

Department of Chemistry
Imperial College London

Towards the Non-enzymatic
Dynamic Kinetic Resolution of Alcohols

By

Zsófia Heckenast

Co-supervised by: Professor Alan C. Spivey
Professor Andrew G. Livingston

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I declare that I personally prepared this thesis, that all the research and data presented in this thesis was carried out personally unless otherwise acknowledged, and that all materials and sources of information are appropriately acknowledged and referenced.

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Abstract

This thesis describes approaches towards the development of a non-enzymatic acylative dynamic kinetic resolution of alcohols, both in a one-pot fashion and also *via* membrane-enhanced processes. Dynamic kinetic resolution (DKR) is a desirable process that if achieved would greatly increase yields of enantioenriched compounds compared to kinetic resolution (KR). The first chapter discusses the large scale synthesis of two key 4-DMAP based catalysts developed in the Spivey group for use in acylative alcohol and amine KR: one based on a 4-(di-*n*-butylamino)pyridine core ('DBAP*') and one based on a 5-azaindoline core ('5-Azy*').

Initial steps towards the syntheses of both catalysts were performed on large scales, and a successful classical resolution procedure was developed by our collaborators at Eli Lilly for the HPLC-free resolution of DBAP*.

The carbamylative KR of phenylalanine methyl ester was investigated, and while conditions whereby the background reaction was minimised were found, the selectivity achieved with the 5-Azy* catalyst was too small (<7) to be developed into a DKR. Further studies into the development of a room-temperature alcohol KR were successful, and moderate selectivity was achieved with DBAP* and an acyl donor compatible with a racemisation catalyst for the KR of 1-(1-naphthyl)ethanol. The focus of the second half of this thesis is the development of the room-temperature KR into a DKR process. Our initial efforts into developing a one-pot process were hampered by deactivation of DBAP* by the ruthenium-based racemisation catalyst, as well as side-reactions occurring during decomposition of the acyl donor. Nevertheless, good *ee* and yield were achieved for the DKR of 1-(1-naphthyl)ethanol using a batch-wise addition process. The viability of a membrane-enhanced process for the DKR was investigated, whereby the two catalytic systems were separated into chambers by nanofiltration membranes. During these studies a MEDKR rig was constructed and tested, showing good initial results, with the promise of improved performance once membrane properties are optimised.

Finally, we discuss the possibility that adding small quantities of a tertiary alcohol into an acylative alcohol KR can significantly increase the selectivity in these reactions, with a 100% increase in selectivity to *s* >100 displayed by optimal substrates in our systems.

Abbreviations

aq.	aqueous
5-Azy*	5-azaindoline-xylyl catalyst
BINOL	1,1-bi-2-naphthol
br	broad
<i>n</i> -BuLi	butyllithium
<i>t</i> -BuLi	<i>tert</i> -butyllithium
Bz	benzoyl
C	conversion
Cbz	benzyloxycarbonyl
CPME	cyclopentyl methyl ether
CSP-HPLC	chiral stationary phase high-performance liquid chromatography
Cy	cyclohexyl
DBAP*	4-dibutylaminopyridine-xylyl catalyst
DBU	1,8-diazobicyclo[5.4.0]ndec-7-ene
DCC	<i>N,N</i> -dicyclohexylcarbodiimide
DIBAL-H	<i>diisobutyl</i> aluminium hydride
DKR	dynamic kinetic resolution
4-DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
<i>dr</i>	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
<i>ee</i>	enantiomeric excess
equiv./eq.	equivalents
<i>er</i>	enantiomeric ratio
g	grams
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HB	hydrogen bond
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
<i>i</i> -	<i>iso</i>
IR	infra-red
<i>J</i>	coupling constant
KR	kinetic resolution
LCMS	liquid chromatography-mass spectrometry

LDA	lithium diisopropylamine
M	molar
mg	milligrams
min	minute(s)
mL	millilitres
mmol	millimoles
mol	moles
Mp	melting point
MS	mass spectrometry
MW	molecular weight
MWCO	molecular weight cut-off
NHC	N-heterocyclic carbene
NMP	<i>N</i> -methylpyrrolidin-2-one
NMR	nuclear magnetic resonance
NOBIN	2-amino-2'-hydroxy-1,1'-binaphthyl
P	product
PEEK	polyether-ether-ketone
PEPPSI- <i>i</i> -Pr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PKR	parallel kinetic resolution
4-PPY	4-(pyrrolidino)pyridine
rt	room temperature
<i>sec</i> -	secondary
SM	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
<i>t</i> -AmOH	<i>tert</i> -amyl alcohol
TBAF	tetrabutylammonium fluoride
<i>t</i> -/ <i>tert</i> -	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMBE	<i>tert</i> -butyl methyl ether
Ts/tosyl	<i>para</i> -toluenesulfonyl
μL	microlitres
UV	ultra-violet

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1 Introduction

1.1 The Importance of Chiral Compounds, Alcohols and Amines

1.1.1 Importance of Chiral Compounds

The chirality of drugs is an increasingly important theme in chemistry, with enantiomers of the same drug often having markedly different effects, such as inactivity, toxicity or even the opposite effect on the body.^[1] Since the 1980s there has been a trend to characterize and test all chiral drugs in both their racemic and enantiopure form, and in 1992 over 25% of pharmaceuticals contained a chiral centre, while 50% of the new drugs approved by the FDA in 2011 were approved as single enantiomers.^[2]

The research presented in this thesis is concerned with the synthesis of enantiopure amines and alcohols, and examples of chiral drugs bearing these functional groups or their derivatives are shown below (Figure 1).

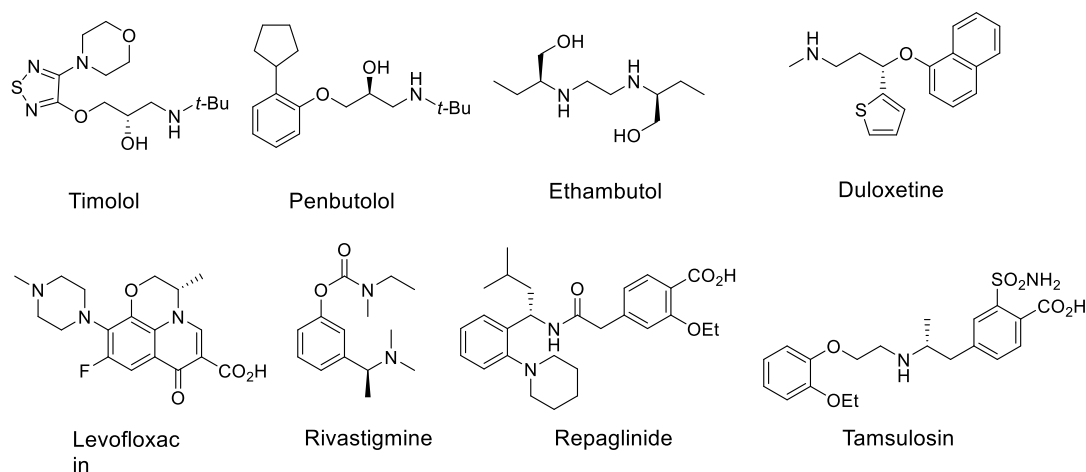


Figure 1. Examples of single enantiomer drugs containing chiral amine or alcohol derivatives.^[1,3]

Timolol is used to treat high blood pressure and to prevent heart attacks, penbutolol is beta blocker also for treating high blood pressure, ethambutol is used to treat tuberculosis, while duloxetine is an anti-depressant. Of the amines, levofloxacin is an antibiotic, rivastigmine is prescribed for Alzheimer's treatment, repaglinide is used to treat Type II diabetes, and tamsulosin was developed to ease the symptoms of benign prostatic hyperplasia.

Many other chiral drugs exist containing alcohols and amines which are marketed in their racemic form, even though occasionally only one enantiomer is responsible for the activity or the other enantiomer is responsible for the side effects.^[1] While this makes production of the drug cheaper, it is administered with an effective 50% impurity, wasting much material and also causing potentially unnecessary side effects.

Since the FDA introduced the requirement in 1992 that all racemic drugs are to be tested in both their racemic and enantiomerically pure forms, much effort has gone into the development of robust, efficient methods for the synthesis of enantiopure compounds.

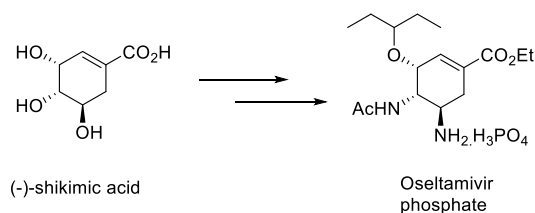
1.1.2 Methods for Preparation of Chiral Amines and Alcohols

There are many different ways in which to make chiral compounds, and these can be divided into three main methods: firstly, starting the synthesis using readily available enantiopure materials from the chiral pool.^[4] Secondly, asymmetric methods can be used to selectively produce enantioenriched materials from prochiral compounds. Thirdly, resolution can be used to separate a racemic mixture.

1.1.2.1 Chiral Pool

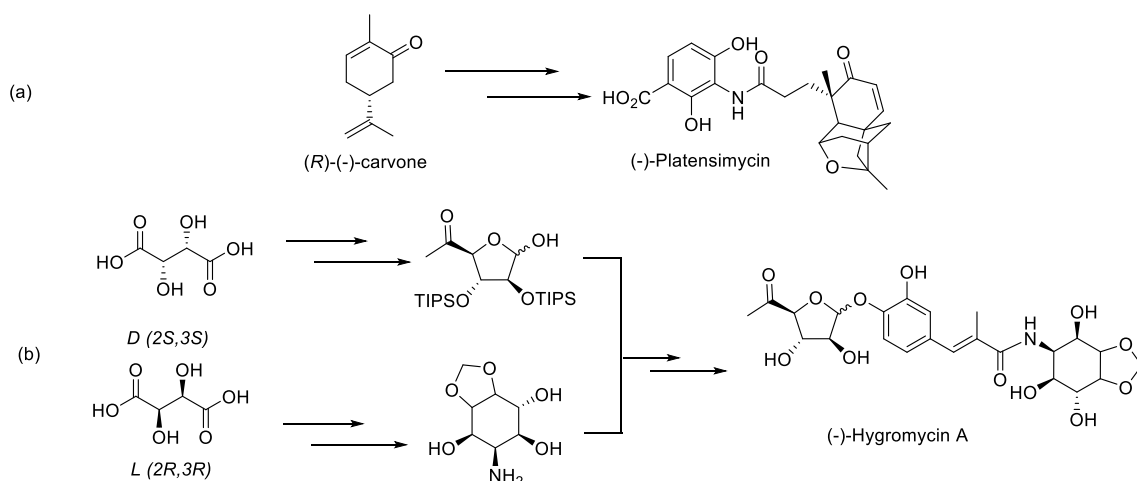
Preparing enantiopure materials from the chiral pool is perhaps the simplest of the methods outlined above. A large number of starting materials are readily available in enantiopure form from nature, most commonly amino acids or monosaccharides, and these can be functionalised in a variety of ways. This area has been reviewed by Casiraghi for the synthesis of carbohydrates and alkaloids^[5] and by Hanessian for the synthesis of natural products.^[6] The main drawback to this method is that only one enantiomer is usually available from nature, and if the other enantiomer is required for the synthesis then the route has to be changed.

One well known example of a chiral pool synthesis is that of the anti-influenza drug oseltamivir, marketed as Tamiflu. The commercial synthesis by Roche uses a molecule from the chiral pool, (-)-shikimic acid, which is isolated from the Chinese star anise (Scheme 1).^[7]



Scheme 1. Chiral pool starting material shikimic acid for the synthesis of anti-influenza drug Tamiflu.

While this is the start of the commercial synthesis, due to the limited availability of shikimic acid, efforts have been made to develop other routes starting from achiral materials.^[8–11] Other examples of chiral pool syntheses include Nicolaou's synthesis of the antibacterial Platensimycin, starting from (*R*)-(-)-carvone which can be isolated from spearmint (Scheme 2, a),^[12] and Yan's formal synthesis of (-)-Hygromycin A from tartaric acid (Scheme 2, b).^[13]



Scheme 2. (a) Synthesis of (-)-Platensimycin from (R)-(-)-carvone^[12] (b) Synthesis of (-)-Hygromycin A from tartaric acid.^[13]

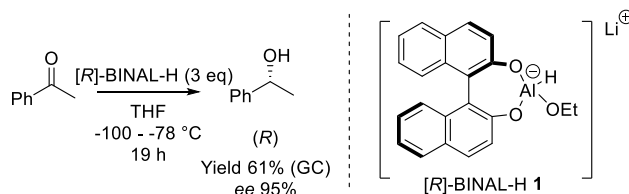
Yan's synthesis interestingly uses both enantiomers of tartaric acid to access the two halves of Hygromycin A.

1.1.2.2 Asymmetric Synthesis

Asymmetric synthesis is a more versatile method for making enantioenriched compounds, and much research has been undertaken in this area. The following briefly gives examples of how chiral alcohols and amines can be produced in this fashion. The most common method used for both functional groups is reduction of a prochiral ketone, imine, oxime or hydrazone.

1.1.2.2.1 Asymmetric Reduction of Ketones

Work on the asymmetric reduction of ketones to give chiral alcohols originated with the modification of metal hydride reducing agents such as LiAlH_4 with alkaloids, sugars or amino alcohols, to produce stoichiometric chiral reducing agents. One successful example of this type of reducing agent was developed by Noyori *et al.* in 1984.^[14] They formed an aluminium complex with 1,1'-binaphthol and a simple alcohol, such as ethanol, coordinated to the aluminium (BINAL-H **1**), ensuring that only one hydride remained on the aluminium which could then add to ketones in an enantioselective manner (Scheme 3).^[14]

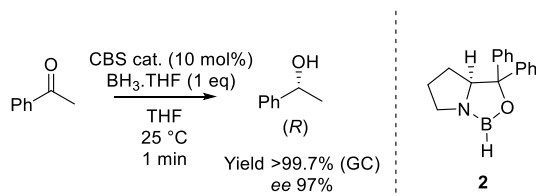


Scheme 3. Noyori's reduction of acetophenone with [R]-BINAL-H **1**.^[14]

The desired alcohol was formed in 61% yield by GC analysis and 95% ee, and this method was extended to the successful reduction of many different alcohols.^[15] Borohydrides have also been modified with chiral

ligands, with reviews by Daverio and Zanda^[16] and Cho^[17] covering many examples of chiral alumino- and borohydrides.

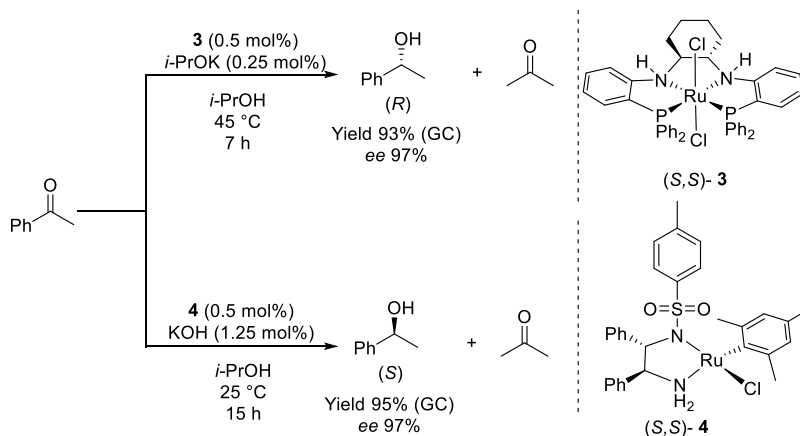
However, these modifications provide stoichiometric reducing agents; catalytic reduction methods are potentially more efficient. The most well-known of the chiral catalytic reducing agents is the Corey-Bakshi-Shibata (CBS) catalyst **2**, formed from (*S*)-diphenylprolinol and $\text{BH}_3 \cdot \text{THF}$ (Scheme 4).^[18]



Scheme 4. Corey's reduction of acetophenone with CBS catalyst **2**.^[18]

In combination with 1 equivalent of $\text{BH}_3 \cdot \text{THF}$, **2** can selectively reduce ketones in 1 minute under optimal conditions.^[18] Varying the group on boron in the catalyst can increase the selectivity in some cases, and the Me-CBS catalyst is most commonly used.

Metal species can also selectively reduce ketones to alcohols *via* either transfer hydrogenation or hydrogenation. In transfer hydrogenation, a sacrificial alcohol or formic acid can be used as the hydrogen source, and a large number of transition metal catalysts have been shown to be effective for this type of transformation.^[19,20] Ruthenium is particularly effective, and two examples developed by Noyori are shown below (Scheme 5).^[21,22]

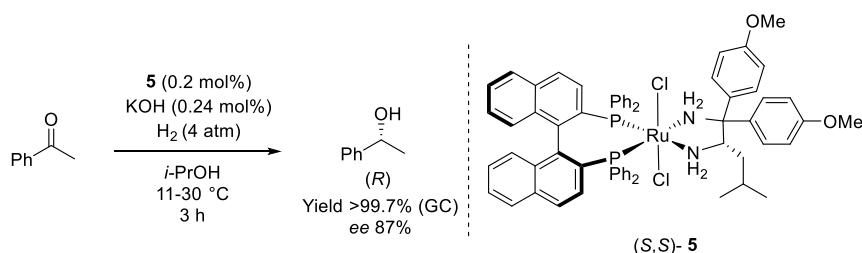


Scheme 5. Noyori's reduction of acetophenone with catalysts (*S,S*)-**3**^[22] and (*S,S*)-**4**.^[21]

The main challenge with these types of reactions in *isopropanol* is suppression of the reverse reaction; achieving high conversions is difficult, particularly for substrates that are relatively easy to oxidise. Since in a racemic mixture of an alcohol the enantiomers may be oxidised at different rates, Noyori has also shown that a derivative of **4** can be used for the kinetic resolution of 1-phenylethanol.^[23] Catalyst **4** can also be used

with formic acid as the hydrogen donor, and in these cases the reverse reaction does not occur, thus providing a useful alternative method for substrates with low oxidation potentials.^[23]

More recently, focus has shifted to the development of hydrogenation catalysts, which use molecular hydrogen as the hydrogen source. The advantages are clear, in that there is high atom economy and no by-products are produced. A recent review by Kitamura summarizes the developments in this field,^[24] including research towards the use of cheap base-metal catalysts instead of traditional transition metals such as Ru, Rh, Ir and Pd. A representative example of a hydrogenation catalyst **5**, again developed by Noyori, is shown below, which utilises diphosphine/diamine ligands, a combination also used by many others in catalyst development (Scheme 6).^[25]

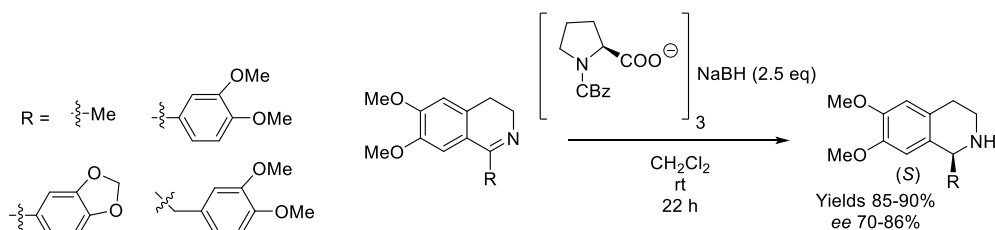


Scheme 6. Noyori's hydrogenation of acetophenone with (S,S)-**5**.^[25]

1.1.2.2.2 Asymmetric Reduction of Imines

The asymmetric reduction of imines and related functional groups with single enantiomer reducing reagents or catalysts to give chiral amines is underdeveloped compared to the analogous aforementioned reactions with ketones. This is because of two main reasons: firstly, imines can exist as mixtures of two geometrical isomers, and therefore addition to the different isomers results in enantiomeric products, and secondly, imines are more basic than ketones and consequently the nitrogen tends to coordinate to Lewis acidic electrophiles or catalysts, thus making it difficult to achieve catalyst turnover. Nevertheless, many different methods for the enantioselective reduction of imines have been developed.

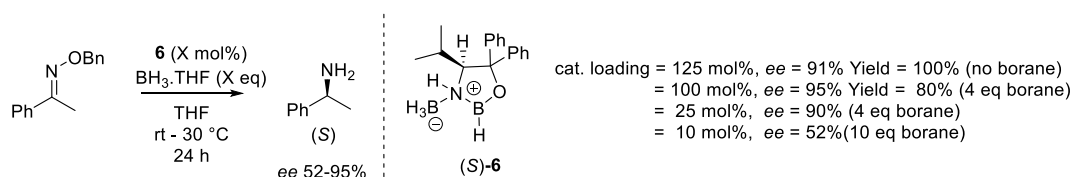
Iwakuma *et al.* developed a successful procedure for the reduction of cyclic imines (which can only exist as one geometrical isomer) with a chiral sodium borohydride reagent derived from *N*-Cbz-proline (Scheme 7).^[26]



Scheme 7. Iwakuma's reduction of cyclic imines with chiral triacyloxyborohydride.^[26]

Iwakuma screened a number of amino acid derivatives as the chiral reducing agent, and found that the *N*-Cbz-proline derived borohydride was the most efficient reagent, providing the reduced amines in good yields and *ee*.

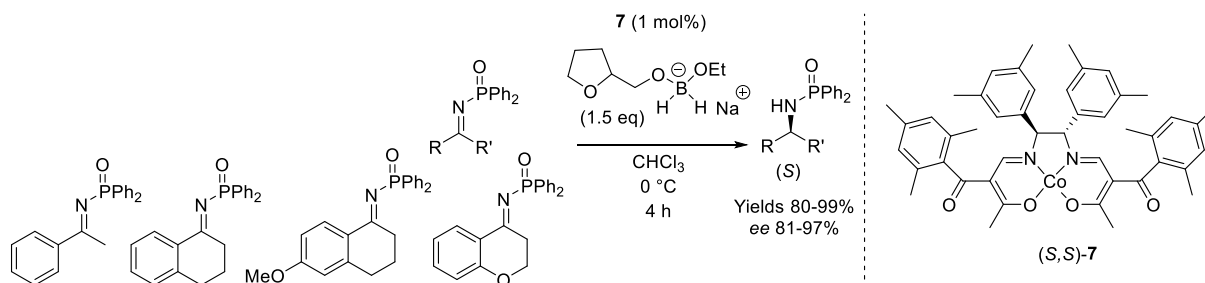
In 1987, Itsuno *et al.* developed a catalytic reduction of imines,^[27] albeit with high catalyst loadings, using an oxazaborolidine catalyst previously developed for stoichiometric reductions. Oximes, which have a higher barrier to *E/Z* isomerism than imines, were used as the substrates, therefore minimising the problems associated with geometrical isomer interconversion (Scheme 8).



