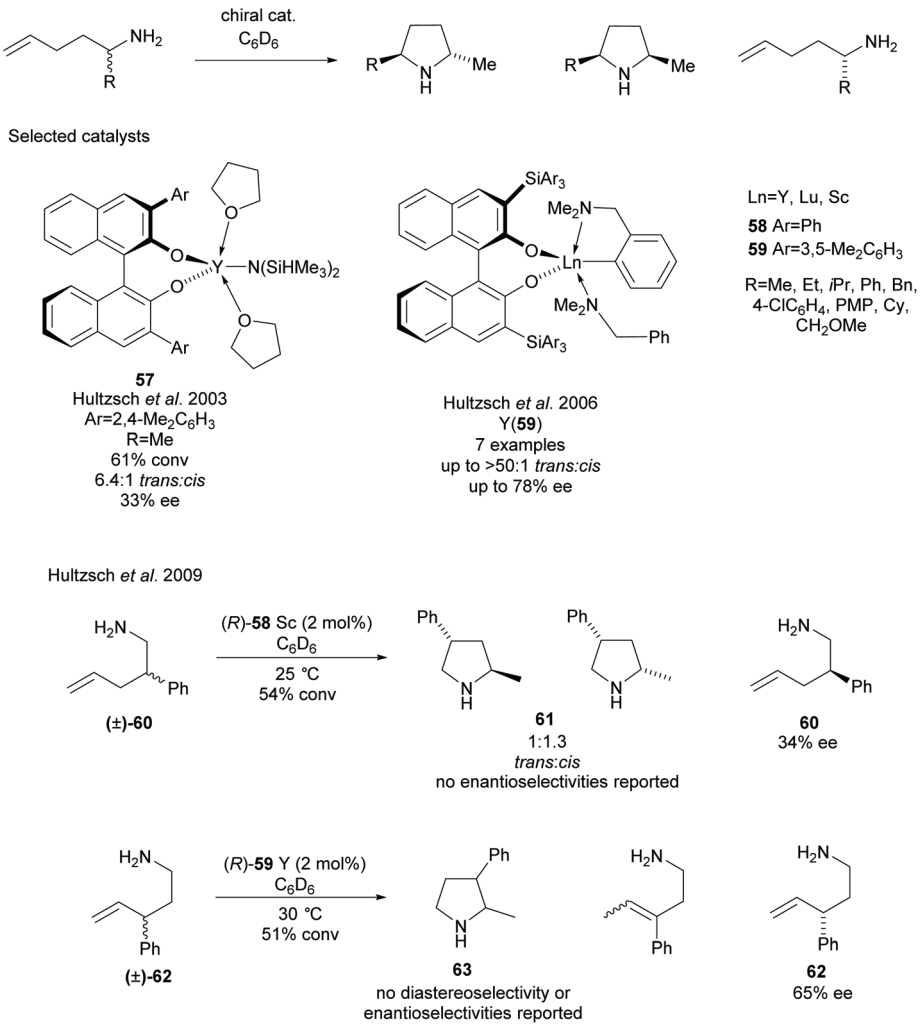
They obtained the Cbz protected pyrrolidine **65** in a poor yield at a low conversion with good enantioselectivity. The yield could be improved with the use of *p*-toluenesulfonyl as the protecting group compared to carboxybenzyl however the enantioselectivity decreased to 60% ee.

(−)-Supinidine, a pyrrolizidine alkaloid, can be synthesised from disubstituted pyrrolidine **70**. In 1991, Takahata and co-workers 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.

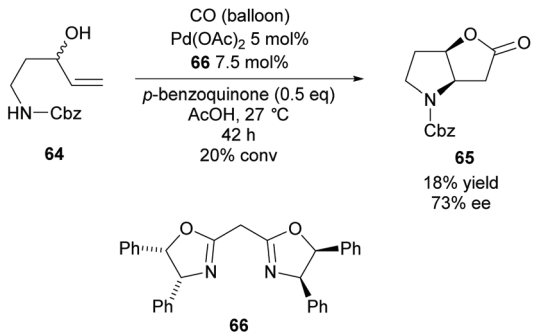
Cyclisation employing dynamic kinetic resolution within the aza-Cope rearrangement was developed by Overman *et al.* (Scheme 19).[59] *N*-Protected bicyclic pyrrolidine **73** was obtained in a good 89% yield over two steps in an excellent 99% ee. Hydrolysis of the formaldiminium ion after the aza-Cope 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**



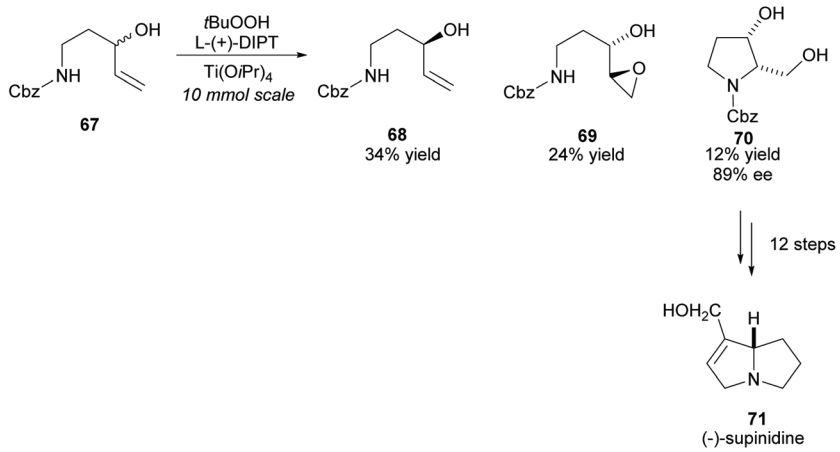
Scheme 16 Asymmetric hydroamination of aminoalkenes reported by Hultzsch *et al.*



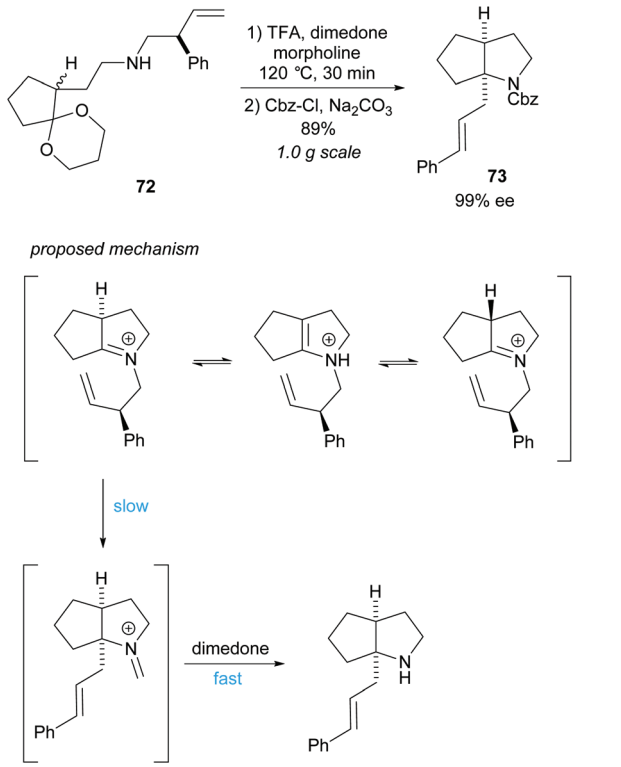
Scheme 17 Carbonylative cyclisation reported by Gracza *et al.*

(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, obtaining 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.