Scheme 8. Itsuno's catalytic reduction of oximes with catalyst 6.^[27,28]

In the above prototypical example, although the *ee* decreased when lower catalyst loadings were used, a 25 mol% catalyst loading provided the desired amine in 90% *ee*.^[27]

A truly catalytic procedure using only 1 mol% catalyst has also been developed by Mukaiyama for the reduction of *N*-diphenylphosphinyl imines, using a cobalt-based chiral catalyst 7 (Scheme 9).^[29]

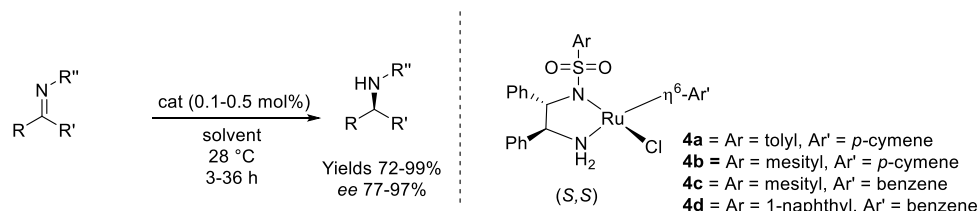


Scheme 9. Mukaiyama's reduction of *N*-diphenylphosphinyl imines with Co-based catalyst (*S,S*)-7.^[29]

Oxime methyl ethers did not react and *N*-tosyl imines had significant background reaction with the borane under the optimised conditions, so *N*-diphenylphosphinyl imines were therefore the optimal substrates, and a number of these substrates were successfully reduced in good yield and *ee*. The product amides could easily be deprotected to the primary amines upon stirring with HCl at ambient temperature, with no loss of enantioselectivity observed. A number of other chiral catalysts are available for the reduction of imines with a borane-based hydrogen source, with a review by Kobayashi detailing these and other protocols for catalytic enantioselective additions to imines.^[30]

Similarly to alcohols, metal-based catalysts can be used to reduce imines *via* either transfer hydrogenation or hydrogenation. The first example of a catalytic transfer hydrogenation was published by Noyori in 1996,

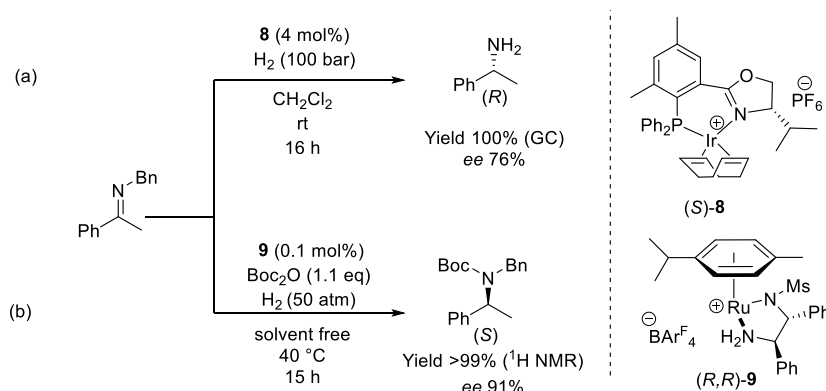
using derivatives of his Ru(II)-based catalyst (**4**) and a formic acid/trimethylamine mixture as the hydrogen source (Scheme 10).



Scheme 10. Noyori's catalytic transfer hydrogenation of imines with catalysts **4a-4d**.^[31]

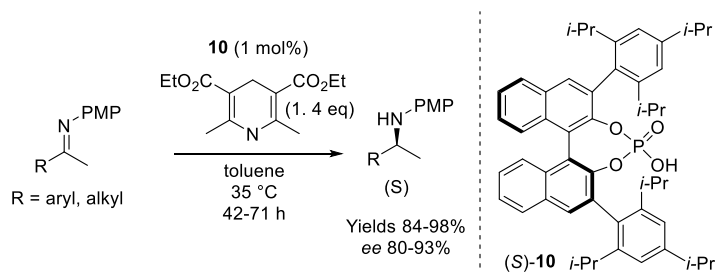
Interestingly, the optimal choice of catalyst was very substrate dependant, and the reaction time, solvent and catalyst loading needed to be varied depending on the substrate. In general, acyclic imines displayed lower selectivities than cyclic imines, presumably due to their unstable geometry.

Reduction of imines *via* hydrogenation is also a growing field, with many catalysts having been developed based on Ru, Rh and Ir.^[30] Two examples are shown below from the groups of Pfaltz^[32] (Scheme 11, a) and Fan (Scheme 11, b).^[33]



Scheme 11. (a) Pfaltz's reduction of imine with Ir catalyst **8**.^[32] (b) Fan's hydrogenation of imine with Ru catalyst **9**.^[33]

Efforts have also been made recently to develop organocatalysts for the reduction of ketones and imines; a metal free transfer hydrogenation of imines developed by List *et al.* is shown below (Scheme 12).^[34]



Scheme 12. List's organocatalytic transfer hydrogenation of imines catalysed by chiral phosphoric acid **10**.^[34]

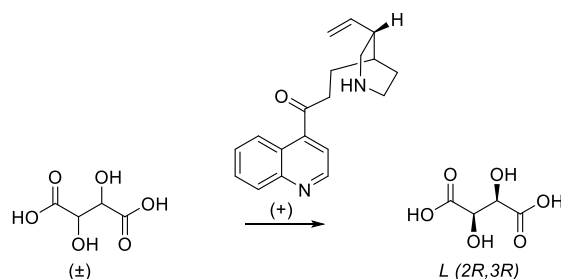
In this case, a Hantzsch ester^[35] is used as the hydrogen source.

In addition to asymmetric hydrogenations, other methods for forming enantioenriched alcohols and amines include asymmetric C-C bond formation from the ketone or imine, for example with stoichiometric chiral lithium reagents, or using chiral catalysts. This area has been reviewed by Kobayashi for the enantioselective addition to imines,^[30] and by Bailey *et al.* for the addition to ketones and aldehydes.^[36]

1.2 Resolution of Racemic Mixtures

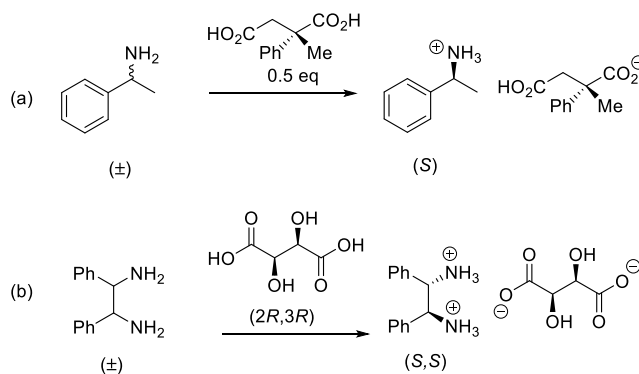
1.2.1 Classical Resolution

Classical resolution is the term given to formation of a diastereomeric mixture of salts from a racemic mixture by treatment with an enantiomerically enriched reagent, whereupon the mixture can then be separated by conventional physical separation. The first example of classical resolution was carried out by Louis Pasteur in 1853, who resolved racemic tartaric acid with (+)-cinchotoxine (Scheme 13).^[37]



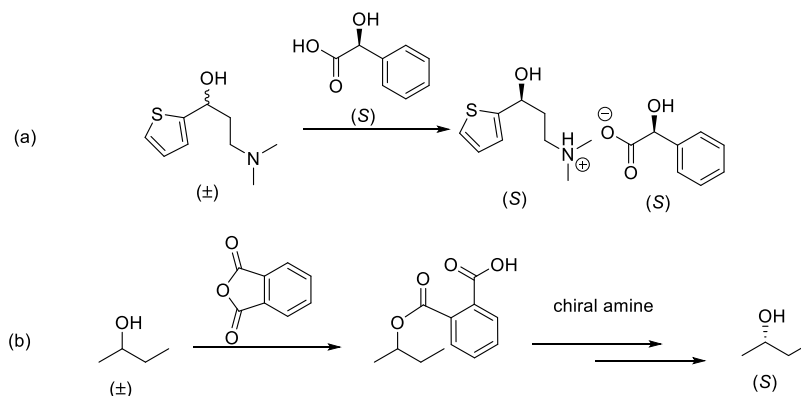
Scheme 13. Pasteur's resolution of tartaric acid with (+)-cinchotoxine.^[37]

In this example the enantiopure alkaloid base is used to resolve a racemic carboxylic acid, but the technique is equally suited to resolving racemic amines using enantiopure carboxylic acids. Many enantiopure carboxylic and sulfonic acids and *sec*- and *tert*-amine bases are readily available, and although screening is usually required to find a suitable reagent for achieving a good resolution, various screening methods have been developed to aid this process. Rao has resolved a number of chiral amines using (*S*)-(+)-2-methyl-2-phenylbutanedioic acid,^[38] while Corey *et al.* used (2*R*,3*R*)-(+)-tartaric acid to resolve 1,2-diphenyl-1,2-ethylenediamine, a commonly used backbone of chiral catalysts^[39] (Scheme 14).



Scheme 14. (a) Rao's resolution of α -methylbenzylamine,^[38] (b) Corey's resolution of 1,2-diphenyl-1,2-ethylenediamine.^[39]

Compounds containing other functional groups, such as alcohols, are much more difficult to resolve *via* classical resolution as they are not prone to salt formation. In general, this can only be achieved if these classes of compound also contain either basic or acidic groups, as in the example shown below of the resolution of an intermediate *en-route* to the drug duloxetine (Scheme 15, a).^[40]



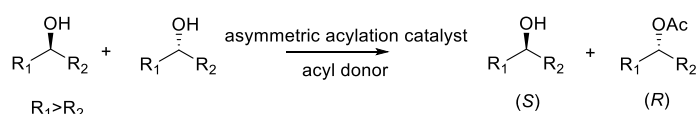
Scheme 15. (a) Classical resolution of racemic alcohol via amine salt formation^[40] (b) Classical resolution of alcohol via functionalisation with anhydride.^[41]

A relatively general method for the ‘temporary’ introduction of an acid function into an alcohol substrate is to react the alcohol with an anhydride such as phthalic anhydride. The resulting free acid can then be resolved using a chiral amine, and the alcohol recovered after hydrolysis (Scheme 15, b).^[41]

1.2.2 Kinetic Resolution

Kinetic resolution (KR) is the term given to the reaction of a racemic mixture, *i.e.* an alcohol or an amine, with an enantiomerically enriched reagent or catalyst in which the two enantiomers react at different rates. For alcohols and amines the reaction is typically either an esterification or an amide formation with a suitable acyl donor, although many other types of reaction are also suitable for KR such as hydrolyses, epoxidations and hydrogenations.^[42]

When two enantiomers in a racemic substrate react with an enantiomerically pure reagent or catalyst they should do so at different rates as the transition states will be diastereomeric; if the respective rates are sufficiently different then both the product and remaining starting material become significantly enantioenriched as the reaction progresses and KR will occur (provided the reaction is stopped before completion in the case of a catalysed reaction using an achiral reactant, as shown below for acylative alcohol KR catalysed by an enantiomerically enriched catalyst, Scheme 16). This can be represented by following the Gibbs free energy of each enantiomer as they react (Figure 2).^[4]



Scheme 16. Generalised acylative alcohol KR reaction.

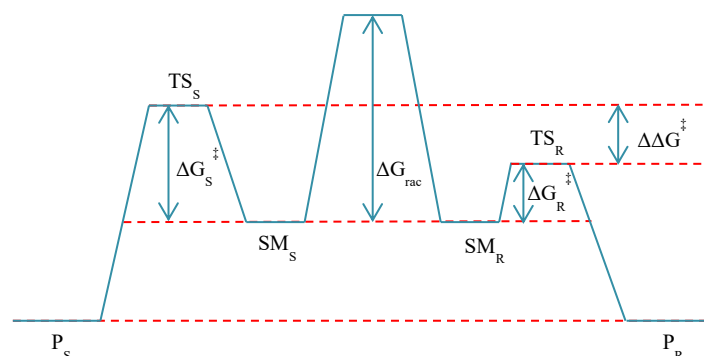


Figure 2. Gibbs free energies in a catalysed KR reaction employing an achiral acyl donor, where *R* is the fast reacting enantiomer.^[4]

While both the starting material and the product have the same Gibbs free energy, during the reaction both enantiomers go through diastereomeric transition states, and these transition states can have a different Gibbs free energy. In the case above, the *R* enantiomer has a lower energy transition state ($\Delta G_R^\ddagger$) and so reacts faster than the *S* enantiomer. The term $\Delta\Delta G^\ddagger$ is used to describe the difference in free energy between the two transition states, and this can be related to the ratio of the rates of reaction for each enantiomer (equation 1):^[4]

$$\frac{k_R}{k_S} = e^{\Delta\Delta G^\ddagger/RT} \quad (1)$$

The ratio of the reaction rates k_R and k_S (k_R/k_S) is also known as the selectivity factor, and is the value used to evaluate the success of a KR. The *ee* of the starting material and the product recovered after the reaction are highly dependent on the conversion (*C*), and KRs are usually stopped at ~50% conversion. In an ideal situation, where $k_R \gg k_S$, only one of the enantiomers will react, and at 50% conversion, the reaction will have 50% of the starting material at >99% *ee*, and 50% of the product at >99% *ee* (the maximum yield of each enantiomer). This situation however does not usually occur, and therefore the reaction can be stopped at different degrees of conversion in order to maximise either the yield or the purity of the recovered materials. For example, if the selectivity factor is $s = 7$, i.e. the reaction of the *R* enantiomer is 7× as fast as the *S* enantiomer, the *ee* of both the starting material (SM) and the product (P) will change as shown over the course of the reaction (Figure 3).

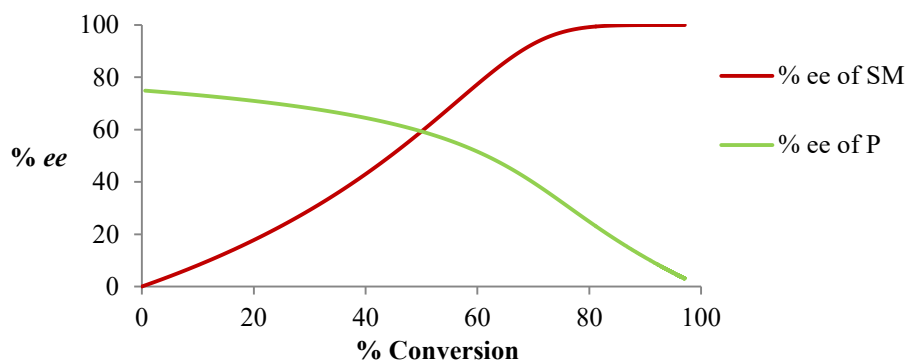


Figure 3. Change in *ee* of starting material and product in a KR as reaction progresses, when $s = 7$.^[42,43]

As can be seen from the graph, the *ee* of the product starts at a maximum of 74% and then decreases, while the *ee* of the starting material increases throughout the reaction. Nevertheless, to recover the starting material in >99% *ee*, in the case above the reaction has to run to 80% conversion and only 20% of the starting material is recovered. It is therefore the starting material and not the product that is usually recovered in greater yield and *ee*, unless the selectivity is very high (>50, see below). A selectivity factor of $s = 7$ was proposed by Kagan as the minimum requirement for a useful KR.^[42] If the selectivity is higher, the starting material can be recovered in greater yield with high *ee*, and the product can also be recovered in high *ee* (Figure 4).

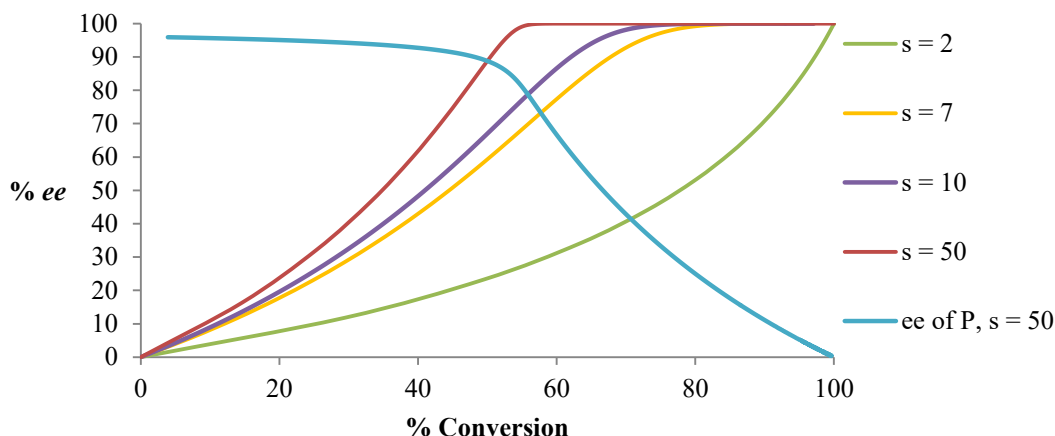


Figure 4. Change in *ee* of starting material and product ($s = 50$) in a KR as reaction progresses, when $s = 2-50$.^[42,43]

When the selectivity is $s = 50$, both the product and the starting material can be recovered at 89% *ee* at 50% conversion. With a selectivity of $s = 500$, the product and the starting material can be recovered at 98% *ee* at 50% conversion. The difference in *ee* of recovered material at a certain % conversion becomes smaller and smaller with higher selectivity. If the selectivity is known for a reaction, the ideal conversion can be calculated where maximum recovery and *ee* are achieved. To calculate the selectivity for a given reaction, a set of equations derived by Kagan are used:^[42]

$$s = \frac{[\ln(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} \quad (2)$$

$$s = \frac{[\ln(1-C)(1+ee')]}{\ln[(1-C)(1-ee')]} \quad (3)$$

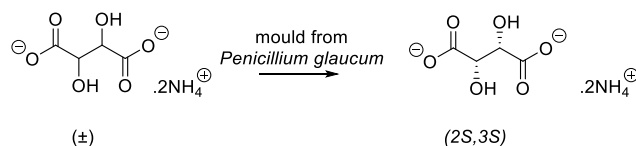
Where C = conversion, '*ee*' is the *ee* of the recovered starting material (equation 2), and '*ee*' is the *ee* of the product (equation 3). It is also possible to determine the conversion (C) from the two *ee* values, and the conversion derived in this way is usually used to calculate the selectivity (equation 4):

$$C = \frac{ee}{ee+ee'} \quad (4)$$

In this way, once the *ee* of the product and the starting material are known, the selectivity can be calculated. These equations however can only be applied when the reaction has pseudo-first-order kinetics, and for second order reactions a different set of equations are used.^[42]

1.2.3 Enzymatic KR of Amines and Alcohols

The first example of a KR was carried out by Louis Pasteur in 1858,^[44,45] who found that upon fermenting a mixture of (2*S*,3*S*)- and (2*R*,3*R*)-tartaric acid with yeast, only the unnatural (2*S*,3*S*)-(-)-tartaric acid was recovered at the end of the process (Scheme 17).

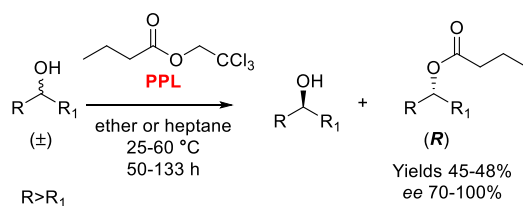


Scheme 17. Pasteur's formation of enantioenriched (2*S*,3*S*)-(-)-tartaric acid via KR.^[44,45]

Pasteur described this method as the most efficient way of making enantiopure (2*S*,3*S*)-(-)-tartaric acid at the time, and since the realisation in the late 1970s of the potential that enzymes have in the transformation of non-natural organic compounds,^[46] their use in the KR of both amines and alcohols has become more popular. Indeed, BASF use immobilised enzymes to produce thousands of tonnes of chiral amines and alcohols every year.^[47] There are many reviews detailing the use of enzymes as biocatalysts, including specifically for the KR of amines and alcohols, with notable examples by Reetz,^[48,49] Gotor,^[50] Ghanem,^[51–54] Rantwijk^[55] and Faber.^[46] The following is a brief overview of some selected examples of the enzymes available and processes published for the acylative KR of alcohols and amines. It should be noted that the selectivity factors for biocatalytic and enzyme-mediated transformations are often denoted with *E* instead of *s*.