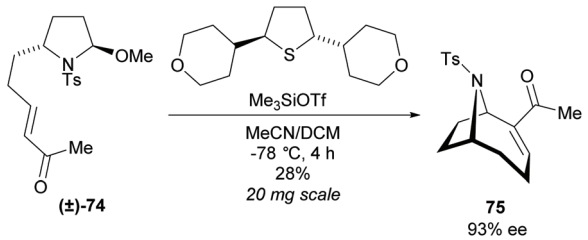
Hydrolysis of esters closely attached to the pyrrolidine ring in disubstituted pyrrolidines is again a popular technique (Scheme 22). In 1996, Kawanami *et al.* employed PS to resolve racemic 2,5-diacetyl pyrrolidine ***trans*-(±)-79** affording the monoacetyl pyrrolidine **80** in moderate enantioselectivity 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.*

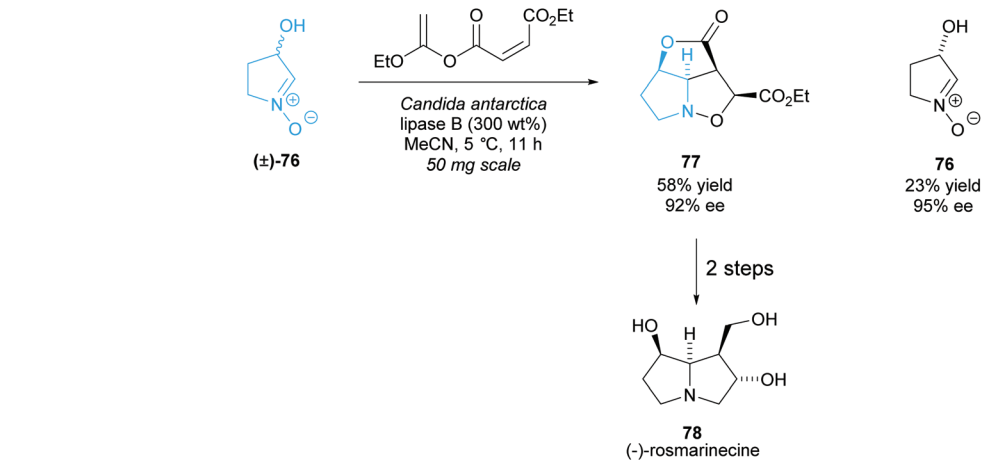


Scheme 20 DKR of disubstituted pyrrolidine **74** reported by Zakarian *et al.*

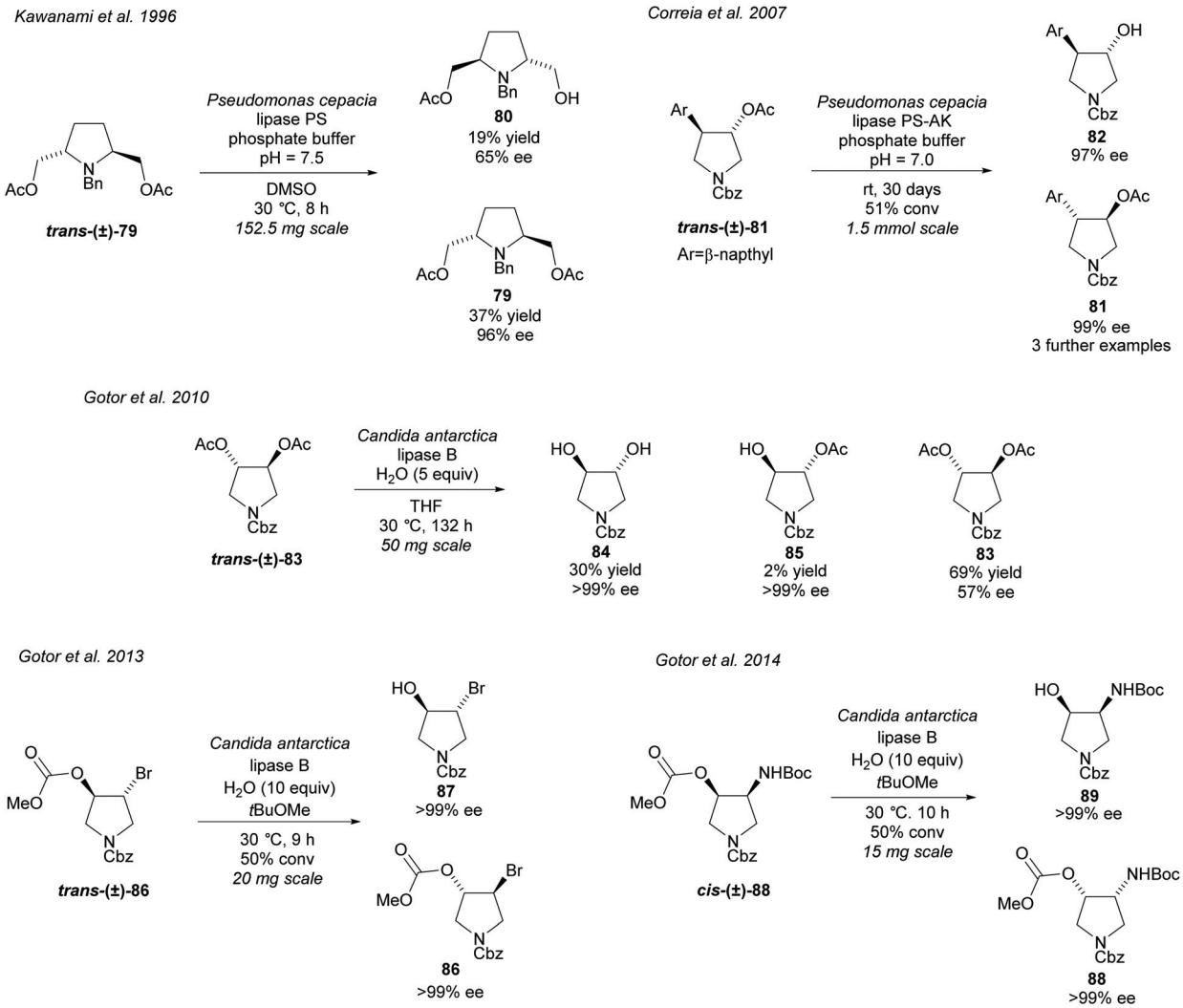
phenyl substituted analogue.[70] CAL-B has been employed by Gotor *et al.* in the hydrolysis of 3,4-diacetylated pyrrolidine ***trans*-(±)-83**, brominated pyrrolidine ***trans*-(±)-86**, and amino pyrrolidine ***cis*-(±)-88**.[71–73] Hydrolysis of racemic diacetate ***trans*-(±)-83** afforded the dihydroxy-pyrrolidine **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.

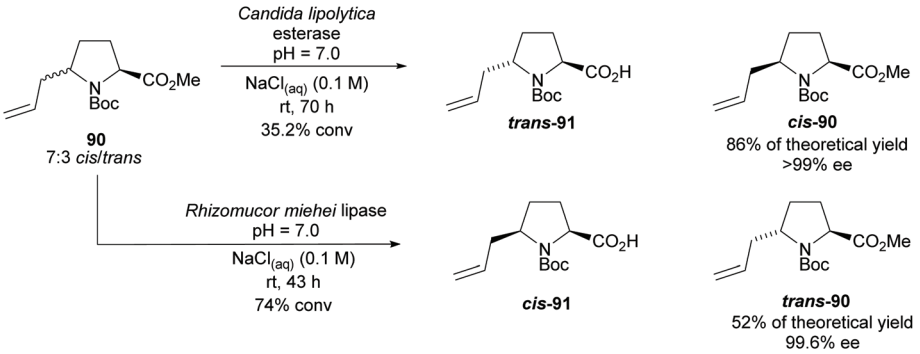
Transesterification of alcohols attached to a pyrrolidine ring promoted by lipases is another popular use of enzymes in the synthesis of disubstituted pyrrolidines (Scheme 24). In 1994, Sibi *et al.* acetylated racemic 2,5-disubstituted-dihydroxy pyrrolidine ***trans*-(±)-92** employing PS lipase, affording 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.



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

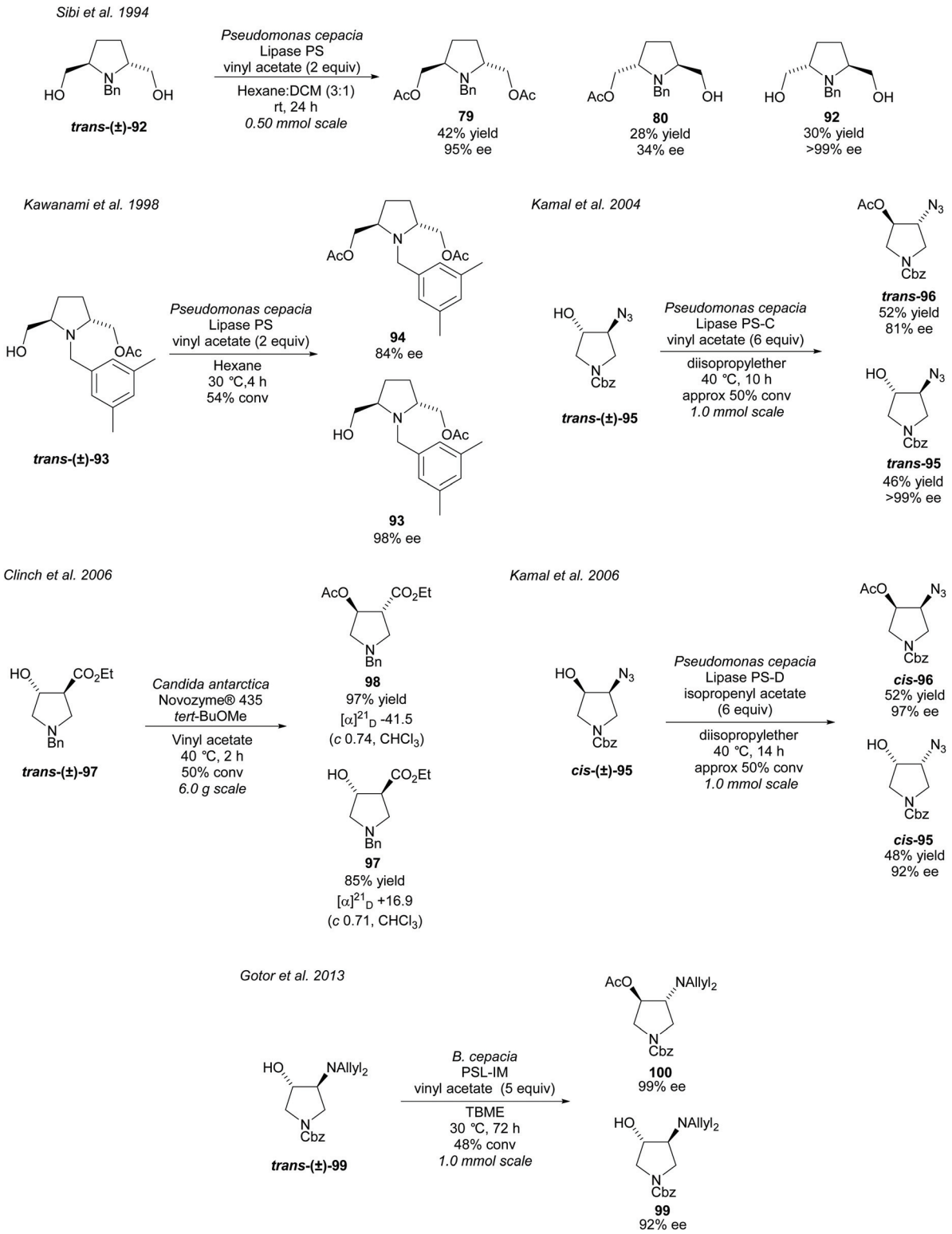
resolution of *trans*- and *cis*-azido pyrrolidines **95**, respectively.[78,79] Good to excellent enantioselectivities were obtained for both the returned alcohols and the acetylated products. In 2006, Clinch *et al.* employed Novozyme® 435 (an immobilized form of CAL-B) in the resolution of 3,4-disubstituted 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*-disubsituted 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 *trans*-isomers, 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*-(±)-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