1.2.3.1 Alcohols

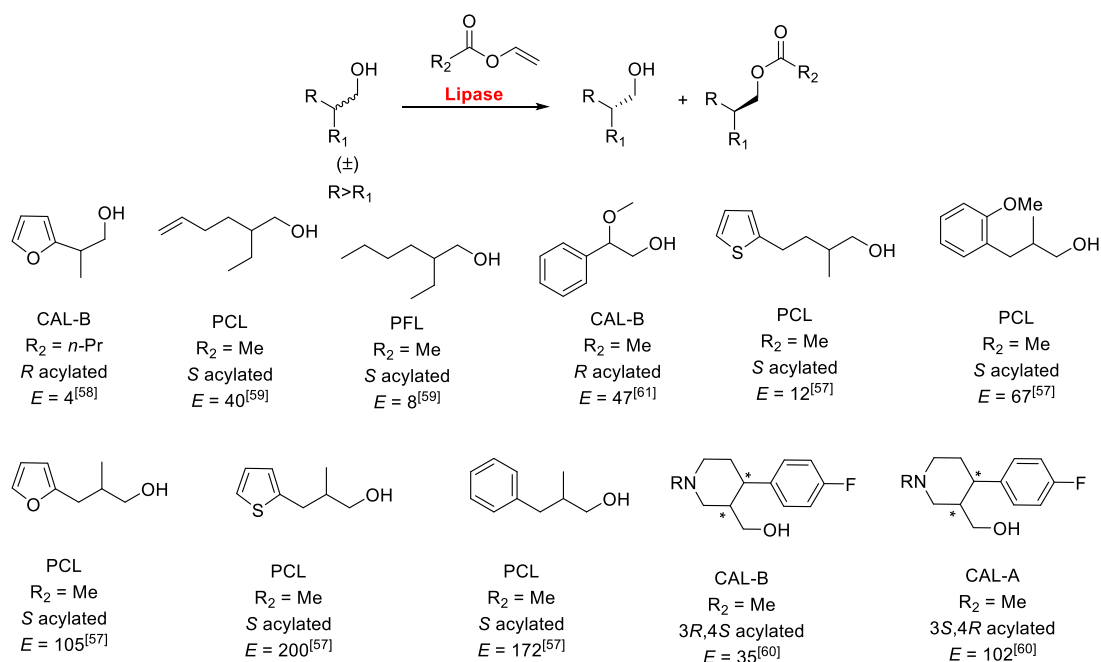
The seminal work published by Klibanov *et al.* on the activity of lipases in organic solvents in 1985 paved the way for the development of acylative alcohol KR.^[56] Previously, alcohols had been resolved by hydrolysis of the corresponding esters in aqueous solvent and the backwards reaction had not been possible due to competing hydrolysis in water. By moving to anhydrous solvents, both esterification with yeast and transesterification with porcine pancreatic lipase (PPL) became possible, using an activated ester for the transesterification (Scheme 18).



Scheme 18. Klivanov's acylative enzymatic KR with PPL.^[56]

Both aliphatic and aromatic substrates were successful in this procedure, including the KR of 1-phenylethanol in 45% yield and 95% *ee*.^[56] Since this work was disclosed a large number of reports have been published on the enzymatic KR of alcohols, using various enzymes including *Pseudomonas cepacia* lipase (PCL), *Pseudomonas fluorescens* lipase (PFL), *Pseudomonas stutzeri* lipase (PSL), *Candida Rugosa* lipase (CRL) and *Candida Antarctica* lipase-B (CAL-B).^[51-53] Vinyl and isopropenyl esters have become the acyl donors of choice, as they are activated relative to ethyl acetate and because the 'alcohol' by-products from the reactions spontaneously tautomerise to acetaldehyde and acetone respectively, thus preventing any backwards reaction. A small number of examples are given below, starting with primary alcohols.

Primary alcohols in general display lower selectivities than *sec*-alcohols in enzymatic KRs; nevertheless there are many reports of primary alcohol KR, of both aromatic and aliphatic substrates, including work by Hogberg,^[57] Metz,^[58] Larpent^[59] and Gotor^[60,61] (Scheme 19).

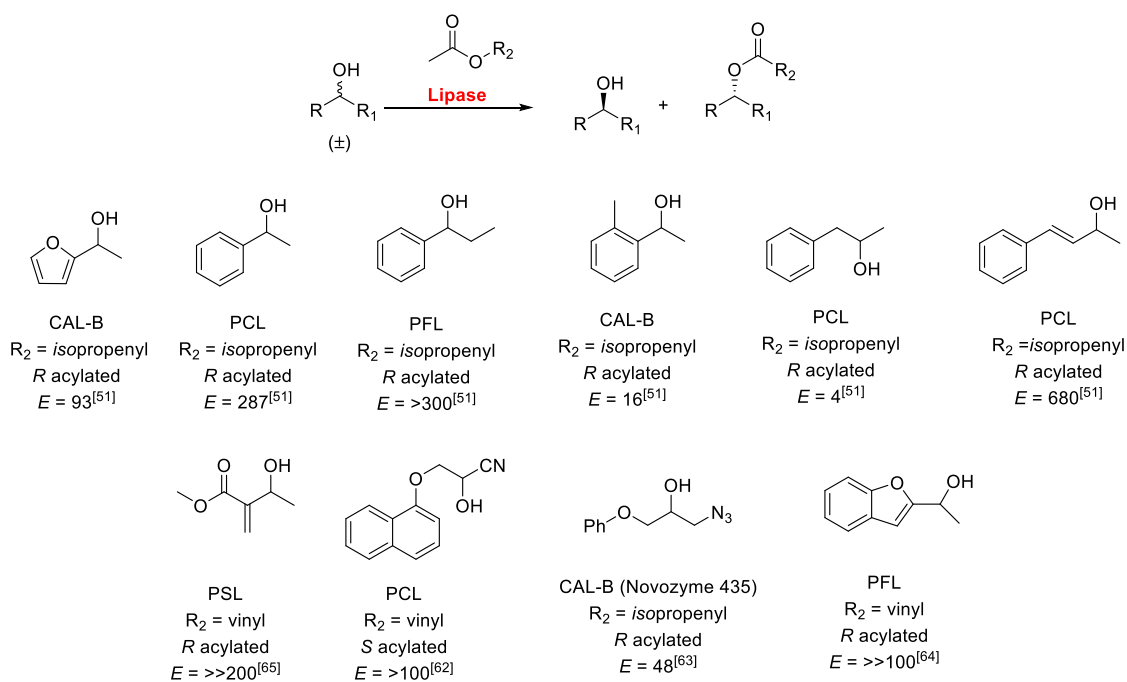


Scheme 19. Enzymatic acylative KR of primary alcohols.^[51,57-61]

Hogberg's group found that the best substrates seemed to be 3-aryl-2-methylpropan-1-ols, generally displaying selectivities *E* > 100, while moving the aryl group closer or further away reduced the selectivity.^[57] Gotor *et al.* successfully developed the KR of an intermediate *trans*-alcohol *en-route* to the anti-depressant

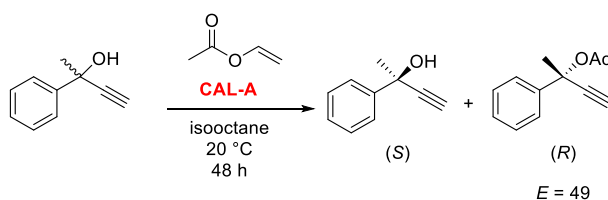
Paroxetine.^[60] Interestingly, CAL-A and CAL-B gave opposing senses of selectivity, with CAL-A providing the desired recovered alcohol in high *ee*.

sec-Alcohols are generally more selective substrates and a large number of procedures are available for these types of transformations. Ghanem and Schurig published a number of papers on the KR of *sec*-alcohols,^[51–53] while Bevinakatti,^[62] Blanco,^[63] Poppe^[64] and Sa^[65] have also contributed to this field among others. A small number of selected example substrates are shown below (Scheme 20).



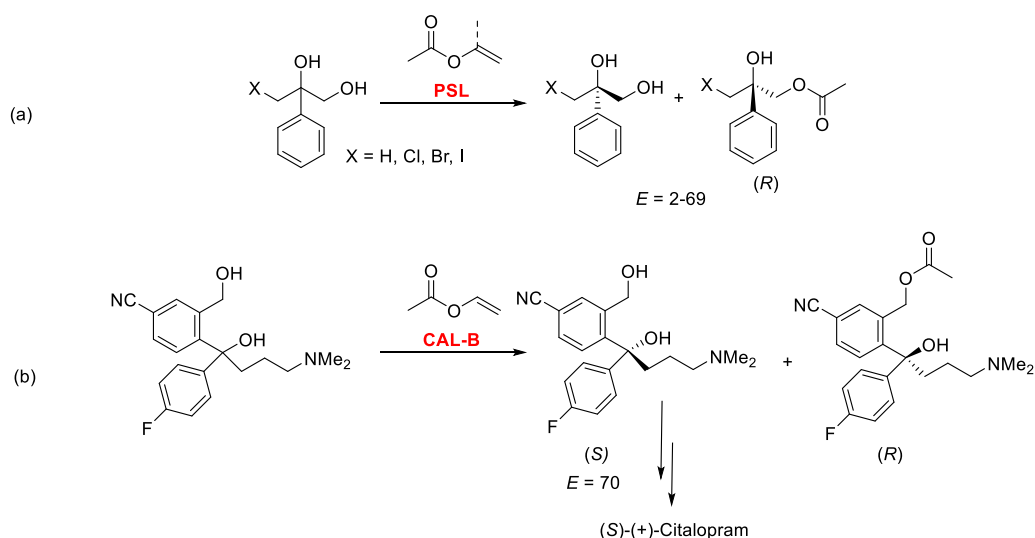
Scheme 20. Enzymatic KR of *sec*-alcohols.^[51,62–65]

tert-Alcohols are not easily resolved by enzymes, with most methods involving enzymatic hydrolysis of the ester instead of direct acylation of the alcohol, although there is one report by Bornscheuer on the direct acylative KR of a *tert*-alcohol (Scheme 21).^[66]



Scheme 21. Bornscheuer's KR of 2-phenylbut-3-yn-2-ol with CAL-A.^[66]

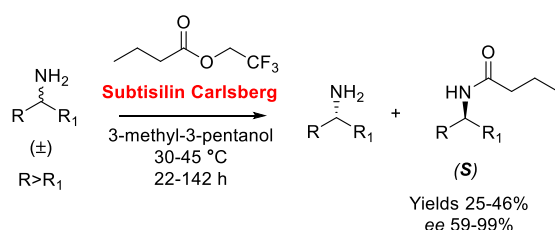
An alternative strategy for the resolution of *tert*-alcohols is possible if a primary alcohol can be installed proximal to the *tert*-alcohol centre and this additional alcohol selectively acylated to achieve the desired KR. This method was initially demonstrated by Fang in 1997^[67] and then used by Gotor in 2004 for the KR of an alcohol *en-route* to anti-depressant Citalopram (Scheme 22).



Scheme 22. Fang's (a) and Gotor's (b) enzymatic KR of *tert*-alcohols via acylation of proximal primary alcohol.^[67,68]

1.2.3.2 Amines

The first example of an enzymatic amine KR was published by Klibanov in 1989.^[69] Initial studies looked at selectivity of six different enzymes in octane, including *Candida Antarctica* lipase, *Pseudomonas cepacia* lipase, porcine pancreatic lipase and Subtilisin Carlsberg lipase, and all were found to give only low levels of selectivity ($E = 1-1.5$). Klibanov however realised that changing the solvent could increase the selectivity, and indeed changing from octane to *tert*-amyl alcohol increased the selectivity from 1.4 to 4.1 with Subtilisin Carlsberg lipase, with a further increase to 7.7 when using 3-methyl-3-pentanol as the solvent. A number of aromatic and aliphatic amines could thus be resolved in this way (Scheme 23).

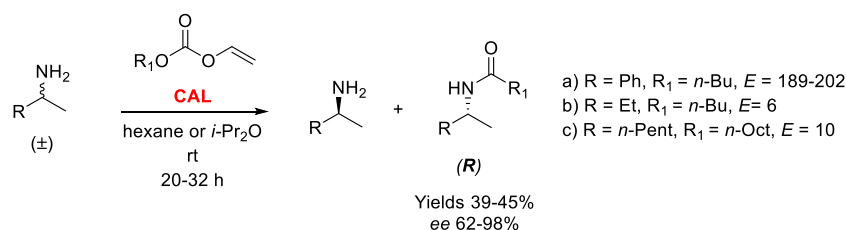


Scheme 23. Klibanov's acylative enzymatic KR of amines with Subtilisin Carlsberg protease.^[69]

Where the data is given, these *ee* values can be calculated to give selectivities of up to $E = 35$.^[42] Interestingly, this is also the first report in which *tert*-amyl alcohol is used as a selectivity-enhancing solvent, a property of this particular solvent which has subsequently been much-exploited in the field of non-enzymatic alcohol KR. Later work however has revealed that the uncatalysed background reaction of amines with many acyl donors is lower in *tert*-alcohols than in other solvents (e.g. octane), which could go some way towards explaining the increases in selectivity when using *tert*-alcohol solvents.^[70]

While providing good selectivities, the products in the above reactions are amides, which can be difficult to deprotect as they require harsh conditions to recover the starting amine. In 1993, Gotor *et al.* published the

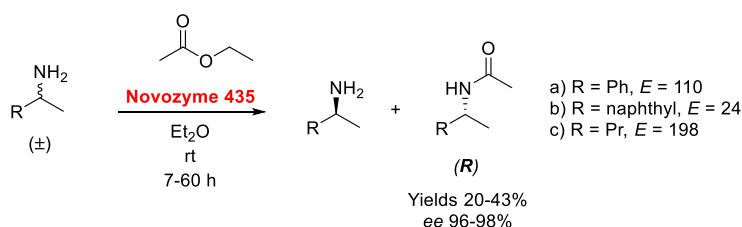
first example of acylative enzymatic KR of amines to form carbamates, which are easily removable protecting groups. The enzyme used was an immobilised form of *Candida Antarctica* lipase (SP 435 A) (Scheme 24).^[71]



Scheme 24. Gotor's enzymatic KR of amines to form carbamates with CAL.^[71]

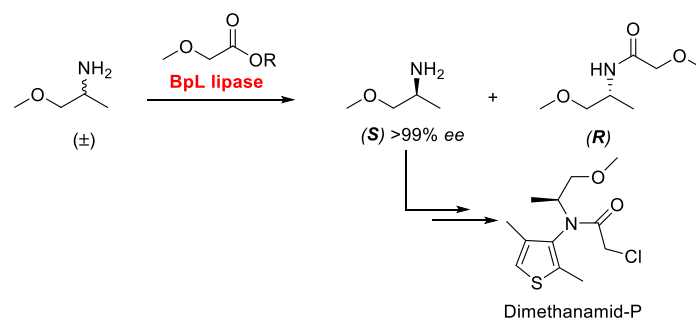
The nature of the amine influenced which acyl donor was most effective for the KR, with *n*-octyl vinyl carbonate proving most effective for 2-butylamine and 1-phenylethylamine, while the shorter chain *n*-butyl vinyl carbamate gave better results with 2-heptylamine. Gotor also found that the solvent had an effect on the selectivity, with both hexane and diisopropylether providing superior levels of selectivity to 1,4-dioxane. While not reported in the paper, calculating the selectivity from the published *ees* and conversions gives low selectivities for the aliphatic amines, and very good selectivities^[42] (*E* = 189-202) for 1-phenylethylamine.^[71]

Reetz *et al.* published the first use of immobilised CAL-B (Novozyme 435) for the acylation of amines to amides, using unactivated ethyl acetate as the acylating agent, achieving good *ees* and selectivities (calculated from data in publication)^[42] (Scheme 25).^[72]



Scheme 25. Reetz's KR of amines using Novozyme 435 and ethyl acetate.^[72]

Subsequently, a large number of procedures have been published for the enzymatic KR of amines, with BASF producing many different enantiopure amines *via* this type of process, including substituted phenylethylamines, bicyclic amines, aliphatic amines, aryl alkyl amines and some *sec*-amines.^[47,73] For example, over 2500 tonnes of (*S*)-(1-methoxy)-2-propylamine, an intermediate in the synthesis of the corn herbicide dimethanamid-P, are produced per year by KR using an immobilised *Burkholderia plantarii* lipase (BpL) (Scheme 26).^[47]



Scheme 26. BASF's procedure for the KR of (1-methoxy)-2-propylamine with methoxyacetic acid ester and BpL.^[47]

Rantwijk and Sheldon have written an extensive review on enzymatic amine KR,^[55] with many further examples of amines classes that can be resolved. Overall, CAL-B has become the enzyme of choice for most amine KRs, with unactivated acyl donors such as ethyl acetate or the faster methoxyacetic acid esters commonly used; activated acyl donors commonly used for alcohol KR often undergo significant uncatalysed background reactions with amines.

1.2.4 Comparative Properties of Enzymatic and Non-enzymatic KR

While enzymes usually display very high levels of selectivity, there are a number of disadvantages as well as advantages of using biocatalysts as compared to non-enzymatic catalysts. A comparison is presented below.

Table 1. Comparative advantages and disadvantages of enzymatic and non-enzymatic KR

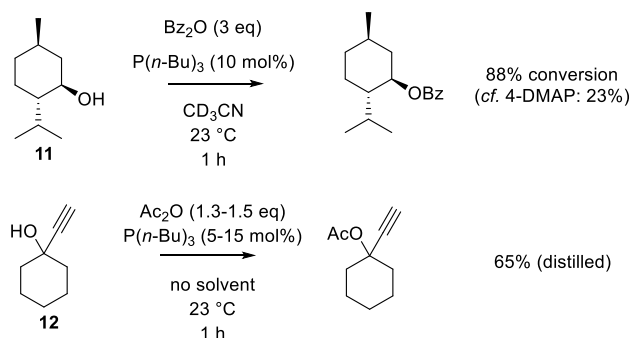
Property	Enzymatic KR	Non-enzymatic KR
Selectivity for Substrate	• Large rate acceleration compared to uncatalysed process • Only small amounts of enzyme usually required	• Rate acceleration smaller, more activated acyl donors usually required • Organocatalysts usually require higher loadings
Availability of Enantiomers	• Each enzyme can only form one enantiomer of product. Different enzymes need to be screened for opposite selectivity	• Can easily change between enantiomers of catalyst to get opposite enantiomer of product
Availability of Catalyst	• Available from nature	• Often require multiple step asymmetric syntheses
Reproducibility	• Often display batch-to-batch irreproducibility	• Usually display reliable, reproducible results
Sensitivity	• Enzymes operate over narrow range of conditions, <i>i.e.</i> temperature and pH tolerance is low	• Reaction conditions can be changed more readily to optimise results, <i>e.g.</i> lowering the temperatures
Reaction Conditions	• Mild reaction conditions mean side and background reactions are minimised	• Relatively low rate acceleration means relatively harsh conditions may be required
Environmental Impact	• Enzymes are degraded in the environment	• Organocatalyst has to be disposed of and synthesis can potentially require use of metals, solvents and other harmful chemicals

1.2.5 Non-enzymatic KR of Amines and Alcohols

While enzymatic KR is a widely used process in the industrial production of enantiopure amines and alcohols, the development of non-enzymatic catalysts for the same processes has been relatively recent, starting in the mid-1990s with work from Vedejs and Fu. Since this pioneering work, many others have taken on the challenge of designing chiral catalysts for the KR of various amines and alcohols, and the following chapter contains a brief review of selected contributions to this field. Other more comprehensive reviews include those by Spivey,^[74–76] Dalko,^[77,78] Miller and Lekta,^[79] Bull,^[80] List,^[81] Pellissier^[82] and Schreiner.^[83]

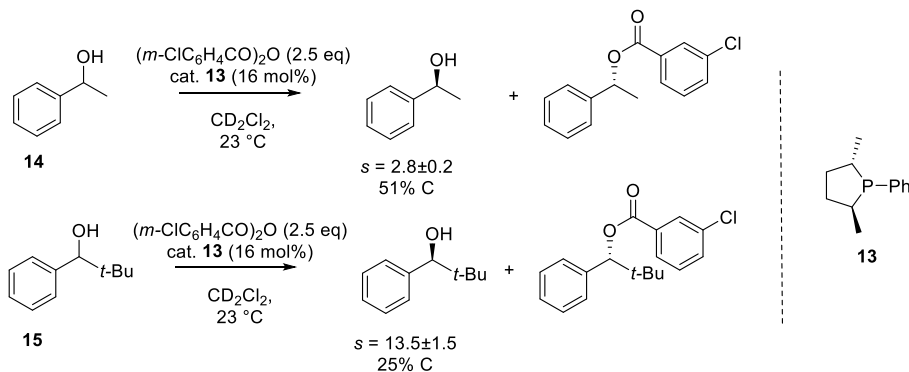
1.2.5.1 Alcohols

Using the knowledge that both bases and nucleophiles catalyse the acylation of alcohols using anhydrides and that alkyl phosphines in particular display weak basicity and strong nucleophilicity, Vedejs published a study of the utility of phosphines as acyl transfer catalysts in 1993.^[84] In fact, tri-*n*-butylphosphine was found to be more reactive than 4-DMAP as a catalyst for the esterification of menthol (**11**) with benzoic anhydride and efficient also for the challenging acetylation of 1-ethynylcyclohexanol (**12**) on a gram scale. Although no definitive evidence was found for the existence of the acyl-phosphonium salt in this study, the available data suggested a Lewis base catalysed mechanism (Scheme 27).^[85,86]



Scheme 27. Vedejs's benzoylation of menthol and acetylation of 1-ethynylcyclohexanol catalysed by $P(n\text{-Bu})_3$.^[84]

The sigma-donor ability of the phosphorus lone pair was suggested to be crucial for activity, with trialkylphosphines being significantly more reactive than diarylalkylphosphines. In order to develop an enantioselective acylation catalyst, aryldialkylphosphines were chosen by Vedejs to form the core catalyst structure. Burke's phosphine **13**, which was originally developed as a ligand for rhodium catalysed enantioselective hydrogenation,^[87] was found to give good reactivity and reasonable selectivity for the KR of certain *sec*-benzylic alcohols by *m*-chlorobenzoic anhydride. For example, whilst 1-phenylethanol (**14**) led to a selectivity of $s = 2.8 \pm 0.2$, 1-phenyl-2-*tert*-butylethanol (**15**) led to a selectivity of $s = 13.5 \pm 1.5$ (Scheme 28).^[88]



Scheme 28. KR of *sec*-benzylic alcohols **14** and **15** by *m*-chlorobenzoic anhydride catalysed by phosphine **13**.^[88]

To further improve reactivity and selectivity, various modifications to the catalyst structure were made.^[89] It was found that replacing the 5-membered ring in phosphine **13** with a 6-membered ring reduced the activity of the catalyst (compound **16**, Figure 5), implicating the 5-membered ring as being important.