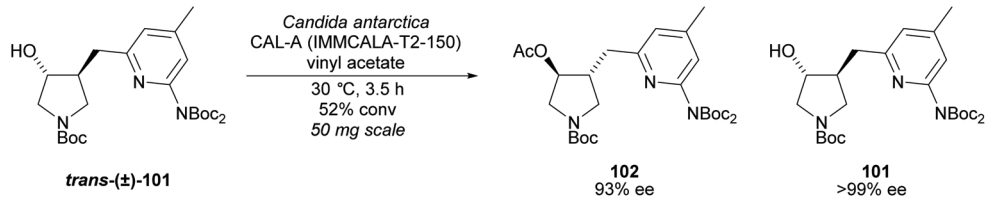
Trisubstituted pyrrolidines have been accessed *via* an organocatalysed aza-Henry/aza-Michael cascade reaction by Huang *et al.* (Scheme 28).[87] The reversable aza-Henry step provided a modest 2 : 1 ratio of *trans* : *cis* **109** and in the subsequent aza-Michael cyclisation only the trans isomer 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 co-workers (Scheme 29).[88,89] A partial kinetic resolution of racemic five-membered ring nitrone **(±)-*cis*-112** was achieved in a 1,3-diploar cycloaddition with isolevoglucosenone **114**.[88] 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.[89] PKRs have the advantage of reacting both enantiomers at the same or similar rates to two different, separable products.[14] Unlike simple KRs, the 1 : 1 ratio of the starting enantiomers is maintained throughout the reaction leading to higher enantioselectivities and higher yields.

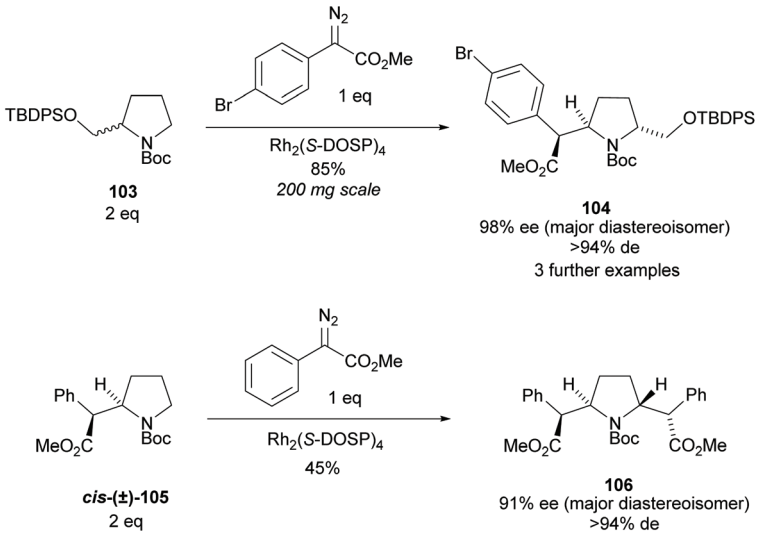


Scheme 24 Enzyme mediated transesterification of various disubstituted pyrrolidines.

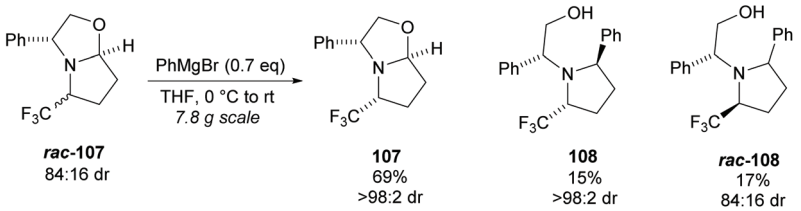
The 1,3-dipolar cycloaddition of α,β-unsaturated δ- and γ-lactones to racemic nitrone ***cis*-(±)-112** was investigated by Chmielewski *et al.* (Scheme 30).[90] δ-Lactone **117** exhibited good yields with excellent diastereoselectivity, obtaining *exo*-cycloaddition product **118** exclusively, with (3*R*,4*S*)-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*-(±)-112** both the *exo* and



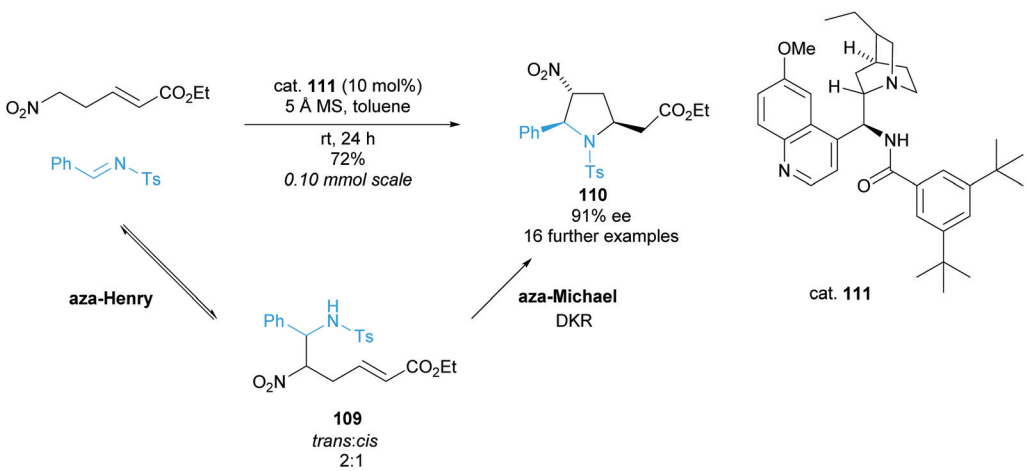
Scheme 25 Nitric oxide synthase inhibitors synthesised by Gotor *et al. via* enzyme catalysed acetylation.



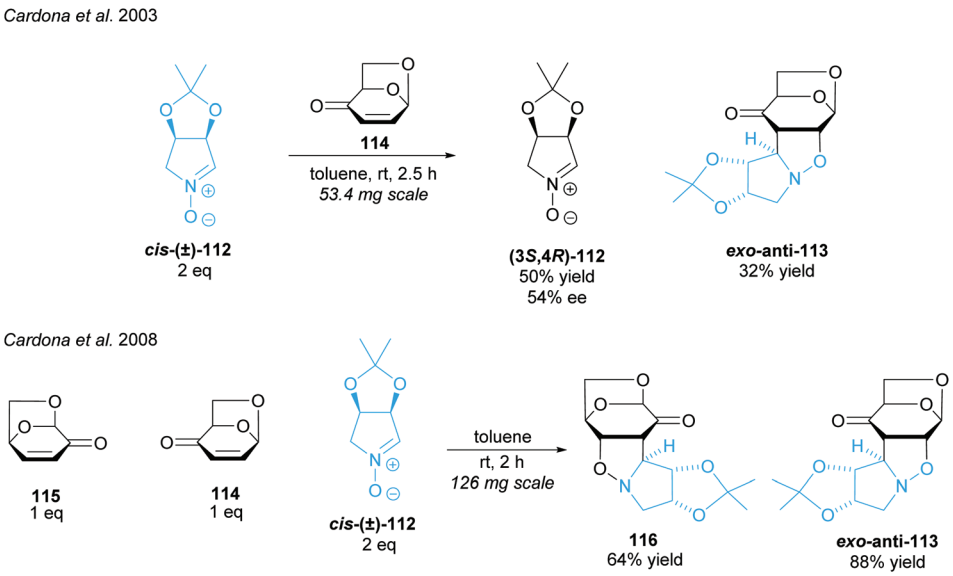
Scheme 26 C–H activation of *N*-Boc pyrrolidines reported by Davies *et al.*



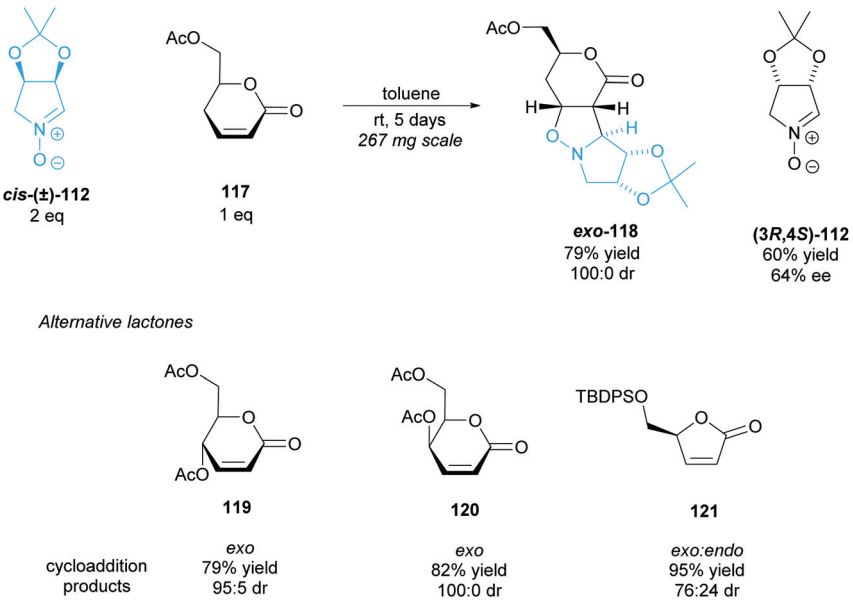
Scheme 27 Phenyl magnesium bromide employed to consume one diastereoisomer reported by Brigaud *et al.*



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



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

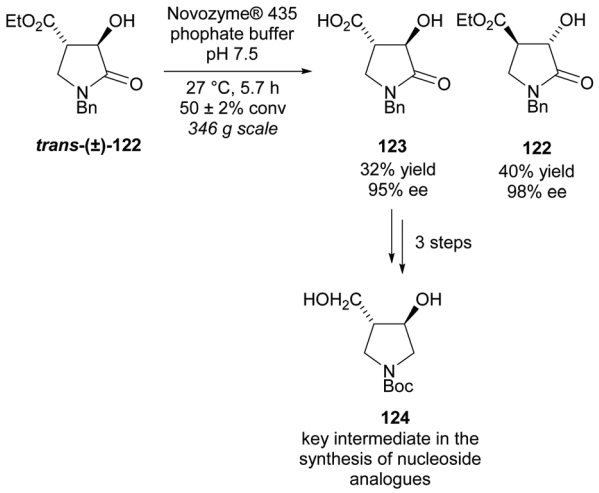


Scheme 30 1,3-dipolar cycloaddition of racemic nitrone **112** to various lactones reported by Chmielewski *et al.*

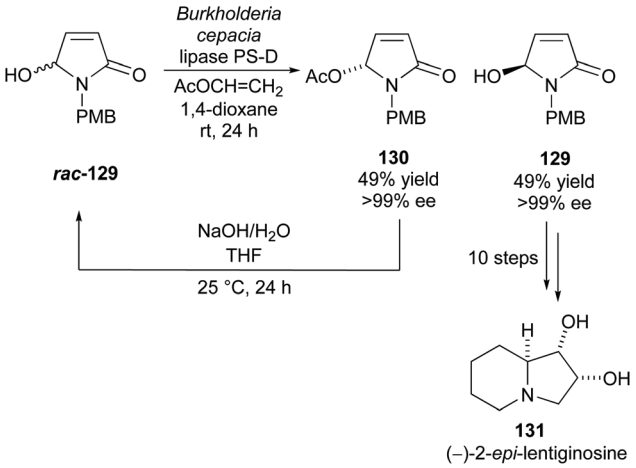
endo products were formed. In this case, the mismatched (3*R*,4*S*)-nitrone reacts, forming the *endo* product.

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.

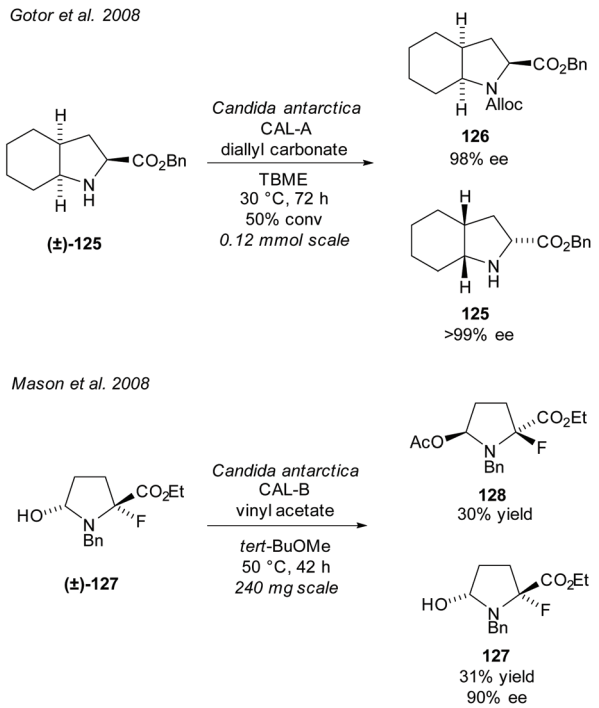
In 2008, Gotor *et al.* resolved bicyclic pyrrolidine **(±)-125** employing CAL-A in an enzyme catalysed carbamate formation (Scheme 32).[92] Excellent enantioselectivities were obtained for both the carbamate product **126** and the unreacted amino ester **125**. In the same year, Mason *et al.* resolved 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.