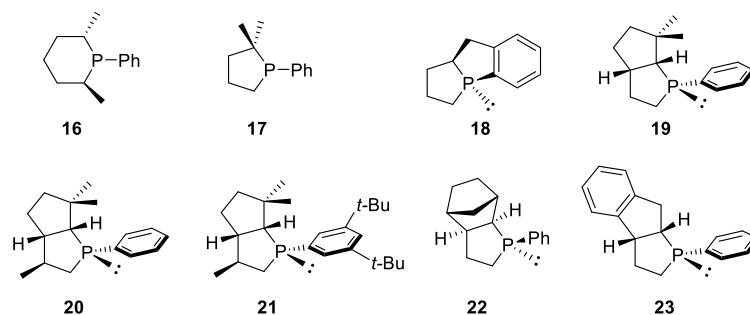


Figure 5. Various chiral phosphine catalysts developed by Vedejs.^[89]

An analogue of phosphine **13** was also synthesized wherein the phenyl ring was constrained to be perpendicular to the 5-membered ring (phosphine **17**, Figure 5). However, while the reactivity of this congener was not diminished, the reaction was essentially unselective. This result prompted synthesis of catalyst **18**, wherein the phenyl ring was constrained to be in the plane of the *P*-heterocycle; this catalyst also imparted no selectivity. This finding inspired the group to develop catalyst **19**, in which the C–P–C–C(Ar) dihedral angle was in the range 10–30°, with the phenyl ring inclined towards the bridgehead hydrogens and away from the ring methylene group (Figure 6).

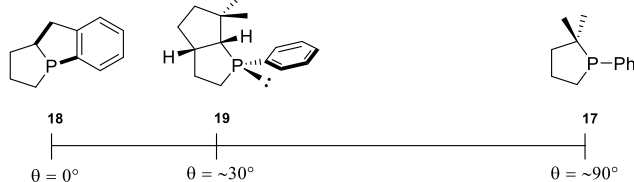


Figure 6. Comparison of the C–P–C–C(Ar) dihedral angle (θ) between the planes defined by the *P*-heterocycle and phenyl ring in Vedejs's phosphine catalysts **17**, **18** and **19**.^[89]

Molecular modeling studies identified structure **19** as having the required dihedral angle and this catalyst was found to provide a selectivity factor $s = 14$ in the KR of 1-phenyl-2-*tert*-butylethanol as depicted in Scheme 28, and displayed a 300-fold rate enhancement relative to phosphine **13**. This bicyclic scaffold also provided a useful platform for tuning the constraints upon the aforementioned C–P–C–C(Ar) dihedral angle. A family of catalysts was developed based upon the phosphabicyclo[3.3.0]octane (PBO) structure (*e.g.* PBOs **20–23**, Figure 5). Modelling studies to find the low energy conformers for catalysts **22** and **23** revealed that for PBO **22**, the lowest energy conformer has $\theta = -40^\circ$, while for PBO **23**, the lowest energy conformer has $\theta = -9^\circ$.^[90] These values are consistent with experimental findings and the design hypothesis in-so-far as catalyst **22** displays higher reactivity than catalyst **23**. Computational studies also showed that tight ion pair interactions exist in the transition state, supported by the fact that the reaction rate is fastest in low polarity solvents.^[91]

Due to limitations imposed by the synthetic route to catalyst **19**,^[92] new catalysts **20** and **21** were synthesized that both displayed improved selectivity at room temperature. Upon performing the acylation at $-40\text{ }^{\circ}\text{C}$, only a 10-fold decrease in rate was observed and selectivity was greatly increased, providing selectivity values in the range $s = 31 - 369$ for the KR of a series of *sec*-benzylic alcohols by *isobutyric* anhydride under optimal conditions ($<-20\text{ }^{\circ}\text{C}$)(Table 2).

Table 2. KR of *sec*-benzylic alcohols by PBO catalyst **21**.^[92]

Entry	Ar	R	Cat./mol%	T (°C)	s
1	Ph	Me	4	rt	22
2	Ph	Me	2.5	-20	42
3	Ph	<i>i</i> -Pr	2.8	-40	100
4	1-Naphthyl	Me	3.9	-40	99
5	Mesityl	Me	12.1	-40	369 ^a

^a All reactions run using catalyst with $ee = 97\%$, except entry 5 which used catalyst with $ee > 99.9\%$.

Mechanistic studies indicated that the strong dependence of selectivity as a function of temperature was due to the significant role of the activation energy in the $\Delta\Delta G^{\ddagger}$ of the transition states.^[88] The relatively high reactivity of the bicyclic system was proposed to reflect the fact that the ground state geometry of this ring system is similar to that of the transition state for the acyl transfer process. In addition to *sec*-benzylic alcohols, *sec*-allylic alcohols were separated with good selectivities using PBO catalyst **21** with selectivities of up to $s = 82$.^[93]

Catalyst **21** was also deployed for the acylative *parallel* KR (PKR) of *sec*-benzylic alcohols.^[94] This process uses two catalysts, each of which reacts selectively with a specific achiral acyl donor to esterify opposite enantiomers of the substrate in a one-pot process. By combining catalyst **21** with a commercial lipase and an acyl donor which is only activated by the lipase, a PKR could be achieved with $ee > 90\%$ at 85-90% conversion. The desymmetrization of hydrobenzoin was also achieved. Although Burke's catalyst proved to be more selective than PBO catalyst **21** in this case, catalyst loadings were high, and PBO catalyst **20** provided the best compromise between reactivity and enantioselectivity.^[95]

Further catalyst optimisation led to the discovery of catalyst **24** which imparted the highest levels of selectivity for challenging substrates.^[96] An air-stable phosphonium tetrafluoroborate salt pre-catalyst **24**·HBF₄ was also developed along with an enantioselective synthesis which avoided the previously required tedious catalyst resolution (Figure 7).^[91]

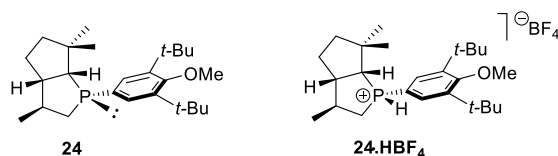
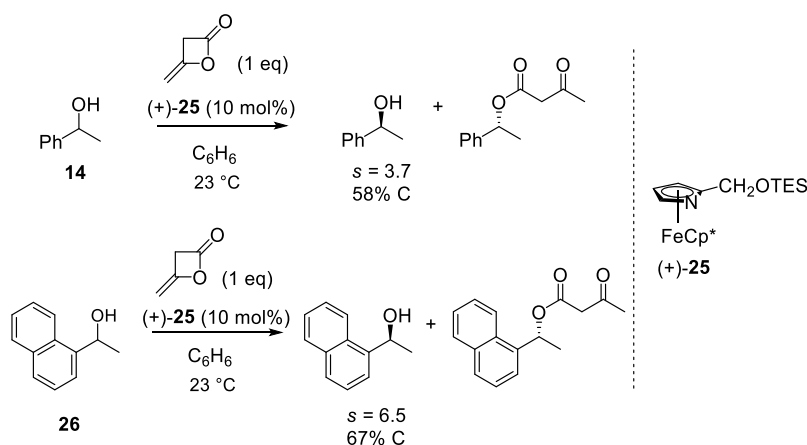


Figure 7. Vedejs's optimised PBO catalyst **24** and its phosphonium tetrafluoroborate salt pre-catalyst **24.HBF₄**.^[91]

Fu's first foray into the field of non-enzymatic KR began in 1996 with the use of chiral pyrrole-based catalyst **25**.^[97] In this pioneering work, it was hypothesised that π -complexation of pyrroles to metal fragments would constitute a novel approach to introducing an asymmetric environment close to the nucleophilic centre of these otherwise planar molecules. The FeCp* moiety was selected as the metal fragment as it was anticipated not only to provide the requisite steric bulk but also to potentially impart enhanced nucleophilicity by electron donation. Enantiomerically pure catalyst (+)-**25** was tested in the KR of *sec*-benzylic alcohols (Scheme 29).



Scheme 29. Fu's KR of *sec*-benzylic alcohols with *azaferrocene* catalyst (+)-**25**.^[97]

Promising levels of selectivity were obtained which were the highest published at the time for non-enzymatic acylation catalysts for these substrates. Further work by Fu *et al.* however focused on superior 4-DMAP based chiral catalysts, which were developed by desymmetrisation through a quadrant model of the parent molecule: the strategy was to remove the “front/back” mirror plane of 4-DMAP by complexation of one face to a metal and to remove the “left/right” mirror plane by substitution at C-3 and/or C-4 (Figure 8).^[98]

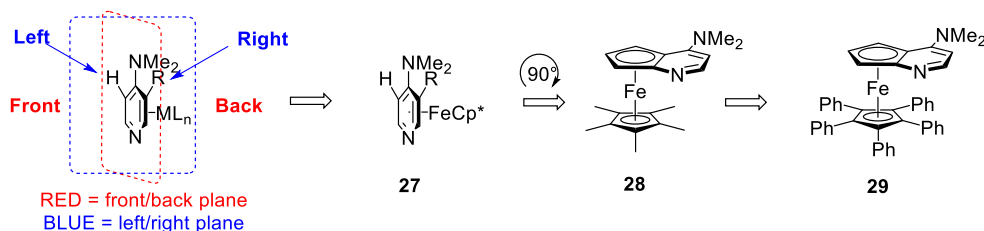
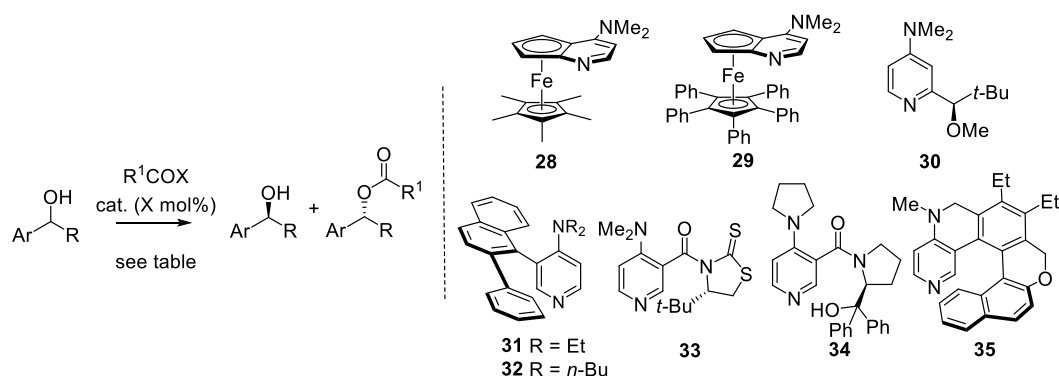


Figure 8. Fu's quadrant-based design strategy for a chiral 4-DMAP.^[98]

Direct complexation of 4-DMAP to the FeCp* unit was not considered possible as it would have led to the 19 electron complex **27**. Anticipating the instability of compound **27**, the 4-DMAP was instead fused to a

five-membered ring which was in turn complexed with the FeCp* unit to give 18 electron complex **28**, which was resolved and tested as an enantioselective catalyst. This catalyst as well as a number of other ‘chiral-DMAP’ catalysts subsequently developed by other groups have been compared directly in the table below (Table 3).^[98]

Table 3. A comparison of the efficiencies of chiral 4-DMAP catalysts **28-35** developed by Fu, Vedejs, Spivey, Yamada, Connon and Carbery for the KR of *sec*-benzylic alcohols.



Entry	Ar	R	R'	Cat. (mol%)	Additive	T(°C)	s ^a
1 ^[98]	Ph	Me	Me	28 (2)	Et ₃ N	rt	1.7
2 ^[99]	Ph	Me	Me	29 (2)	Et ₃ N	rt	14
3 ^[99]	Ph	<i>t</i> -Bu	Me	29 (2)	Et ₃ N	0	95
4 ^[99]	1-Naphthyl	Me	Me	29 (2)	Et ₃ N	0	65
5 ^[100]	Ph	Me	OC(Me) ₂ CCl ₃	30 (100)	Et ₃ N, ZnCl ₂	rt	38
6 ^[101]	Ph	Me	<i>i</i> -Pr	31 (1)	Et ₃ N	-78	13
7 ^[101,102]	1-Naphthyl	Me	<i>i</i> -Pr	31 (1)	Et ₃ N	-78	16
8 ^[102]	1-Naphthyl	Me	<i>i</i> -Pr	32 (1)	Et ₃ N	-78	31
9 ^[103]	Ph	Me	<i>i</i> -Pr	33 (0.5)	Et ₃ N	rt	7.6
10 ^[103]	1-Naphthyl	Me	<i>i</i> -Pr	33 (0.5)	Et ₃ N	rt	13
11 ^[104]	Ph	Me	<i>i</i> -Pr	34 (1)	Et ₃ N	-78	6.3
12 ^[104]	1-Naphthyl	Me	<i>i</i> -Pr	34 (1)	Et ₃ N	-78	6.6
13 ^[105]	Ph	Me	<i>i</i> -Pr	35 (0.5)	Et ₃ N	0	17
14 ^[105]	Ph	Et	<i>i</i> -Pr	35 (0.5)	Et ₃ N	0	23

^a |s| = Magnitude of selectivity factor, the absolute sense of induction depicted in the scheme is *not* implied for all the catalysts.

Catalyst **28** yielded a disappointing selectivity of $s = 1.7$ for 1-phenylethanol (Ar = Ph, R = Me, entry 1),^[98,106] while changing the Cp* ring for the bulkier pentaphenyl congener (C₅Ph₅) **29** improved the selectivity from $s = 1.7$ to 14 (entry 2). A number of other *sec*-benzylic alcohols were then surveyed in the KR. Increasing the bulk of the alkyl group was found to increase the selectivity (e.g. $s = 54$ when Ar = Ph, R = *t*-Bu),^[106] which further increased to $s = 95$ when *tert*-amyl alcohol was used as the solvent instead of diethyl ether (entry 3).^[98,99] Fu then went on to use this catalyst and further structurally modified derivatives (e.g. incorporating a 4-pyrrolidino unit in place of the 4-dimethylamino unit and with even bulkier pentasubstituted cyclopentadiene ligands on the Fe) in a number of studies,^[107] including the KR of

propargylic alcohols,^[108] allylic alcohols,^[109] and an oxazolone dynamic KR (DKR).^[110] Others have also used Fu's catalysts for the KR of 1,2-azidoalcohols,^[111] and for determining the absolute configuration of *sec*-allylic and *sec*-propargylic alcohols.^[112] A shorter synthesis of catalyst **29** featuring a classical resolution protocol in place of separation by chiral stationary phase HPLC has been developed and the catalyst is now commercially available.^[113,114]

Yamada and coworkers have also designed an induced fit chiral-4-DMAP catalyst **33**, for which formation of the acyl pyridinium salt is proposed to promote π -cation self-complexation of the cyclic dithiocarbamate moiety to the pyridinium ring (Figure 9).^[115]

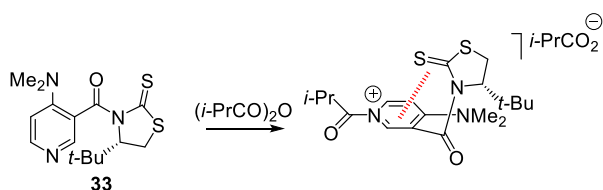


Figure 9. Yamada's chiral 4-DMAP catalyst **33** and the proposed conformational change induced upon reaction with an anhydride.^[115]

Evidence for the rigidifying interaction between the π electrons of the thiocarbonyl group and the cationic pyridinium ring, in the case of model systems lacking the 4-dimethylamino substituent on the pyridine ring, come from the short sulfur to pyridine C-3 bond distance evidenced by ¹H NMR, UV and X-ray analysis.^[116] A *t*-Bu group at the stereogenic centre was found to provide higher levels of selectivity than *i*-Pr or benzyl groups; lowering the temperature and using acyclic ethers as solvents was also advantageous. Selectivity values of $s = 7.6$ for 1-phenylethanol and $s = 13$ for 1-(1-naphthyl)ethanol were achieved using just 0.5 mol% of catalyst **33** (entries 9 and 10, Table 3).^[103] The same catalyst was also applied to the KR of ($\pm$)-1,2-diols, the desymmetrisation of *meso*-1,2-diols and the DKR of hemiaminals.^[103,115,117]

A further type of 4-DMAP-based acylation catalyst was developed by Spivey *et al.* which incorporated a hindered biaryl axis at the 3-position creating configurationally stable atropisomers. A number of different structures were explored, including 4-PPY-, 4-DMAP- and 5-azaindoline-based catalysts.^[101,102,118–125] Once the optimal level of substitution around the biaryl axis required to ensure configurational stability had been established,^[119,120] KR studies using lead catalyst **31** gave values of $s = 13$ for 1-phenylethanol and $s = 16$ for 1-(1-naphthyl)ethanol (entries 6 and 7, Table 3).^[101,102] Further changes to the catalyst and conditions allowed for a maximum selectivity of $s = 31$ to be reached with 4-(di-*n*-butylamino)pyridine-Ph **32** (entry 8, Table 3).^[122] The anhydride also had a large effect on the selectivity: *isobutyric* anhydride gave significantly higher selectivities than acetic anhydride (e.g. $s = 16$ vs. $s = 8.9$ for the reactions of 1-(1-naphthyl)ethanol with *isobutyric* anhydride and acetic anhydride respectively).^[101,102] These selectivity trends and the sense of stereoinduction were rationalised using a transition state model.^[121] Subsequently, Zipse performed DFT calculations on this and other systems. His computational studies confirmed that the carbonyl bond in the

acyl pyridinium salt intermediate aligns parallel to the atropisomeric biaryl axis (as originally postulated on the basis of ^1H NMR investigations) whilst also revealing a degree of induced fit face-to-face π - π stacking between the phenyl blocking group and the pyridinium ring in the acyl pyridinium salt (Figure 10).^[126]

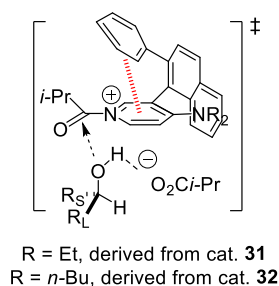


Figure 10. Spivey's transition state model accounting for the sense of stereoselection in *sec*-benzylic alcohol KR using atropisomeric catalysts **31** and **32**.^[126]

Canon *et al.* have also used the induced-fit paradigm to transmit chiral information from a remote, proline-derived stereogenic centre linked as an amide to the C-3 position of 4-PPY: *i.e.* catalyst **34** (Table 3).^[104,127–131] Catalyst **34** provided selectivities in the range $s = 6 - 30$ for an array of *sec*-benzylic alcohols, with substrates containing more bulky alkyl groups displaying the highest selectivities. 1-Phenylethanol was resolved with a selectivity factor of $s = 6.3$ and 1-(1-naphthyl)ethanol gave $s = 6.6$ (entries 11 and 12, Table 3). ^1H NMR studies on the catalyst showed little evidence for face-to-face π - π stacking but suggested an edge-to-face interaction between one of the phenyl substituents and H-2 of the pyridine as being important in ordering the transition state for acyl transfer from the acyl pyridinium intermediate. Interestingly, removal of the hydroxyl group from catalyst **34** reversed the sense of stereoinduction in KR reactions, accompanied by a reduction in selectivity from $s = 6.3$ to $s = -2.8$, suggesting that the *tert*-alcohol also has a significant role in the transition state complex.^[104] Various H-bond donors and acceptors were introduced in place of this alcohol function and a congener containing the H-bond acceptor group NMe_2 was also found to give the opposite sense of induction for the same substrate ($s = -2$ with Ac_2O ^[132]) compared to catalyst **34** ($s = 6$ with *isobutyric* anhydride^[104]).^[132] ^1H NMR studies suggested that significantly different conformations are adopted by their respective acyl pyridinium salts, possibly contingent upon the hydrogen-bond donor/acceptor ability of the OH and NMe_2 groups.^[132]

Carbery *et al.* reported 4-DMAP-based chiral catalyst **35** with a unique helical architecture (Table 3).^[105] In this catalyst design, one face of the pyridine core is shielded by the fused naphthyl “tail” of the helical catalyst skeleton.^[105] Benchmarking of the catalysts' activity using 1-phenylethanol and 1-phenylpropanol established selectivity factors of $s = 17$ and $s = 23$ respectively at 0 °C in *tert*-amyl alcohol (entries 13 and 14, Table 3). Recently, a resolution-free, gram scale asymmetric synthesis of this catalyst has been reported.^[133]

Many other 4-DMAP-based chiral catalysts for the KR and desymmetrisation of alcohols have been described, notably by Kotsuki (**37**)^[134,135] Richards (**39**),^[136,137] Campbell (**40**)^[138–141] and others^[142–149] (Figure 11).