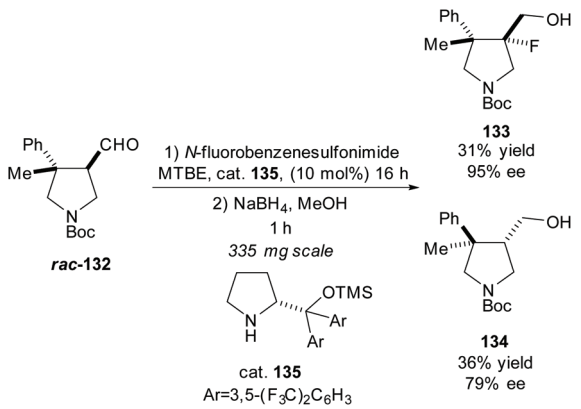
Scheme 31 Enzyme catalysed hydrolysis reported by Mason *et al.*



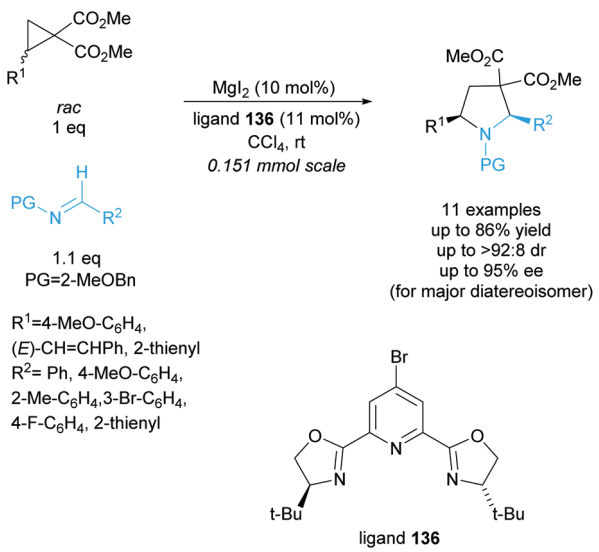
Scheme 33 Synthesis of (–)-2-*epi*-lentiginosine reported by Takabe *et al.*



Scheme 32 Alcohol and amine enzyme mediated protection.

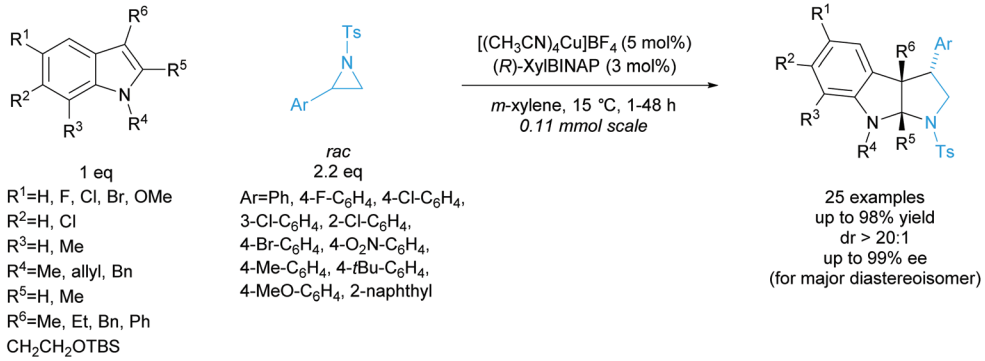


Scheme 34 Fluorination of trisubstituted pyrrolidine ***rac*-132** reported by Juhl *et al.*

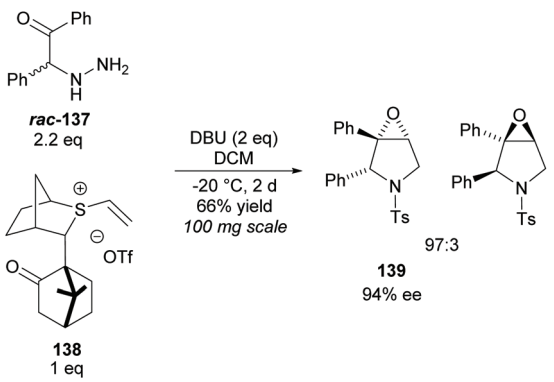


Scheme 35 DKR [3 + 2] annulation of racemic cyclopropanes to aldimines reported by Johnson *et al.*

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



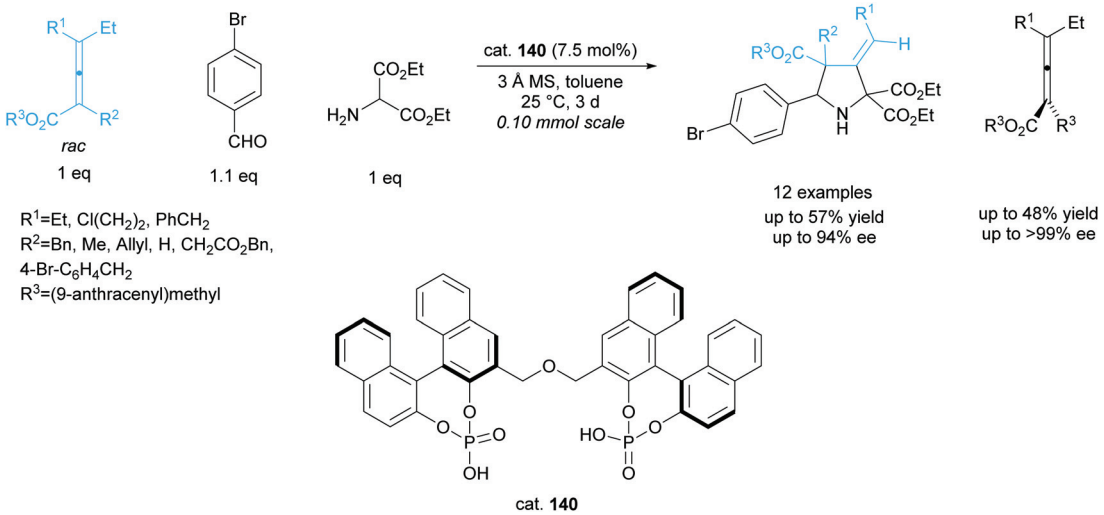
Scheme 37 Synthesis of epoxy-pyrrolidines *via* KR of racemic amidoketone ***rac*-137** reported by Aggarwal *et al.*

In 2016, Juhl *et al.* developed a method for accessing 3,4-substituted 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 ytterbium 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(I)/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.*