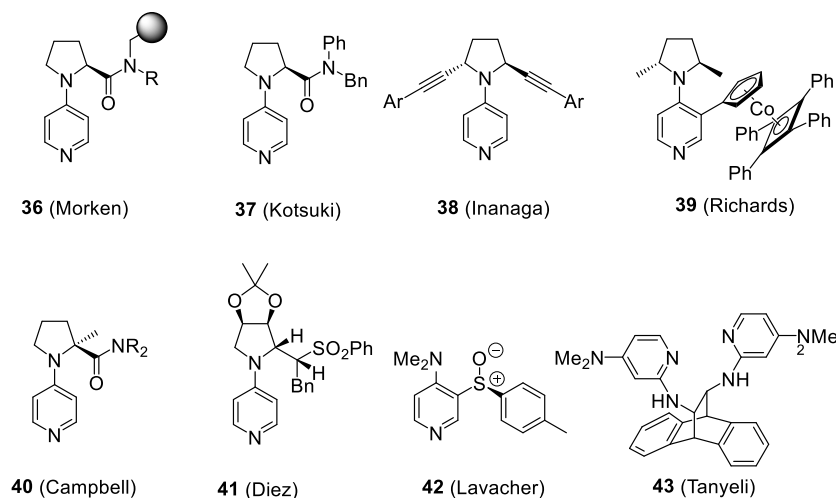


Figure 11. A selection of chiral 4-DMAP-based organocatalysts.^{[134,135][136,137][138–141][142–149]}

The Birman group have developed an alternative acylative KR catalyst based on a 2,3-dihydroimidazole[1,2-a]pyridine core (DHIP) instead of the 4-DMAP used in previous examples. The development of these catalysts has been summarised by Birman in a comprehensive review,^[150] and so only brief mention of this work follows. Birman *et al.* hypothesised that the DHIP core could be easily constructed in two steps from commercially available enantiopure starting materials, and that the R group located on the chiral centre would block attack from the bottom face of the molecule (Figure 12).^[151]

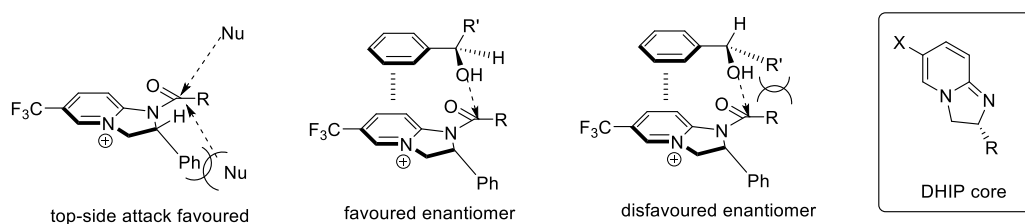
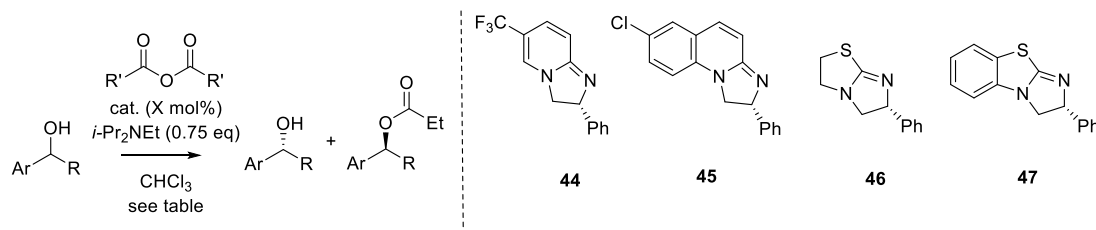


Figure 12. Origin of enantioselectivity for *sec*-benzylic alcohols with Birman's DHIP catalyst series.^[151]

Table 4. Birman's KR of sec-benzylic and cinnamyl alcohols with catalysts CF₃-PIP **44**, Cl-PIQ **45**, TM **46** and BTM **47**.^[151–154]



Entry	R	Ar	R'	Cat.(mol%)	T(°C)	s
1	Et	Ph	Me	44 (2)	rt	14
2	Et	Ph	Et	44 (2)	0	36
3	<i>t</i> -Bu	Ph	Et	44 (2)	0	85
4	<i>t</i> -Bu	Ph	Et	45 (2)	0	117
5	Me	1-Naphthyl	Et	44 (2)	0	55
6	Me	1-Naphthyl	Et	45 (2)	0	56
7	Me	2-Naphthyl	Et	44 (2)	0	42
8	Me	2-Naphthyl	Et	45 (2)	0	74
9	Me	PhCHCH-	Et	45 (2)	0	27
10	Me	2-OMe-PhCHCH	Et	45 (2)	0	31
11 ^a	Et	Ph	Et	46 (10)	0	32 ^b
12 ^a	<i>t</i> -Bu	Ph	Et	47 (8)	0	166
13 ^a	<i>t</i> -Bu	1-Naphthyl	Et	47 (8)	0	307
14 ^a	<i>t</i> -Bu	Ph	<i>i</i> -Pr	47 (8)	0	192
15 ^a	<i>t</i> -Bu	1-Naphthyl	<i>i</i> -Pr	47 (8)	0	207

^aNa₂SO₄ present in reaction mixture. ^b(S)-enantiomer formed.

The catalytic activity and enantioselectivities imparted by catalysts based on the DHIP core were increased when changing the X group from H (*s* = 3.3) to Br (*s* = 8.6), NO₂ (*s* = 11) and finally CF₃ (*s* = 14) (CF₃-PIP **44**), with the electron withdrawing ability of these groups increasing the electrophilicity of the acylated intermediate (Table 4, entry 1).^[151] Attractive π - π and cation- π interactions were proposed to take place between the substrate and the acylated catalyst, and the facial selectivity of the reaction was due to unfavourable steric interactions between the R group of the substrate and the R' group of the acylating agent during approach by the disfavoured enantiomer (Figure 12).^[151] The selectivity was further increased at lower temperatures and by increasing the bulk of the anhydride from acetic- to propionic anhydride (entry 2). The best selectivity value achieved with this catalyst was with 1-phenyl-2-*tert*-butylethanol as the substrate (entry 3).^[151]

A second generation catalyst Cl-PIQ (**45**)^{[153][152]} was initially designed to give a better selectivity with cinnamyl alcohols, as the π structure of these types of substrates did not overlap well with the CF₃-PIP catalyst **44**. The π structure of the catalyst was therefore extended with a phenyl group, providing a new core structure of 1,2-dihydroimidazo[1,2-*a*]quinolone (DHIQ), which could overlap with the both the aryl and alkene groups of the cinnamyl alcohol (Figure 13).

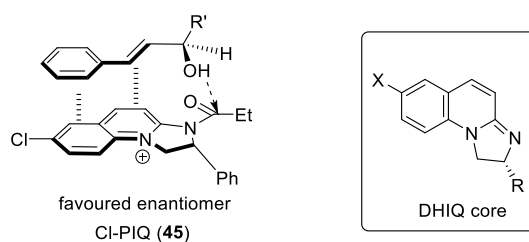


Figure 13. Origin of enantioselectivity for the KR of cinnamyl alcohols with Birman's Cl-PIQ catalyst **45**.^[153]

A simple two-step synthesis furnished Cl-PIQ **45** and this catalyst proved to be selective for cinnamyl alcohols (Table 4, entries 9-10), as well as more selective than CF₃-PIP **44** for almost all *sec*-benzylic alcohols (Table 4, entry 3 vs entry 4). The one exception to this was 1-(1-naphthyl)ethanol, which was found to give the same selectivity with both catalysts. This was hypothesised to be due to the inability of the second phenyl ring in 1-(1-naphthyl)ethanol to interact with the extended π system of the Cl-PIQ catalyst **45**, while 1-(2-naphthyl)ethanol provided an optimal overlap increasing the selectivity from 42 to 74 (entries 5-8).^[153]

It was found, through studying commercially available tetramisole **46**, that pyridine was not an integral part of the catalyst structure (Figure 14).^[154]

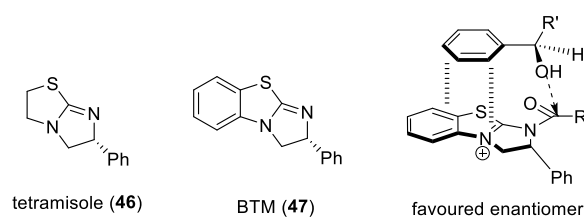
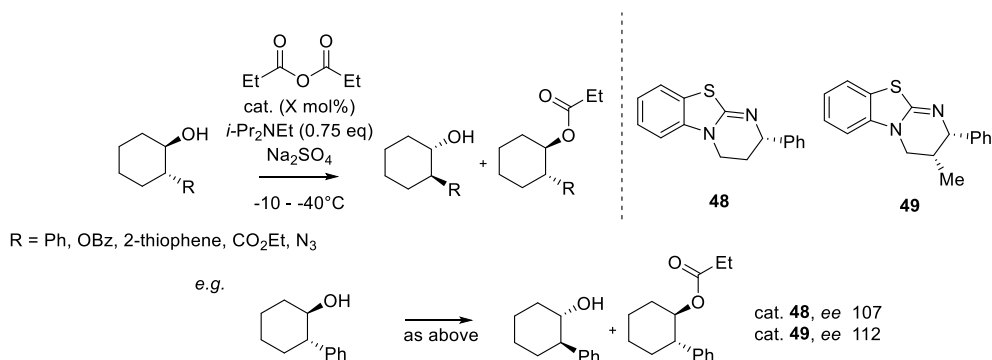


Figure 14. Tetramisole **46** and Birman's BTM catalyst **47**, with origin of enantioselectivity for the KR of *sec*-benzylic alcohols.^[154]

Tetramisole **46** was less active than the previous two catalysts **44** and **45**, displaying moderate to good levels of selectivity (Table 4, entry 11). In the same way that CF₃-PIP **44** was improved by extension with a benzene ring, tetramisole **46** was also extended to give benzotetramisole (BTM) **47** (Figure 14). At room temperature this catalyst was two times more selective than **46**, and now also compared favourably with the previous generation catalysts in terms of rate (Table 4, entry 12).^[154] The selectivity of unhindered substrates could be further improved with this catalyst when using *isobutyric* anhydride instead of propionic anhydride (Table 4, entry 14); although a decrease in selectivity was observed for hindered substrate 1-(1-naphthyl)-2-*tert*-butylethanol upon the use of propionic anhydride (entry 15 vs entry 13). BTM **47** was also successfully used for the KR of propargylic alcohols,^[155] while it was less selective for cinnamyl alcohols than Cl-PIQ **45**.^[154]

A fourth generation catalyst HBTM^[156] **48** was developed by changing the previously used imidazoline moiety to a tetrahydropyrimidine moiety in the core catalyst structure (Scheme 30). This change had a

significant effect on the structure-selectivity profile of this compound, which, while less effective for *sec*-benzylic alcohols, proved to be more effective for 2-aryl-cycloalkanols (Scheme 30).



Scheme 30. Birman's KR of 2-aryl-cycloalkanols with catalysts HBTM **48** and HBTM-2 **49**.^[156,157]

A methyl substituted analogue of HBTM (HBTM-2 **49**)^[157] was found to be more active and selective for cycloalkanols, but still was outperformed by BTM **48** for the KR of *sec*-benzylic alcohols.^[157]

This series of amidine-based catalysts (ABCs) have been put to a number of different uses, including work by Birman on the DKR of azlactones,^[158,159] by Shiina on the KR of various alcohols with free carboxylic acids as acyl donors^[160–165] and by Chen on the KR of various fluorinated *sec*-benzylic alcohols.^[166–168] Smith *et al.* have further developed the HBTM catalyst structure, with modification to incorporate a stereogenic *i*-Pr group *cis* to the phenyl group (**50**) allowing selectivities of *s* > 100 to be achieved for a number of *sec*-benzylic alcohols, along with low catalyst loadings (0.1 – 0.25 mol%)^[169] (Table 5, entry 1).

Table 5. Catalysts **50–53** as published by Smith^[169] and Deng^[170,171] with selectivities for the KR of 1-phenyl-2-*tert*-butyl-ethanol **15**.

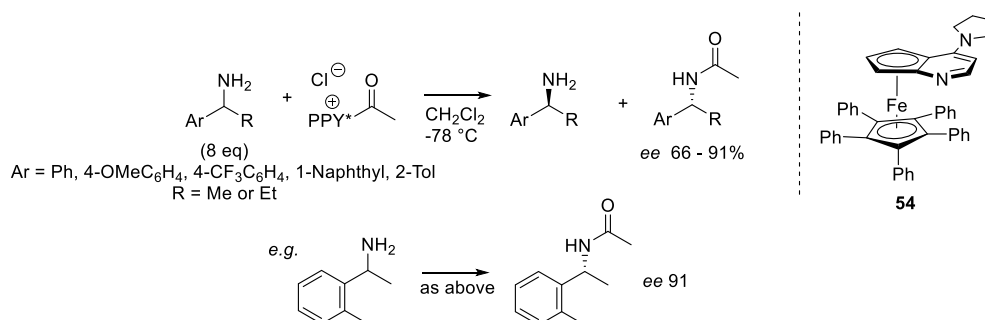
Entry	Cat. (mol%)	T(°C)	<i>s</i>
1 ^[169]	50 (0.25)	0	>100
2 ^[170]	51 (5)	-40	1892
3 ^[171]	52 (5)	0	530
4 ^[171]	53 (5)	0	450

Deng *et al.* have also made modifications to the ABC catalyst structure, preparing an interesting hybrid structure incorporating design elements of both Birman's Cl-PIQ catalyst and Fu's ferrocenyl catalysts: catalyst **51**. This catalyst provides good to excellent selectivities for *sec*-benzylic alcohols, notably with *s* > 500 (purportedly *s* = 1892!) for 1-phenyl-2-*tert*-butylethanol **15**^[170] (entry 2). A further modification by Deng

provided catalysts **52** (anthryl) and **53** (naphthyl), used successfully for the KR of *sec*-benzylic alcohols,^[171] ($s = 530$ and $s = 450$ respectively for 1-phenyl-2-*tert*-butylethanol **15** (entries 3 and 4)), α -methylene- β -hydroxy esters,^[172] and α -aryl substituted allylic alcohols.^[173]

1.2.5.2 Amines

Although the non-enzymatic catalytic KR of *sec*-alcohols has been widely studied, the analogous catalytic KR of amines is a relatively under-developed field, recently reviewed by Krasnov.^[174] One of the challenges associated with acylative amine KR is the high nucleophilicity of amines, which makes it difficult for a nucleophilic catalyst to comprehensively outcompete the direct non-enantioselective background reaction between the amine and the acyl donor to give racemic product. Consequently, a number of chiral acyl ammonium/pyridinium salts have been deployed in stoichiometric quantities to achieve acylative amine KR, including work by Shibuya,^[175] Atkinson,^[176–181] Murakami,^[182] Arseniyadis,^[183–187] and others.^[188–191] In particular, Fu *et al.* described the use of the acyl pyridinium salt of their chiral ferrocenyl 4-PPY-based catalyst **54** in stoichiometric quantities to effect KR of certain primary amines achieving *ees* of up to 87% at $-78\text{ }^{\circ}\text{C}$ (Scheme 31).^[192]



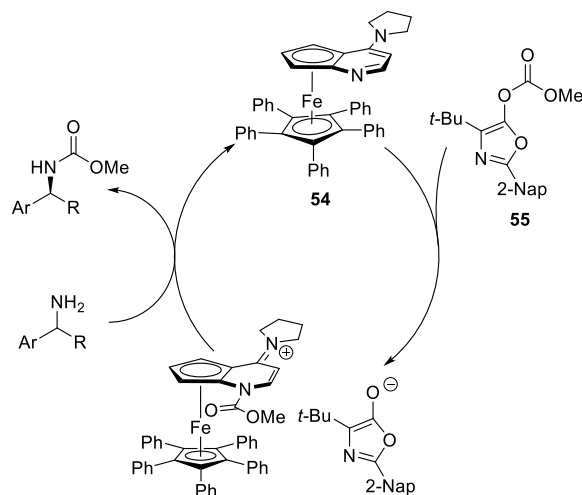
Scheme 31. Fu's KR of primary amines using a stoichiometric quantity of chiral 4-PPY **54**.^[192]

Subsequently, Fu developed the first example of a non-enzymatic *catalytic* amine KR.^[193] The key to rendering the process catalytic was the development of an oxazolone acylating agent **55** that apparently reacts preferentially with the 4-PPY-based catalyst **54** rather than the substrate primary amine. This minimizes the background reaction and promotes product formation exclusively *via* the catalysed pathway. 1-Arylethyl- and 1-arylpropylamines gave selectivity factors in the range $s = 12 - 27$ at $-50\text{ }^{\circ}\text{C}$, with substrates having *ortho*-substituents on the aromatic ring giving the highest levels of selectivity (Table 6).^[193]

Table 6. Fu's first catalytic acylative KR of *sec*-benzylic primary amines using 4-PPY **54**.^[193]

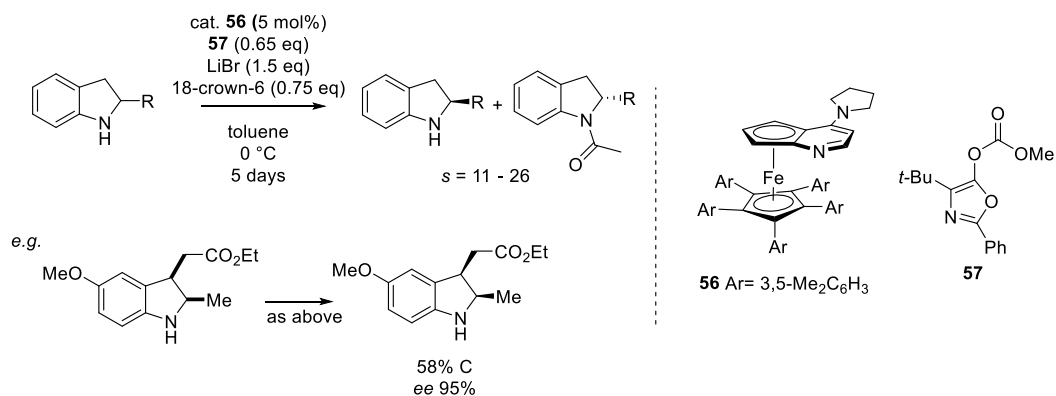
Entry	Ar	R	s
1	Ph	Me	12
2	Ph	Et	16
3	1-Naphthyl	Me	27
4	2-Me-C ₆ H ₄	Me	16
5	3-OMe-C ₆ H ₄	Me	22

Fu's proposed catalytic cycle for these reactions proceeds *via* the addition of the amine to the acylated catalyst as the stereodetermining step (Scheme 32).^[193]



Scheme 32. Catalytic cycle proposed by Fu for the acylation of *sec*-benzylic primary amines.^[193]

Further work encompassed the KR of 2-substituted indolines using an improved catalyst **56**, the phenyl analogue of the oxazolone acylating agent (*i.e.* **57**), and several additives (Scheme 33).^[194]



Scheme 33. Fu's acylative KR of indolines using catalyst **56**.^[194]

In preliminary studies, Fu demonstrated that the counter anion to the pyridinium salt strongly affected the selectivity of acylation. In particular, halide anions were found to give good selectivity but no turnover and this led to the idea of adding LiBr and 18-crown-6 as additives. The effect of these two additives, despite the fact that they are mismatched in terms of mutual interaction,^[195] was dramatic: they increased the selectivity from $s = 2$ to $s = 23$ for indoline ($R = \text{Me}$), which was hypothesized to be due to anion exchange of the pyridinium salt. A range of 2-substituted indolines gave selectivity values from $s = 11$ to $s = 26$ at 0 °C but reasonable levels of conversion required reaction times of 5 days. Increasing the reaction temperature to 25 °C lowered the reaction time to 2 days, but also significantly reduced the selectivities.^[194]

Seidel *et al.* have described a non-enzymatic catalytic KR of *sec*-benzylic primary amines using benzoic anhydride together with 4-DMAP. Their approach employs a chiral anion binding agent **58**, which can chelate *via* a pair of H-bonds (HBs) to the counter anion of the pyridinium salt formed between 4-DMAP itself and an achiral acylating agent (Figure 15).^[196]

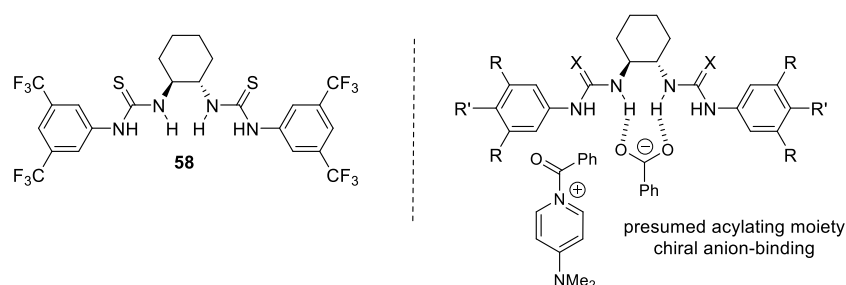


Figure 15. One of Seidel's chiral thiourea anion binding agents **58** and a general structure of the resulting presumed chiral acylpyridinium salt/complex.^[196]

A number of chiral thiourea -based HB donors were assessed for this process, and thiourea **58** was found to give the highest selectivities. Low temperature (−78 °C) and low concentrations (0.01 M) were used to minimize the background reaction between the amine substrates and the benzoic anhydride acylating agent. Interestingly, 4-DMAP alone was shown not to catalyse the reaction under these conditions, whereas the HB donor alone did catalyse the reaction to 40% yield after 1 hour, albeit with very low selectivity (*i.e.* $s = 1.4$, 1-phenylethylamine), presumably due to direct activation of the anhydride by the HB donor **58**. The combination of 4-DMAP and HB donor **58** gave 45% conversion after 1 hour, with selectivity values $s = 10$ for 1-phenylethylamine, and up to $s = 24$ for 1-naphthylethylamine (Table 7).^[196]

Table 7. Seidel's KR of *sec*-benzylic primary amines using 4-DMAP and chiral thiourea co-catalyst **58**.^[196]

Entry	Ar	R	s
1	Ph	Me	10
2	Ph	<i>n</i> -Bu	7.7
3	1-Naphthyl	Me	24
4	Ph	Bn	15
5	2-Me-C ₆ H ₄	Me	17

Further work to optimise the structure of both the 4-(dialkylamino)pyridine and the HB donor co-catalyst led to the optimal combination of 4-(dipropylamino)pyridine **59** and *mono*-thiourea **60** (Figure 16).^[197]

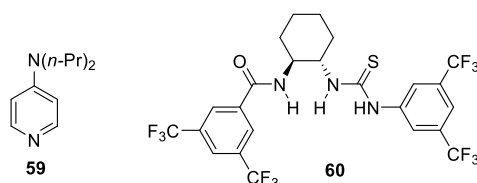


Figure 16. Seidel's second generation co-catalyst combination: 4-(dipropylamino)pyridine **59** and chiral *mono*-thiourea based HB donor catalyst **60**.^[197]

Interestingly, Seidel *et al.* also tested enantiopure HB donor catalyst **60** with both enantiomers of Fu's chiral 4-DMAP-based acylation catalyst **29** (Figure 8), and found very low levels of selectivity for both matched and mismatched combinations, essentially indistinguishable from the results obtained with the HB donor alone. The combination of Fu's catalyst **29** with an achiral thiourea did not increase the selectivity although it did increase the conversion. Further work by Seidel demonstrated the successful KR of 1,2-diaryl-1,2-diaminoethanes,^[198] propargylic amines,^[199] and allylic amines,^[200] as well as desymmetrisation of *meso*-diamines^[201] using analogous conditions.

Birman *et al.* have evaluated their ABCs in the KR of both 2-oxazolidinones^[202] and β -lactams,^[203] and other related lactams and thiolactams.^[204] In 2006, they initially looked at oxazolidinones as potential substrates for amine KR, the first time chiral *sec*-amides had been resolved (Table 8).^[202]

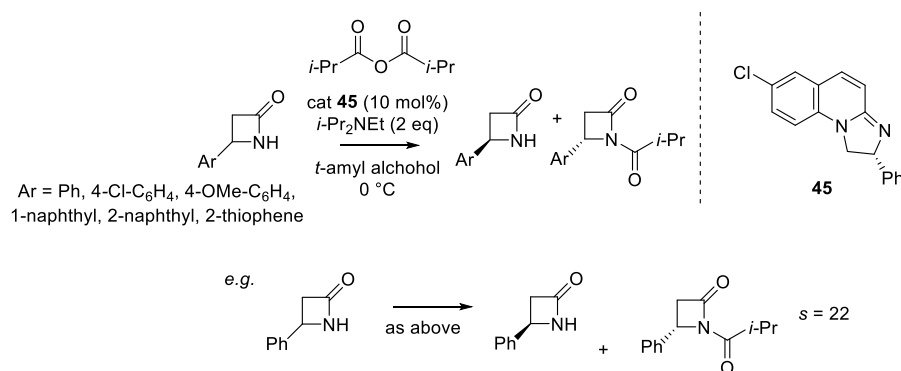
Table 8. Birman's KR of oxazolidinones with catalysts **44**, **45** and **47**.^[202]

Entry	Ar	R	R'	Cat. (mol%)	Solvent	T(°C)	s
1	Ph	H	Et	44 (2)	CHCl ₃	0	7.8
2	Ph	H	Et	45 (4)	CHCl ₃	0	10
3	Ph	H	<i>i</i> -Pr	45 (4)	<i>t</i> -amyl alcohol	0	24
4 ^a	Ph	H	<i>i</i> -Pr	47 (4)	CHCl ₃	rt	200
5 ^a	1-Naphthyl	H	<i>i</i> -Pr	47 (4)	CHCl ₃	rt	450
6 ^a	1-Naphthyl	Me	<i>i</i> -Pr	47 (8)	CHCl ₃	rt	520

^a Na₂SO₄ present in reaction mixture.

While the first three generations of catalyst, CF₃-PIP **44**, Cl-PIQ **45** and BTM **47** all gave reasonable levels of selectivity, the combination of *isobutyric* anhydride and BTM **47** was found to be superior, giving selectivity factors of >100 in some cases at room temperature (Table 8, entries 4-6).

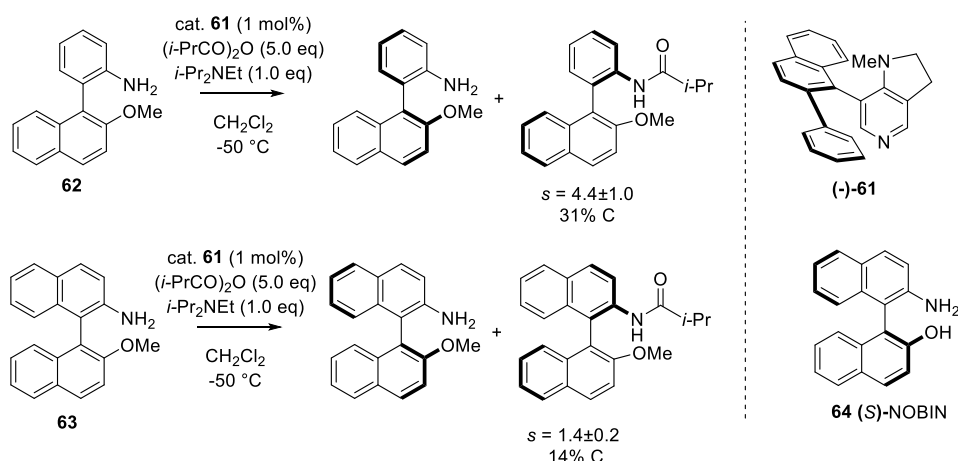
Oxazolidinones are resolved more easily than primary amines due to their comparatively decreased nucleophilicity and hence low background reactivity. β-Lactams share this favourable characteristic and this substrate class was successfully resolved with Cl-PIQ **45** (BTM **47** showed reduced selectivity factors) (Scheme 34).^[203]



Scheme 34. Birman's KR of β-lactams by Cl-PIQ **45**.^[203]

Birman *et al.* also used BTM **47** for the deacylative KR of *N*-acyl thiolactams,^[205] as well as for the KR of *N*-acyl-β-lactams by enantioselective alcoholysis.^[206]

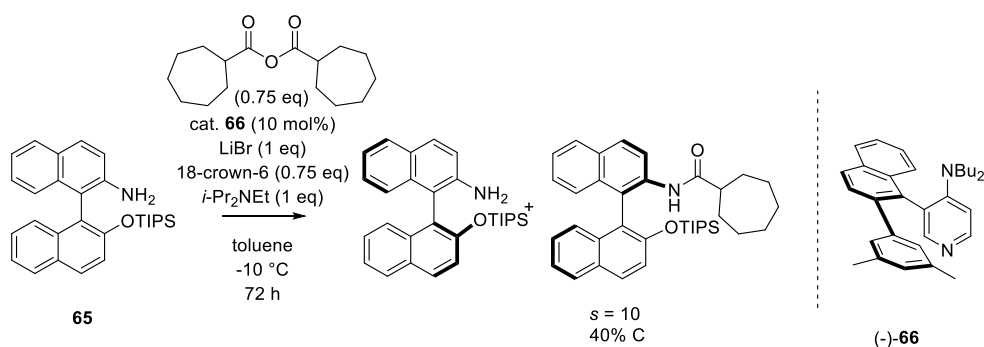
Spivey *et al.* have employed their atropisomeric 4-(diethylamino)pyridine-based catalyst **31** and 5-azaindoline-based catalyst **61** for the catalytic KR of atropisomeric 2-methoxynaphthyl aniline **62** and its benzo-fused analogue **63**, with a view to developing an approach to the synthesis of the ligand (*S*)-NOBIN (**64**) (Scheme 35).^[207]



Scheme 35. Spivey's acylative KR of biaryl anilines towards the synthesis of (S)-NOBIN (**64**).^[207]

Initial experiments with 2-methoxynaphthyl aniline **62** as substrate revealed that although 4-DMAP catalysed *N*-acylation, the 4-(diethylamino)pyridine-based chiral catalyst **31** (Table 3) was essentially inactive despite the fact that the pyridinium salt was shown to be formed under the reaction conditions. Subsequent systematic modification of the catalyst structure determined that the 5-azaindoline-based catalyst **61** was sufficiently reactive but displayed a modest selectivity factor of $s = 4.4$ at 31% conversion after 1 hour for aniline **62**, which dropped to $s = 1.4$ at 14% conversion after 43 hours for aniline **63**.

Further catalyst modifications to improve both activity and selectivity (*vide infra*) increased the selectivity to $s = 10$ with aniline **65** and catalyst **66** (Scheme 36).^[208]

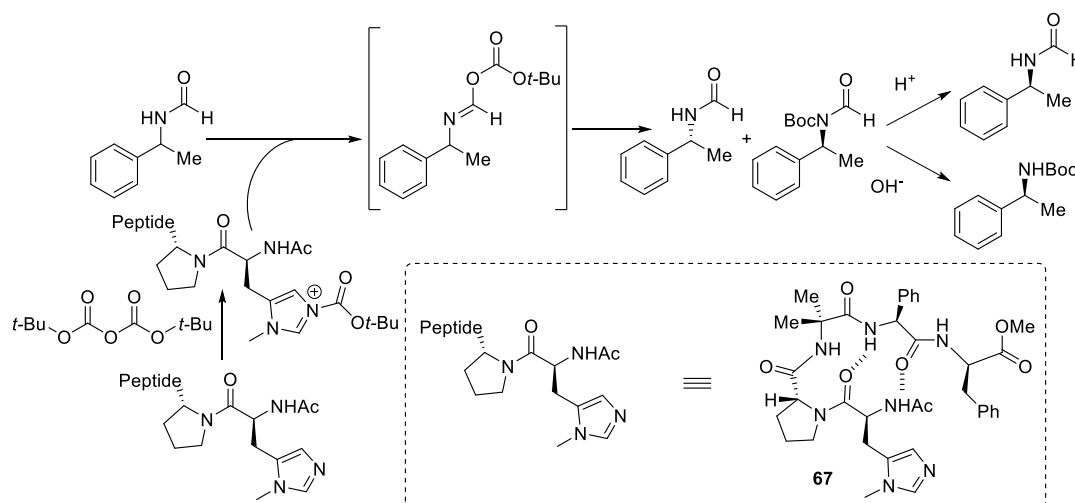


Scheme 36. Spivey's acylative KR of biaryl aniline **65** with modified dibutylaminopyridine catalyst **66**.^[208]

The combination of a more selective catalyst, a bulkier acyl donor and the presence of LiBr and 18-crown-6 as used by Fu^[209] have thus improved the selectivity with aniline **65**, although long reaction times were observed.

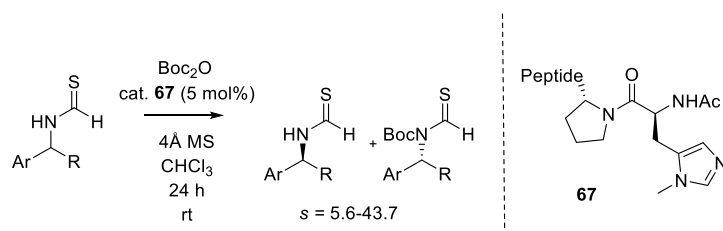
Miller has developed a peptide based catalyst **67** which provides an alternative approach to the KR of amines. While free amines are known to be very reactive, formamides and thioamides were used as

substrates which were initially *O*-acylated before rearranging to the *N*-acylated products with minimal background reaction (Scheme 37).^[210]



Scheme 37. Miller's KR of formamides with peptide catalyst **67**.^[210]

While formamides gave selectivities of $s = 9.6$ ($C \sim 35\%$ after 36 hours at rt) for the above reaction, thioformamides were superior substrates in terms of both reactivity and selectivity (Scheme 38).^[210]

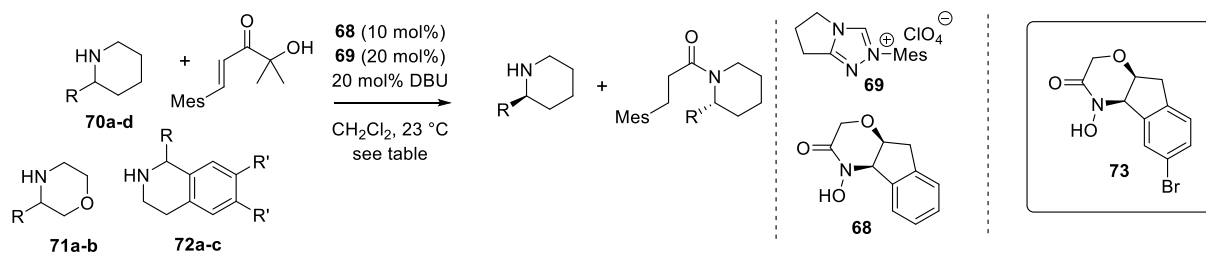


Scheme 38. Miller's KR of thioformamides with peptide catalyst **67**.^[210]

A number of substituents on the aromatic ring were tolerated by the catalyst, including halides, -OMe and -OPh in the 2-position, -OMe and -Ph in the 4-position, and 3,5-dimethoxy substitution, while the R groups also include 2-pyridine, giving the lowest selectivity of 5.6, with methyl or ethyl groups preferred.

Bode has developed a protocol for the KR of cyclic *sec*-amines using a tandem catalytic cycle in which an achiral NHC was used in conjunction with a chiral hydroxamic acid additive.^[211] The key finding was that the initially formed achiral NHC-based acylating agent shows high selectivity for acylation of the hydroxamic acid over the *sec*-amine substrate and so *N*-acylation of the substrate is exclusively *via* the chiral acyl hydroxamate and this latter event constitutes the stereodifferentiating step.^[211] Using 10 mol% of both the chiral hydroxamic acid **68** and of an achiral NHC precursor **69** in the presence of 20 mol% of DBU gave selectivity values up to $s = 23$ in the KR of various cyclic *sec*-amines, increasing to $s = 74$ for tetrahydroisoquinoline **72c** (Table 9).

Table 9. Bode's KR of cyclic sec-amines **70a-d**, **71a-b** and **72a-c** using a tandem chiral hydroxamic acid **68**/achiral NHC precursor **69** catalysis system.^[211]



Entry	Substrate	R	R'	s
1	70a	Me	-	17
2	70b	Et	-	12
3	70c	Bn	-	23
4	70d	CH ₂ (3-CF ₃ -C ₆ H ₄)	-	21
5	71a	Me	-	11
6	71b	Bn	-	23
7	72a	Me	H	13
8	72b	Ph	H	53
9	72c	Ph	OMe	74

Further work to optimise the process and expand substrate scope led to the use of bromine-containing catalyst **73** and to the successful KR of lactams and other difficult substrates, such as those with *N*-carbamate protecting groups.^[212] These substrates had previously been problematic due to hydrogen bonding of lactam and carbamate carbonyl groups to the hydroxamic acid catalyst, but use of *isopropyl* acetate as the solvent instead of CH₂Cl₂ apparently disrupted these interactions, allowing an efficient KR. The new conditions also increased the selectivities achievable for previous substrates up to *e.g.* *s* = >100 for tetrahydroisoquinolines **72a-c**. The catalytic and stoichiometric KR of disubstituted piperidines was also achieved, with a marked difference in selectivity depending on whether the substrate had *cis* or *trans* substitution.^[213] A polymer supported variant of the catalyst has also been developed, although this is currently used in stoichiometric amounts with the need to reform the acylated species between reactions.^[214] Further development of the polymer-supported catalyst has allowed for the large scale (18-25 g/batch) resolution of malaria drug mefloquine, with good selectivity (*s* = 23±3) and the ability to recycle the polymer for up to seven batches.^[215]

1.2.6 Acylative Enzymatic DKR of Amines and Alcohols

1.2.6.1 Introduction to DKR

Dynamic KR (DKR) is a process developed to overcome the inherent 50% yield limitation present in a standard KR, by combining an *in situ* racemisation with a KR.^[216] As the KR progresses, the remaining

enantioenriched substrate will be racemised, ensuring that only the desired enantiomer is transformed to the product, and increasing the theoretical yield to 100%, as shown below for the acylative DKR of alcohols.

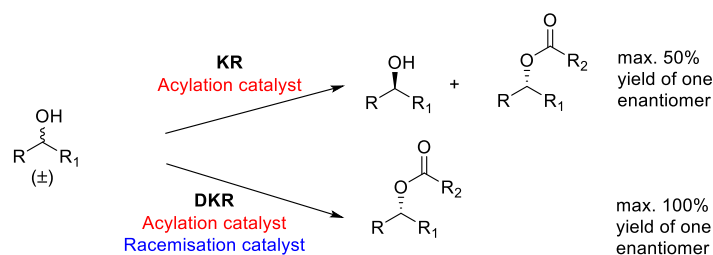


Figure 17. Classical KR vs DKR as shown for the acylative DKR of alcohols.

However, a number of chemical and kinetic parameters must be met in order for this process to be successful.

- No racemisation of the product should occur
- The rate of racemisation must be faster than reaction (*i.e.* acylation) of the slow enantiomer
- The resolution step must be non-reversible
- High selectivity is required to achieve good *ee* of product. This is one key difference between KR and DKR, as in DKR the maximum *ee* of the recovered material is set by the selectivity factor *s*, while in KR this is set by a combination of the selectivity *s* and the extent of conversion of the reaction (Figure 18).

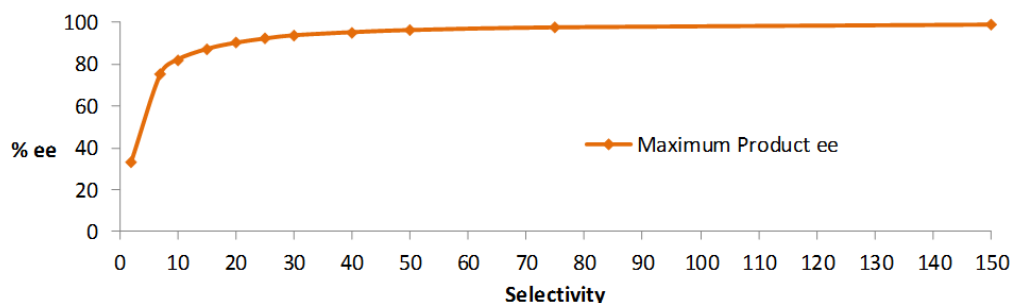


Figure 18. Change in maximum possible *ee* of recovered product in DKR as selectivity of KR changes.

- Highly selective KR catalysts are also particularly advantageous in DKR processes because when the selectivity is very high, the efficiency of the racemisation process is less critical, as even if the substrate deviates substantially from being racemic during the course of the DKR only one enantiomer will undergo the reaction.

1.2.6.2 Acylative Enzymatic DKR Procedures and Available Racemisation Catalysts

Chemo-enzymatic DKR is a powerful approach to the synthesis of enantioenriched materials in high yield. Since the first-reported work in 1996 by Williams for the enzymatic DKR of alcohols and by Reetz for the enzymatic DKR of amines,^[217] many others have contributed to this growing field, with Bäckvall playing a

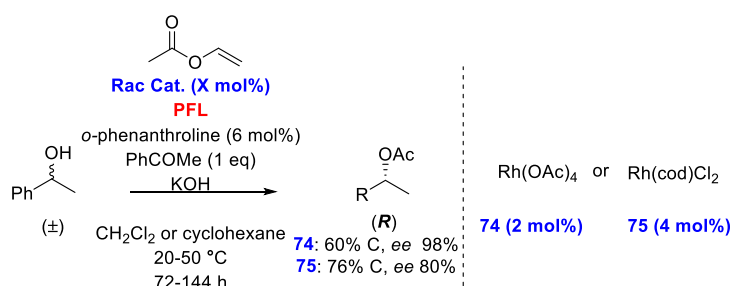
notable role in the development of these processes. The following sections present a brief overview of the contributions made to the field of acylative enzymatic DKR of alcohols and amines. More comprehensive reviews on this subject include work by Park,^[218,219] Bäckvall,^[220,221] Cheng^[222] and Ghanem^[54] as well as an extensive review on all types of DKR by Pellissier.^[216]

1.2.6.2.1 One-pot DKR

The two catalytic processes to form a DKR can be combined into a one-pot process, and a brief summary of some types of one-pot alcohol and amine DKR are described below. A separate section will summarise work in the area of multi-pot, or separated DKR, where the two catalytic processes have been separated in some fashion.

1.2.6.2.2 Alcohol DKR

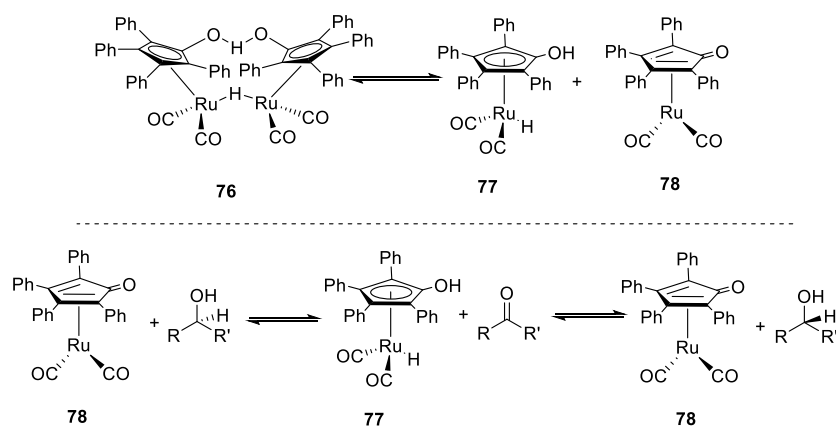
The first example of a DKR of simple *sec*-benzylic alcohols using both enzymes and metals was disclosed by Williams *et al.* in 1996, aiming to find a general approach for the DKR of alcohols.^[223] They hypothesised that catalysts previously used for transfer hydrogenation could catalyse the racemisation of alcohols. To this end they carried out studies on the racemisation capabilities of complexes based on various metals including iridium, aluminium, ruthenium and rhodium. Although individually both the racemisation and enzymatic KR were found to work well, the combination of the two processes presented some challenges including reduced yield and reduced *ee* (Scheme 39).



Scheme 39. Williams' DKR of 1-phenylethanol with catalysis of racemisation by rhodium complexes **74** and **75**.^[223]

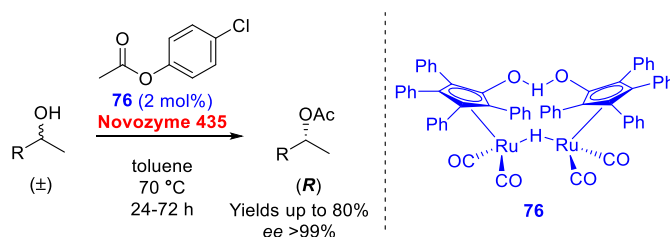
The rhodium complexes shown above gave the best results in the DKR, although there appears to be a trade-off between level of conversion and level of enantioselectivity achieved (*cf.* catalyst **74** vs. **75**).