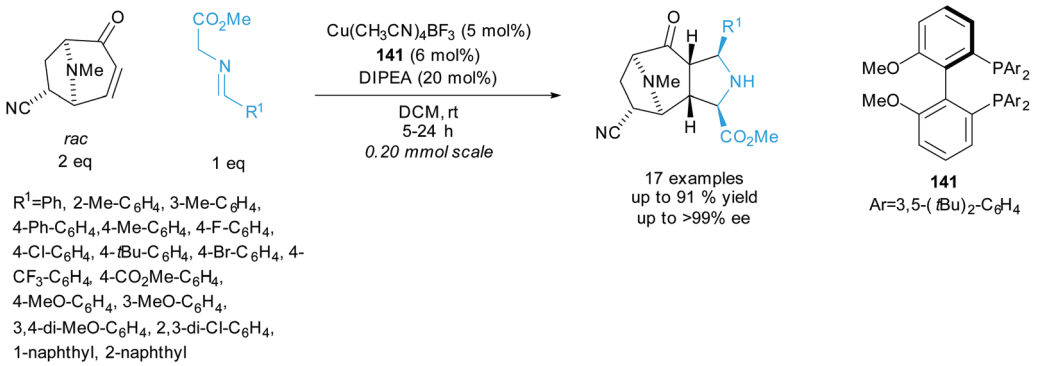
selectivities across 25 examples. Under the optimised reaction conditions, 2-arylaziridines containing election donating groups proceeded more rapidly in the reaction than those containing electron withdrawing groups. 2-Alkylaziridines were reported to barely react and so are a limitation for this reaction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

Epoxy-pyrrolidines have been synthesised *via* epoxy-annulations of vinyl sulfonium salts with α-amido ketones by Aggarwal and co-workers (Scheme 37).[100] 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]

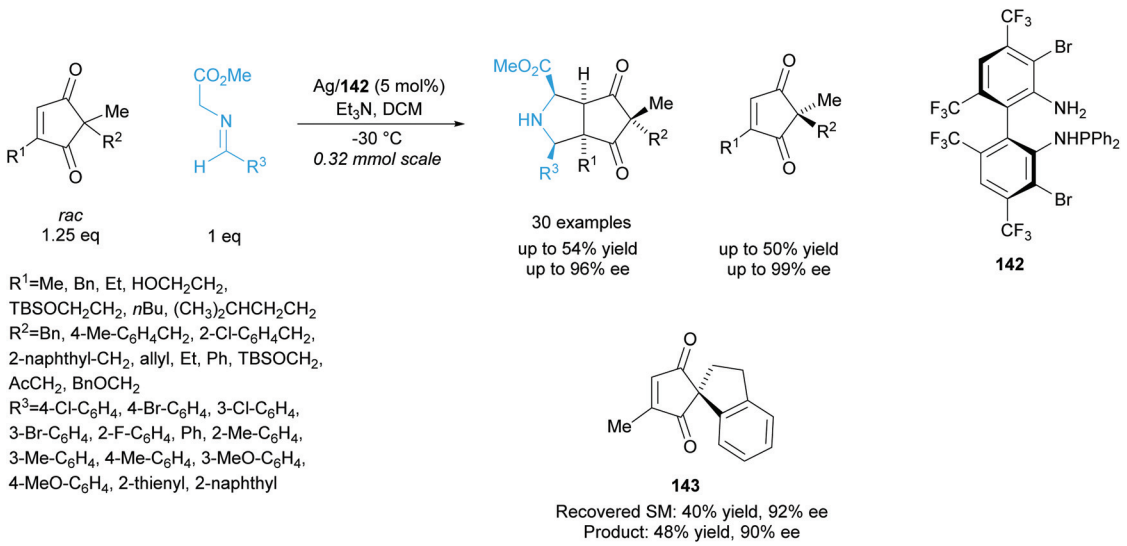
The kinetic resolution of racemic axially chiral allenes during 1,3-dipolar cycloadditions has been investigated by Gong *et al.* employing a bisphosphoric acid organocatalyst **140** (Scheme 38).[101,102] They obtained excellent yields across 12 examples, affording the 3-methylenepyrrolidines in good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

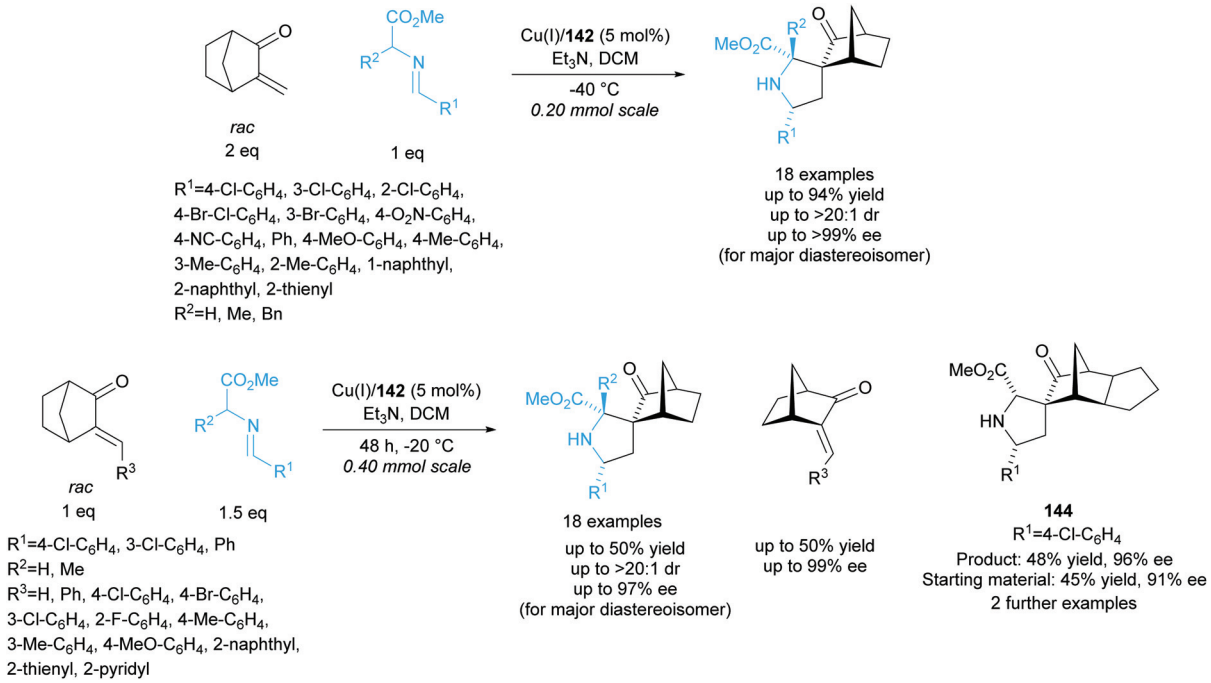


Scheme 39 1,3-dipolar cycloaddition of azomethine ylides with racemic tropanes reported by Waldmann *et al.*