Since its discovery in 1985 by Youval Shvo,^[224] the dimeric diruthenium catalyst **76** has been used for a wide variety of transformations, including the hydrogenation of aldehydes, ketones, alkynes and alkenes, transfer hydrogenation and the oxidation of amines to imines.^[225] It was first put to use in the DKR of alcohols by Bäckvall,^[226,227] following on from work by Williams showing that transfer hydrogenation catalysts can be efficient catalysts for the racemisation of alcohols.^[220,223]



Scheme 40. Mechanism of activation of Shvo pre-catalyst **76** and mechanism of racemisation.^[228]

The Shvo catalyst is in fact a pre-catalyst and activates at high temperature to dissociate into the two species shown above, **77** and **78** (Scheme 40). The mechanism of hydrogen transfer of the Shvo catalyst has been widely studied, with complex **78** acting as the dehydrogenation catalyst and complex **77** acting as the hydrogenation catalyst, allowing efficient racemisation of the alcohol.^[228] Bäckvall used this catalyst in combination with commercially available Novozyme 435, a supported form of the thermostable enzyme *Candida Antarctica* lipase B to achieve good yields and *ees* in the DKR of a number of *sec*-benzylic alcohols as well as non-aromatic substrates.^[226,227]



Scheme 41. First example of enzymatic alcohol DKR with racemisation catalysed by Shvo's catalyst **76** as developed by Bäckvall.^[226,227]

Although this was the first example of a practical one-pot enzymatic DKR of alcohols, drawbacks included the need for an activated acyl donor, *para*-chlorophenyl acetate, as well as the elevated temperatures required for the pre-catalyst activation (70 °C) which precluded the use of more temperature sensitive enzymes.

Much research was therefore directed towards the development of racemisation catalysts requiring lower temperatures, with the first real breakthrough coming in 2002 from the group of Park, with the development of catalyst **79**, a monoruthenium analogue of the Shvo catalyst **76** containing an amine substituent on the cyclopentadiene ring (Figure 19).

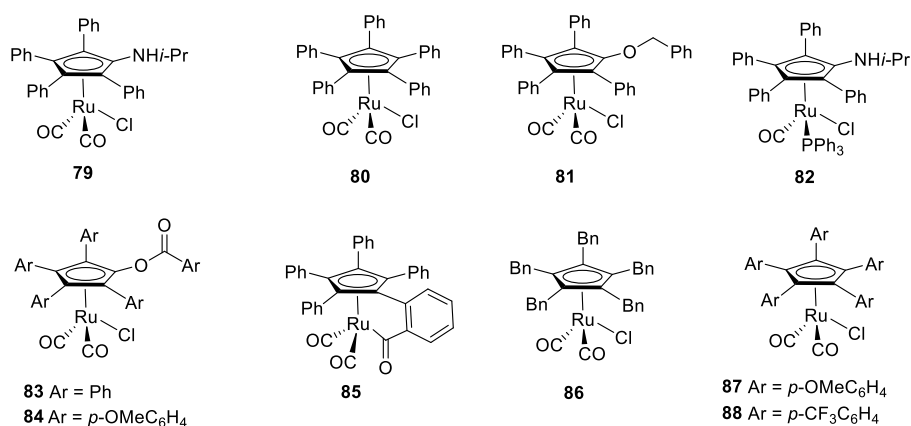
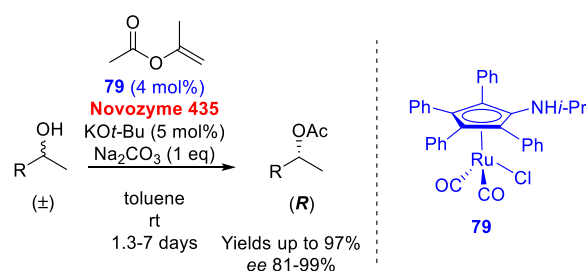


Figure 19. Ruthenium-based racemisation catalysts as developed by Bäckvall,^[229,230] Park,^[231–234] Yuan^[235,236] and Leino.^[237–240]

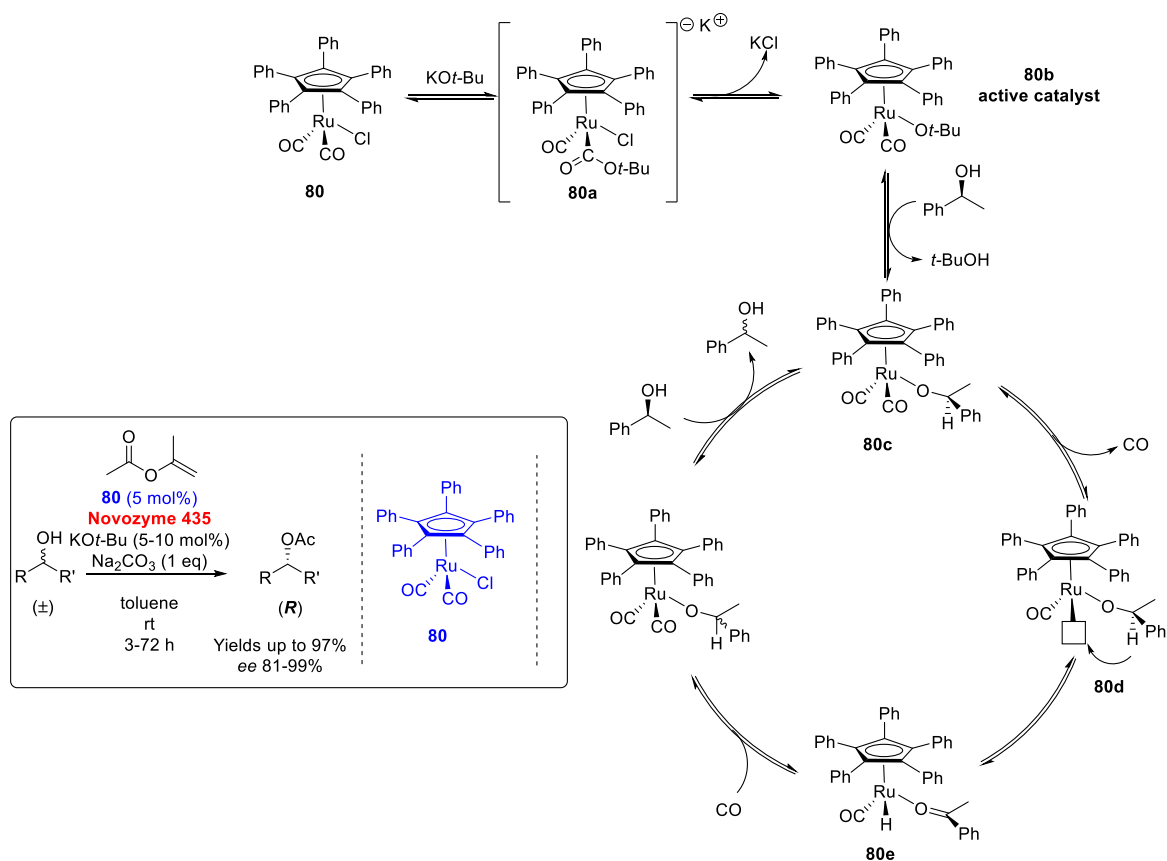
The Park group chose **79** as their optimal catalyst after looking at the effect of various amine substituents and also investigating other variously substituted cyclopentadiene derivatives ligated to the ruthenium centre.^[231,241] While this catalyst was found to effect rapid racemisation of alcohols, its incorporation into a DKR produced a disappointingly slow process, and the addition of one equivalent of Na₂CO₃ was required for complete conversion (Scheme 42).



Scheme 42. Park's room temperature DKR of sec-alcohols with racemisation catalysed by monomeric Ru catalyst **79**.^[231,241]

This process could be carried out at room temperature with activation of the catalyst by addition of a catalytic amount of KOt-Bu, while cheap and readily available isopropenyl acetate could be used as the acyl donor, achieving good yields and *ees* of over 99% for most substrates. The low temperature also allowed the combination of **79** with the (*S*)-selective enzyme Subtilisin Carlsberg to produce *S* configured esters.^[242]

In 2004 the group of Bäckvall also developed a slightly modified monomeric ruthenium-based racemisation catalyst **80**, which has since become commercially available and is one of the fastest ruthenium-based catalysts developed to date.^[220,228,229,243,244]



Scheme 43. Mechanism of racemisation with Bäckvall's catalyst **80** and use in DKR of sec-alcohols in combination with Novozyme 435.^[228,244]

(S)-1-Phenylethanol was racemised in just ten minutes with a 0.5 mol% catalyst loading at room temperature, and the resulting DKR was also very fast, presumably due to better compatibility with the enzyme, allowing isolation of the ester of 1-phenylethanol in 98% yield and 99% *ee* after just three hours. The substrate scope for the DKR was very wide, with aromatic, allylic, benzylic, heteroaromatic and allyl alcohols well tolerated.^[244] After extensive mechanistic studies, the group believe that the reaction proceeds *via* an inner-sphere mechanism, with loss of CO to provide the free coordination site on the ruthenium centre instead of the originally proposed η^5 - η^3 ring slippage.^[228]

Further modifications to the nature of the aromatic groups on the cyclopentadiene in a similar manner to Park (*vide infra*) allowed for faster racemisation depending on the substrate chosen (Figure 20).^[230]

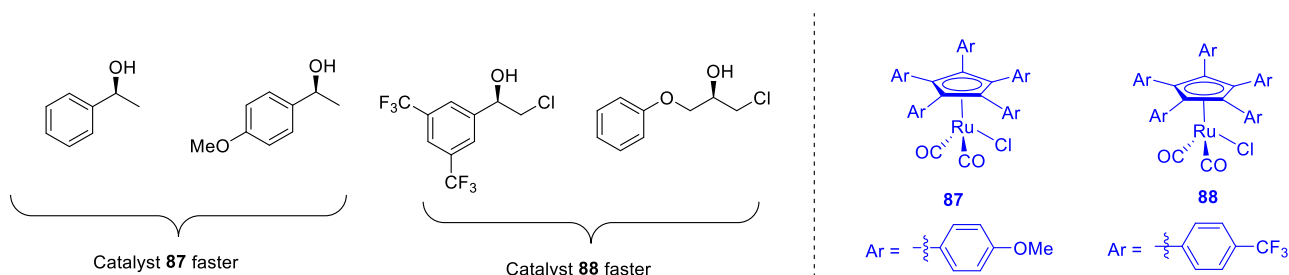
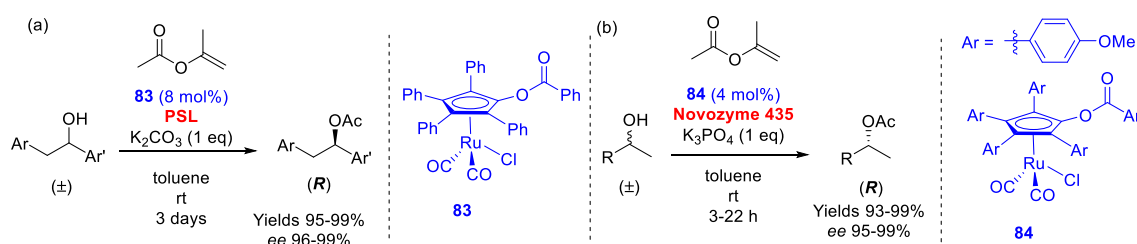


Figure 20. Variation of the electronic properties of racemisation catalysts **87** and **88** and dependence of rate of racemisation on electronic properties of substrate and catalyst.^[230]

It was found that electron-rich aryl groups promoted faster racemisation with electron-rich alcohols, while electron-poor aryl groups on the catalyst were better for electron-poor alcohols.

The Park group has also further developed their series of catalysts with a number of monomeric ruthenium catalysts, including catalysts **81**, **82** and the electronically modified **83** and **84**. In 2005 they reported **81** containing an *O*-benzyl group on the cyclopentadiene ring.^[232] This catalyst was the first example of an air-stable ruthenium racemisation catalyst, and was used in the room temperature DKR of *sec*-alcohols with stoichiometric K₃PO₄ as the activator instead of KO*t*-Bu, although the process was slower than with **80**. Further attempts to increase rate of racemisation and air-stability of the catalyst resulted in **82**, an analogue of **79** with a triphenylphosphine group replacing a CO ligand.^[233] Although Park *et al.* had initially hoped for a catalyst that did not require a base activator, they found that Ag₂O could act as a mild activator, allowing for air-stable DKR of *sec*-alcohols in 8-20 hours.^[233] Final modifications to the core catalyst structure included a benzoyl group instead of a benzyl on the cyclopentadienyl ring in **83** (Ar = Ph) and **84** (Ar = 4-OMe-Ph). While **83** had similar activity and air stability to **81**, it was much easier to synthesise in higher yields and was used successfully in the first example of a DKR of 1,2-diarylethanols using *Psuedomonas stutzeri* lipase (PSL) as Novozyme 435 is not active for 1,2-diarylethanols (Scheme 44, a).^[245]

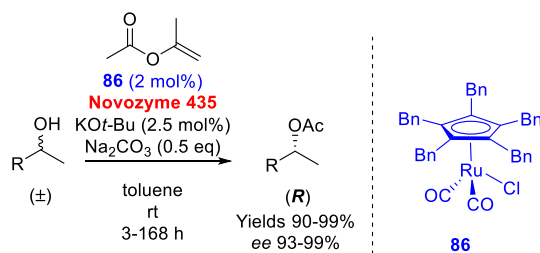


Scheme 44. (a) Park's DKR of 1,2-diarylethanols with racemisation catalysed by **83**.^[245] (b) Fast, air-stable DKR of *sec*-alcohols with racemisation catalysed by **84**.^[234]

As part of their optimisation studies, the group looked at varying the electronics on the aromatic rings of catalyst **83**.^[234] From numerous combinations, they found that having all *para*-methoxyphenyl groups gave the fastest rate of racemisation for (*S*)-1-phenylethanol, reportedly faster than Bäckvall's **80**. Catalyst **84** was used in the DKR of a number of *sec*-alcohols (Scheme 44, b), providing very similar yields and *ees* as **80** in the same time *in an ambient atmosphere*. Interestingly, electron-withdrawing groups such as 4-fluorophenyl and pentafluorophenyl groups on the catalyst gave lower rates of racemisation for (*S*)-1-phenylethanol, although as seen from work by Bäckvall since then, this trend might be reversed for electron-poor substrates.^[230]

Yuan *et al.* reported a ruthenium racemisation catalyst without a halide ligand (**85**), a fundamentally different structure from those seen before, with one of the phenyl groups on the cyclopentadienyl directly coordinated to the ruthenium centre.^[235,236] This catalyst was shown to be active in the DKR of *sec*-alcohols and had a wide substrate scope tolerating sulfonyl groups and phosphonates.

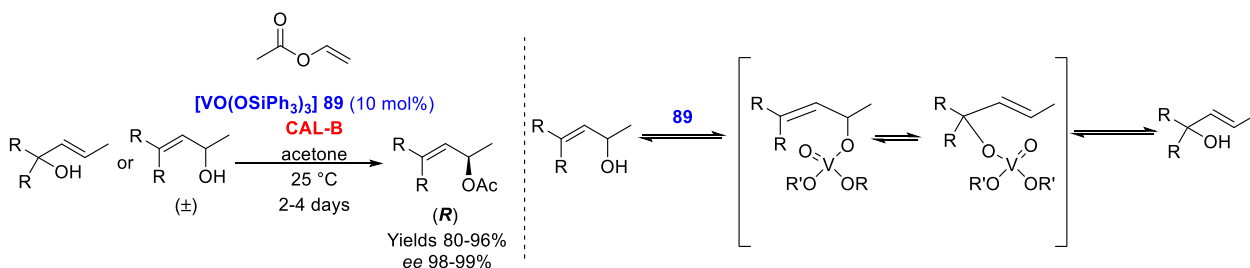
More recently, Leino *et al.* reported the racemisation catalyst **86** which is a modification of catalyst **80** with benzyl groups instead of phenyl groups on the cyclopentadiene.^[237–240] This catalyst has the advantage over catalyst **80** of having a facile large scale method of preparation,^[238,239] as well as increased stability (although not air stability). The benzyl groups were postulated to be hindering access to the metal centre thereby reducing catalyst decomposition by hydrolysis.^[238] The wide substrate scope of this catalyst is directly comparable to that of **80**, with generally faster rates of DKR and higher yields with half the catalyst loading (Scheme 45).^[237]



Scheme 45. Leino's rapid DKR of *sec*-alcohols with racemisation catalysed by **86**.^[237]

Detailed kinetic studies comparing the electronic structures of Bäckvall's **80** and Leino's **86** by NMR spectroscopy and cyclic voltammetry found that **80** was inherently more electron-poor, while **86** was more electron-rich.^[240] As has been seen before, this has a direct relationship with the rate of racemisation of electron-poor or electron-rich substrates, such that **86** is more efficient than **80** for electron-rich substrates while **80** is more efficient for electron-poor substrates.

While homogeneous ruthenium-based racemisation catalysts are most commonly used in DKRs, other types of homogeneous catalyst have also been used. In 2006, Akai *et al.* first described the DKR of allylic alcohols with a vanadium complex $[\text{VO}(\text{OSiPh}_3)_3]$ **89** as the racemisation catalyst (Scheme 46).^[246]

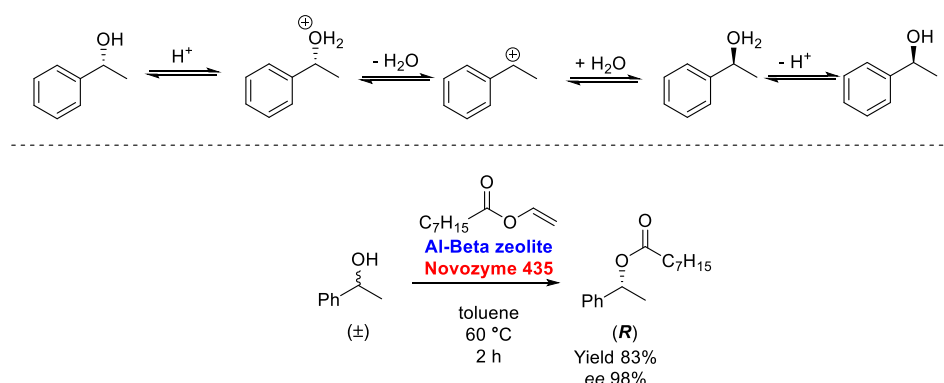


Scheme 46. Akai's DKR of allylic alcohols with racemisation catalysed by $[\text{VO}(\text{OSiPh}_3)_3]$ **89**.^[246]

The oxovanadium(V) complex **89** can catalyse the 1,3-isomerisation of allylic alcohols, and thus can also racemise chiral *sec*-allylic alcohols. This was combined with CAL-B and vinyl acetate at room temperature to achieve an efficient DKR, starting either from a *sec*-alcohol or from a *tert*-alcohol, which can easily be obtained by reduction of the corresponding ketone. In further work, supporting the vanadium catalyst on mesoporous silica enabled better separation of the lipase and metal catalyst as well as better racemisation activity than for the non-supported vanadium analogue.^[247]

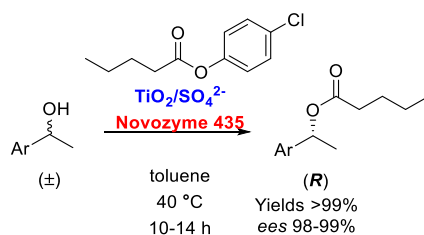
Also in 2006, Berkessel *et al.* reported the use of an aluminium/binol complex and Novozyme 435 in the DKR of various *sec*-alcohols, although different acyl donors had to be used for each substrate.^[248] Feringa's group demonstrated that a moisture-tolerant iridium-based catalyst could also be used for DKR, notably for the DKR β -haloalcohols *via* formation of the corresponding epoxide with a haloalcohol dehalogenase enzyme.^[249] Iridium was also used by Corberan and Peris to achieve the DKR of primary alcohols *via* reduction of the corresponding aldehyde with their iridium catalyst and KR with Amano lipase PS-D I, albeit with low yields and *ees*.^[250] Finally Bäckvall has also reported the first DKR of axially chiral allenes with a NHC-palladium dimer catalyst [$\text{Pd}(\text{IPr})\text{Br}_2$]₂ and porcine pancreatic lipase (PPL).^[251]

A number of heterogeneous catalysts also exist for the racemisation of alcohols, although processes that require separation of the catalytic species in any form will be discussed later. In 2007, Jaenicke *et al.* developed a one-pot method for the DKR of alcohols, using metal-doped acid zeolites for racemisation and Novozyme 435 as the acylation catalyst.^[252] While acid zeolites are usually active in water, an alternative synthesis and doping with zirconium or aluminium was found to provide hydrophobic zeolites, which could be combined with the enzyme and larger acyl donors such as vinyl butyrate or vinyl octanoate to achieve the DKR of 1-phenylethanol (Scheme 47).



Scheme 47. Jaenicke's DKR of 1-phenylethanol^[252] and mechanism of racemisation with acid zeolites as described by Jacobs.^[253]

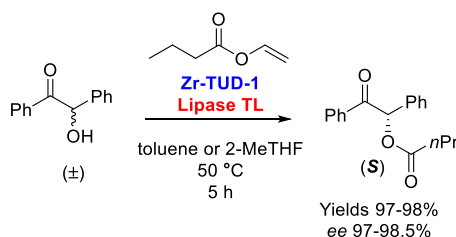
In 2013 the group of Yang developed the DKR of a number of *sec*-alcohols using Novozyme 435 and an inexpensive super acid racemisation catalyst $\text{TiO}_2/\text{SO}_4^{2-}$.^[254] Previous work using alternate acid catalysts had found that these could eventually dissolve in the solvent and thus deactivate the enzyme,^[255] while Yang's catalyst did not exhibit this problem. $\text{TiO}_2/\text{SO}_4^{2-}$ was found to be compatible with the lipase and a large number of substituted phenylethanols could be efficiently resolved, while the catalyst could be recycled up to ten times without any loss in activity or ester *ee* (Scheme 48).^[254]



Scheme 48. Yang's DKR of sec-alcohols using super acid $\text{TiO}_2/\text{SO}_4^{2-}$ for racemisation.^[254]

More recent work by Yang in 2014 found an even more efficient racemisation catalyst in the form of sulfonated sepiolite, a readily available and cheap mineral. This catalyst was active at 25 °C, and could thus in theory be combined with the other more temperature-sensitive enzymes apart from Novozyme 435.^[256]

In 2014, Ansorge-Schumacher *et al.* reported the one-pot DKR of benzoin.^[257] An acidic mesoporous silicon-based framework with incorporated metal was studied as the racemisation catalyst (Zr-TUD-1, Si/Zr = 25), while the commercial *Pseudomonas stutzeri* lipase (Lipase TL) was the acylation catalyst. These catalytic systems were successfully combined, with excellent yields and *ees* reported (Scheme 49).