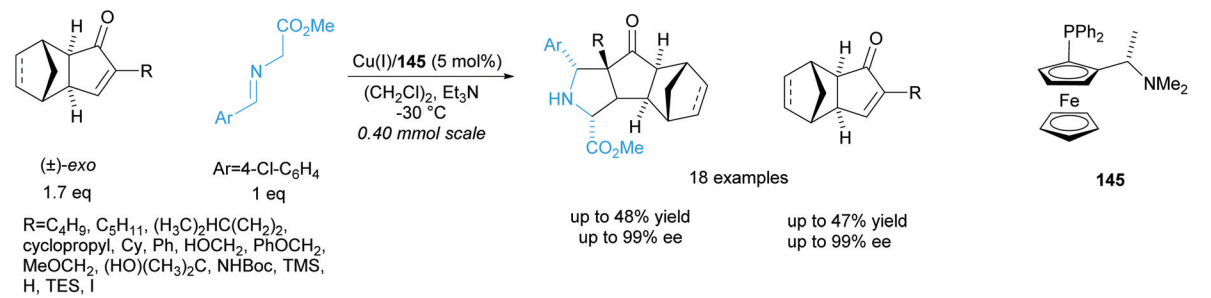


Scheme 40 1,3-dipolar cycloaddition of azomethine ylides with racemic cyclopenenediones reported by Wang *et al.*

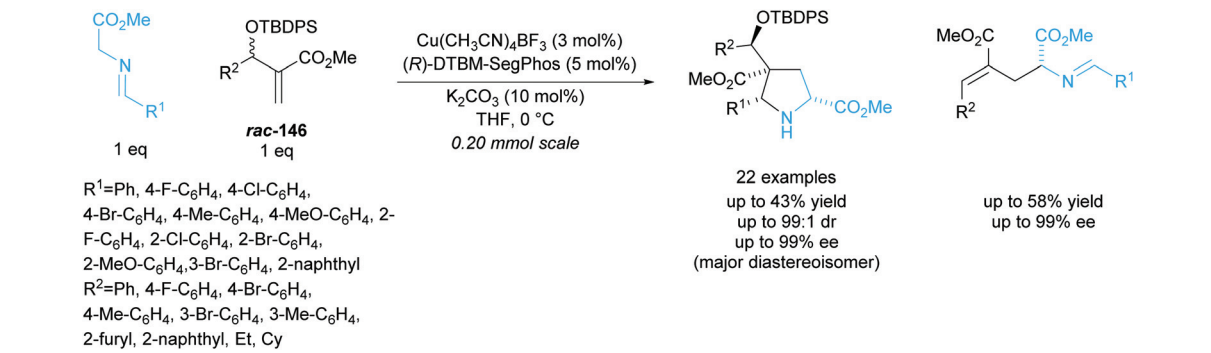
lic pyrrolidines (Scheme 40).[104] Silver catalysis was employed in the 1,3-cycloaddtion reaction between cyclopentenediones and azomethine ylides, achieving excellent enantioselectivities for both the recovered starting cyclopentenediones and the bicyclic pyrrolidine products. Good enantioselectivity was also obtained for the spiro-moiety containing cyclopentenedione **143.**



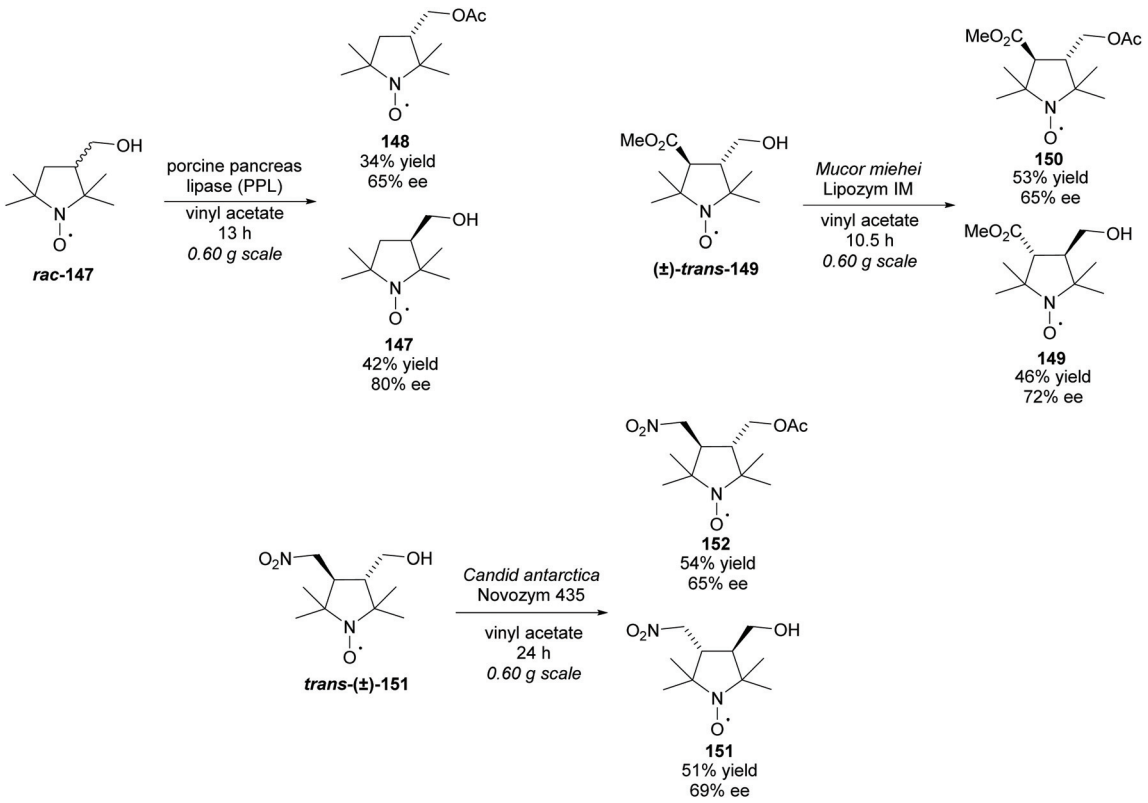
Scheme 41 1,3-dipolar cycloaddition of azomethine ylides with racemic alkylidene norcamphors reported by Wang *et al.*



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).[105] 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-oxodicyclopentadienes in a copper catalysed 1,3-cycloaddition reaction with a glycine aldimino ester (Scheme 42).[106] 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 cycloaddition between racemic Morita–Baylis–Hillman (MBH) adducts ***rac*-146** and glycine aldimino esters (Scheme 43).[107] 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).[108] 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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