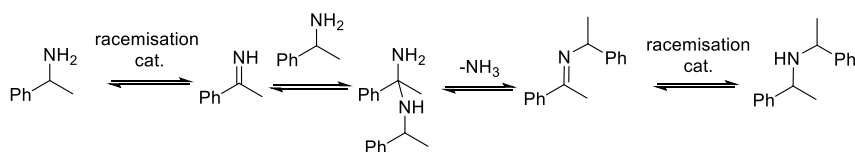


Scheme 49. Ansorge-Schumacher's DKR of benzoin using **Zr-TUD-1** as racemisation catalyst.^[257]

Further research on developing this work into a continuous process is detailed in the next chapter.^[258]

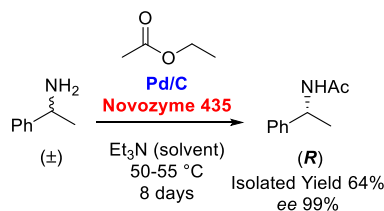
1.2.6.3 Amine DKR

Mirroring the situation for standard KR processes, enzymatic amine DKR poses additional challenges relative to those encountered for alcohol DKR. Firstly, the number of mild racemisation catalysts available is much reduced as amines can be strong coordinating ligands for metals, thus reducing the activity of the catalyst at lower temperatures. Secondly, imines formed by dehydrogenation can act as electrophiles for the substrate amines forming side products in the reaction (Scheme 50).



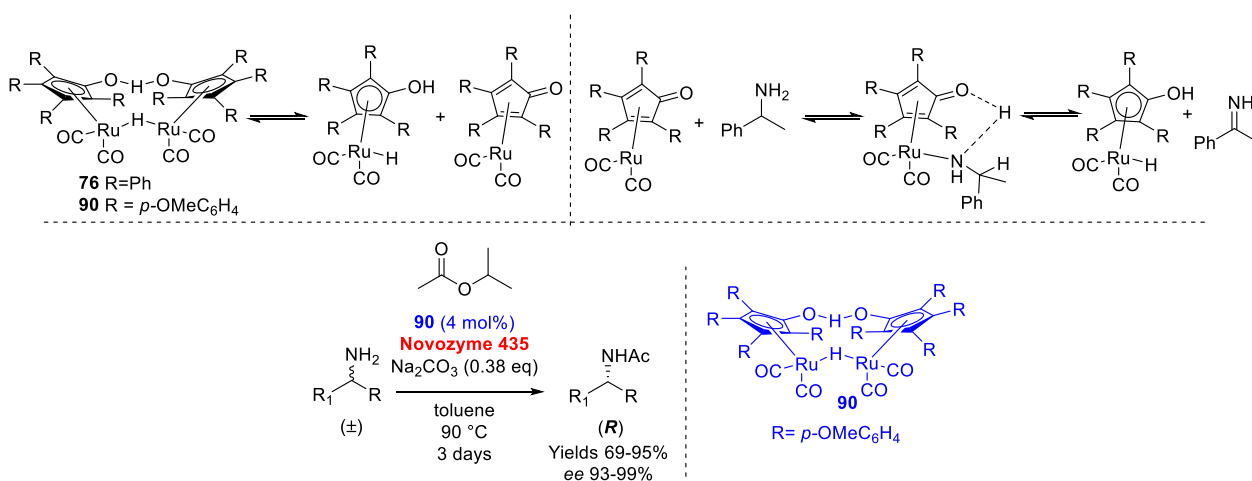
Scheme 50. Formation of dimeric side-products during catalysed racemisation of primary amines by coordination to Ru catalyst and loss of ammonia as described by Bäckvall.^[259]

The first example of the DKR of amines was published by Reetz and Schimossek in 1996, combining CAL-B with a Pd/C racemisation for the DKR of 1-phenylethylamine (Scheme 51).^[217]



Scheme 51. Reetz and Schimossek's DKR of 1-phenylethylamine using Pd/C as racemisation catalyst.^[217]

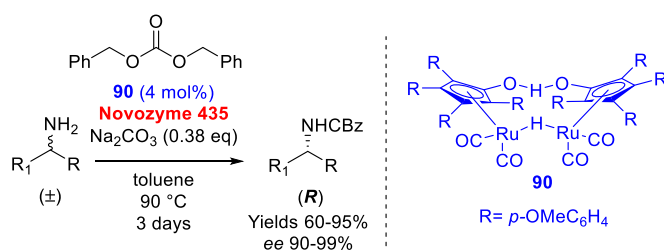
The reaction was however found to be very slow and only 60% conversion was obtained after 8 days, with large amounts of side-product formation. In an attempt to improve this result, Bäckvall *et al.* found that the Shvo catalyst **76** can be used to catalyse the racemisation of amines at 110 °C^[259] (Scheme 52).



Scheme 52. Bäckvall's racemisation of primary amines by Shvo catalyst **76** ($R=\text{Ph}$) and analogue **90** ($R=p\text{-OMeC}_6\text{H}_4$) and the use of catalyst **90** for the DKR of amines.^[259,260]

The very high temperatures required did not allow the combined use of an enzyme and therefore only a stepwise DKR was possible.^[259] Later modifications to the catalyst however, changing a phenyl group to a *para*-methoxyphenyl group (**90**) allowed lower temperature (90 °C) racemisation and therefore a one-pot DKR of primary amines was developed in combination with the temperature stable Novozyme 435 (Scheme 52).^[260]

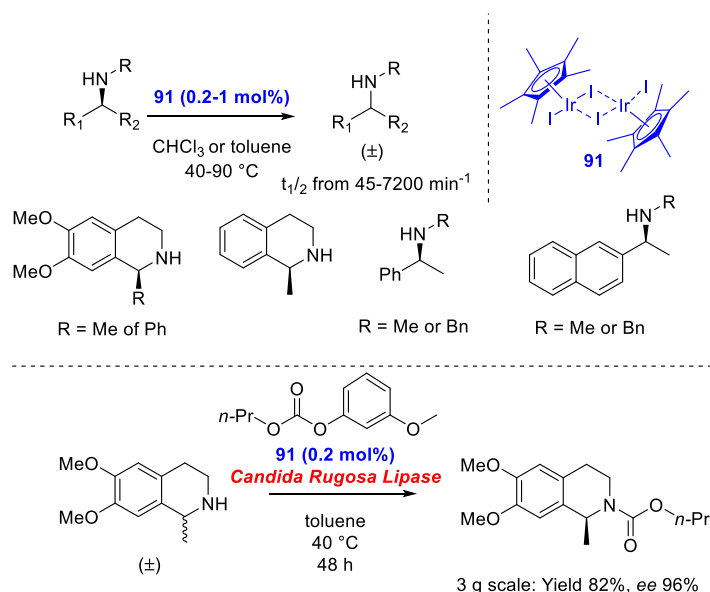
One of the drawbacks associated with the above procedure is the formation of amides as products; as indicated previously, these require high temperatures and harsh conditions for deprotection. Bäckvall therefore developed a procedure wherein dibenzyl carbonate is used as the acyl donor to form carbonates in high yield and *ee* (Scheme 53).^[261,262]



Scheme 53. Bäckvall's DKR of primary amines using the Shvo catalyst analogue **90** ($R=p\text{-OMeC}_6\text{H}_4$) to effect racemisation and using a carbonate acyl donor to form carbamate products.^[261,262]

This procedure was used for a number of substituted benzylic amines, as well as non-aromatic substrates, and was shown to be effective in the DKR of a precursor of nersertraline (70% yield, 99% *ee*), a drug in clinical trials at the time for the treatment of CNS disorders.^[262] A large scale (10 mmol) procedure for the resolution of 1-phenylethylamine with this catalyst was also recently developed.^[263]

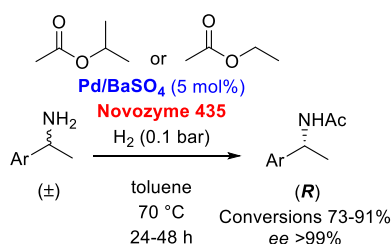
Page *et al.* developed an iridium-based amine racemisation catalyst, based on an observation that the *ee* of an isoquinoline substrate decreased during attempted transfer hydrogenation with the chloride analogue of catalyst **91**.^[264] The iridium-iodo complex **91** gave faster rates of racemisation, and this catalyst was found to be effective for racemisation of a number of amines (Scheme 54).



Scheme 54. Blacker's racemisation of *sec*-amines by iridium dimer **91** and DKR of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline when used in combination with *Candida Rugosa* lipase.^[264,265]

The procedure was found to be successful for a number of *sec*-amines with isoquinolines giving the fastest rates of racemisation, while primary amines were found to give mostly dimeric impurities *via* the imine (see Scheme 50 for mechanism). Catalyst **91** was successfully combined with *Candida Rugosa* lipase for the successful large scale DKR of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, forming an easily deprotected carbamate in 82% yield and 96% *ee*.^[264,265]

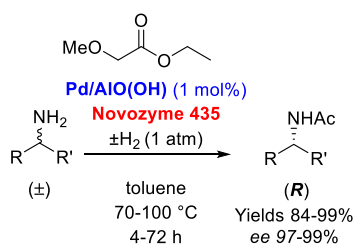
Since the pioneering work of Reetz and Schimossek, a number of others have looked at the DKR of amines using heterogeneous palladium based catalysts and heterogeneous DKR racemisation catalysts have recently been reviewed by de Vos.^[266] In 2005, the group of Jacobs and De Vos looked at varying the palladium support of palladium catalyst and found that alkaline earth supports (e.g. Pd/BaSO₄, Pd/CaCO₃, Pd/BaCO₃) all gave superior results in terms of selectivity for the amine compared to Pd/C.^[267] The likely mechanism proceeds *via* dehydrogenation of the amine and hydrogenation of the resulting imine. They propose that the increased selectivity with these supports is due to reduced condensation of the amine with the imine. Combination of the most selective of these supports (Pd/BaSO₄) with *Candida Antarctica* lipase B (Novozyme 435) in a DKR gave good yields and *ees* for a number of different aromatic amines (Scheme 55).^[267,268]



Scheme 55. Jacobs' DKR of aromatic amines using Pd/BaSO₄ as the racemisation catalyst.^[267,268]

In 2008 the group found that using microwave irradiation instead of conventional heating gave better selectivity for the amine and faster reaction times, with amine DKRs carried out in 90 minutes or less, yields of over >80% and *ees* between 95-98%.^[269] Further changes to the palladium support found that the even more basic 3-aminopropyl or 3-(1-piperazino)propyl functionalised silica support gave the best results in the DKR of 1-phenylethylamine, with good yields (>90%) and high *ee* (>99%) obtained in 24 hours.^[270] Although these processes were only applicable to aromatic amines, Jacobs *et al.* found Raney nickel was an efficient racemisation catalyst in the DKR of aliphatic amines.^[271]

Park *et al.* also developed an alternative palladium support for the DKR of amines, using a palladium nanocatalyst entrapped in aluminium hydroxide (Pd/AlO(OH)), in combination with Novozyme 435.^[272] A number of benzylic and aliphatic amines, as well as one example of an amino acid amide were successfully used in the DKR (Scheme 56).^[272]

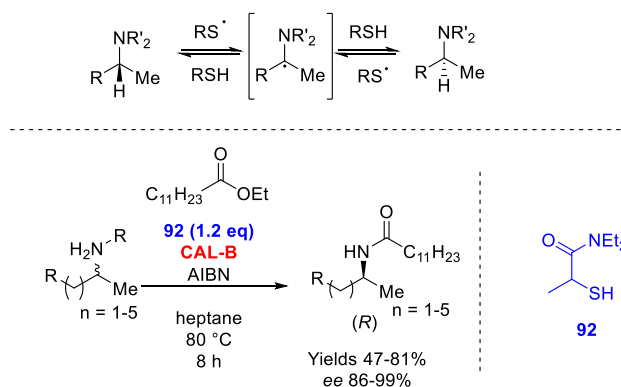


Scheme 56. Park's DKR of aromatic and aliphatic amines using a palladium nanocatalyst Pd/AlO(OH) for racemisation.^[272]

Reactions with aromatic amines were run at 70 °C with an argon atmosphere over 3 days, while aliphatic amines were run at 100 °C with a hydrogen atmosphere over 4 hours. Both the Pd catalyst and the lipase could also be recovered and recycled up to eight times without a reduction in conversion and only small loss in *ee* (1% loss per new run).

Andrade *et al.* also applied Pd/BaSO₄ to the DKR of selenium-containing amines,^[273] while Aron *et al.* found that a Zn(OAc)₂/picolinaldehyde complex and Subtisilin protease (Alkalase) could be used in the DKR of amino acid esters.^[274]

Recently a metal-free method for the DKR of amines has been reported by Gil and Bertrand. After the development of a thionyl radical amine racemisation,^[275,276] in 2007 they reported the first combination of this with an enzyme, specifically the DKR of alkyl amines with CAL-B (Scheme 57).^[277]



Scheme 57. Bertrand's DKR of alkyl amines using thionyl radical **92** for racemisation.^[277,278]

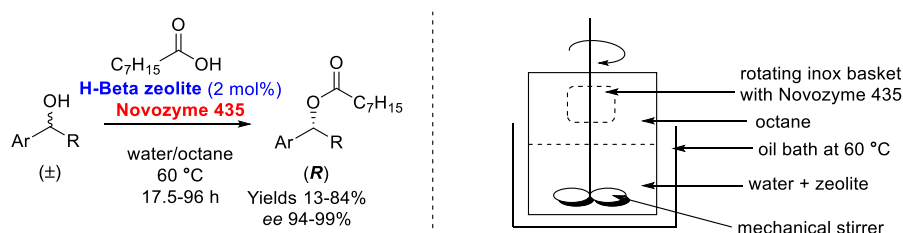
Since this work Bertrand *et al.* have developed a low temperature (30 °C) method for the racemisation of amines^[278] and have applied this to the (*S*)-selective DKR of aliphatic amines^[279,280] which is inherently more challenging as (*S*)-selective proteases are much less temperature stable than the (*R*)-selective lipase commonly used, whilst also developing an (*R*)-selective low temperature (40 °C) DKR process with CAL-B.^[281]

1.2.6.4 Catalyst Compartmentalisation and Flow in DKR Processes

While the above discussion has highlighted notable successes in the development of DKR procedures, the challenges associated with developing new DKR processes are still numerous. In particular, mutual catalyst incompatibility or interference is a significant challenge for many processes, as are accommodating their respective reaction rates and different temperature and/or solvent requirements. A possible solution to these problems is compartmentalisation of the two catalysts to avoid interference, and various methods have been developed to achieve this separation, including membrane separation, biphasic systems and catalyst immobilization/encapsulation.

1.2.6.4.1 One-pot Catalyst Compartmentalisation

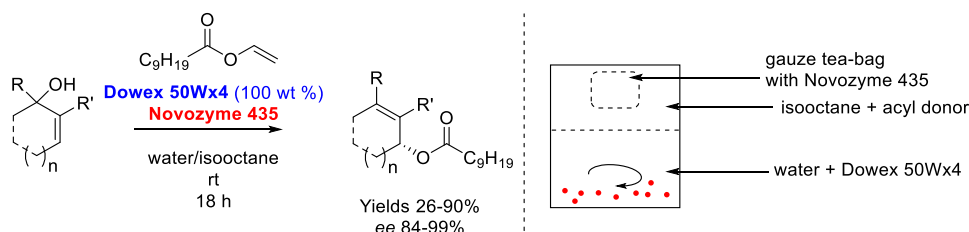
In 2003, De Vos and Jacobs published the first example of a biphasic DKR with chemo- and enzymatic catalysts,^[282] combining acid zeolites for racemisation (Scheme 58)^[253] with Novozyme 435 for acylation. While the zeolites are active in aqueous solutions, the enzyme requires an organic phase and therefore a biphasic system was designed, with the enzyme suspended in an inox basket in the organic phase to limit contact with the aqueous solution. This system was applied to the DKR of a number of *sec*-benzylic alcohols with good yields and excellent *ees* for most substrates (Scheme 58).^[253,282]



Scheme 58. Jacobs' biphasic DKR system with racemisation by acid zeolites.^[253,282]

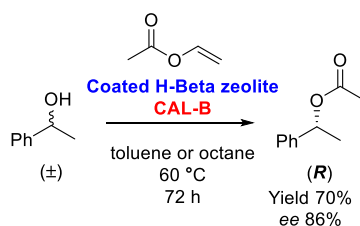
Jacobs *et al.* also used a heterogeneous vanadyl sulfate catalyst (VOSO_4) in combination with Novozyme 435 for the DKR of 1-phenylethanol.^[283] While the reaction was conducted in octane, the immobilised lipase had to be suspended in a basket in a similar manner to previous work (Scheme 58) in order to minimise contact between the enzyme and the vanadyl sulfate, and a yield of 93% with 99% *ee* was achieved for 1-phenylethanol in 3.5 hours.

In 2014 Bäckvall used a similar biphasic/enzyme suspended method to achieve the migratory DKR of carbocyclic allylic alcohols, with the enzyme suspended in a gauze 'tea-bag' in the organic layer (Scheme 59).^[284]



Scheme 59. Bäckvall's biphasic DKR of carbocyclic allylic alcohols with Novozyme 435 contained in a catalytic tea-bag and racemisation catalysed by Dowex 50Wx4.^[284]

An alternative catalyst compartmentalised one-pot approach was developed by Masters *et al.* for the DKR of 1-phenylethanol.^[285] Here CAL-B was again used as the enzyme and an acid zeolite was used as the racemisation catalyst. As enzymes are usually sensitive to acids, the zeolite (Zeolite H-Beta) was enclosed in a polyelectrolyte nanocapsule, which allows small molecules such as the alcohol to permeate through but not macromolecules such as the enzyme.



Scheme 60. Masters's DKR of 1-phenylethanol using an encapsulated zeolite racemisation catalyst.^[285]

The rate of racemisation with the encapsulated zeolite was studied and found to be only slightly slower than the free zeolite, and the DKR provided the ester with a 70% yield and 86% *ee*.

1.2.6.4.2 Continuous or Semi-continuous Flow DKR

An alternative potential solution to the challenges associated with developing a DKR is to compartmentalise the catalysts in a flow processes. Flow chemistry can be advantageous over batch chemistry with regards to efficiency, reproducibility and volume of production possible. The following is a brief overview of the field of continuous or semi-continuous DKRs.

Livingston *et al.* used their expertise on organic solvent stable nanofiltration (OSN) membranes to develop a membrane-enhanced DKR (MEDKR) process for the synthesis of enantioenriched 1-phenylethylamine.^[286] While work towards this goal was initially hampered by the base-lability of the OSN membranes,^[287] by evolving a two-step DKR process from Bäckvall^[259] and using a microfiltration membrane to retain the temperature-sensitive enzyme acylation catalyst, a DKR of 1-phenylethylamine was achieved (Figure 21).

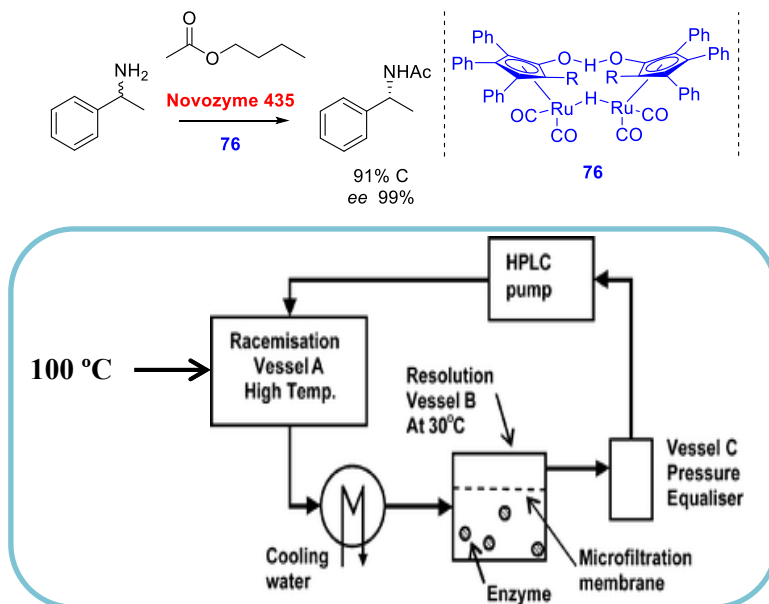


Figure 21. Schematic and reaction scheme of Livingston's MEDKR process for the DKR of 1-phenylethylamine.^[286]

The acylation catalyst used in this process was the enzyme CAL-B immobilised as Novozyme 435, while the racemisation catalyst was the commercially available Shvo catalyst **76**. While the enzyme preferred lower

temperatures (30°C), the racemisation catalyst was only active at higher temperatures (>90 °C). In this process, both catalysts could operate at their optimal temperatures, as the enzyme was retained by the microfiltration membrane, and the ruthenium catalyst could travel round the system to reach the high temperature reaction vessel. Butyl acetate was used as the acyl donor instead of ethyl acetate, as the boiling point of this is higher and closer to that of toluene. After 72 hours, the reaction proceeded to 91% conversion and 99% *ee* of the amide, with proof of both an efficient racemisation and KR, although isolated yields after this process were poor and only 55% of the mass balance was recovered.

Miranda *et al.* also used a semi-continuous loop system to separate the Novozyme 435 used as an acylation catalyst and the Pd/BaSO₄ racemisation catalyst in order to achieve a continuous flow DKR of 1-phenylethylamine (Figure 22).^[288]

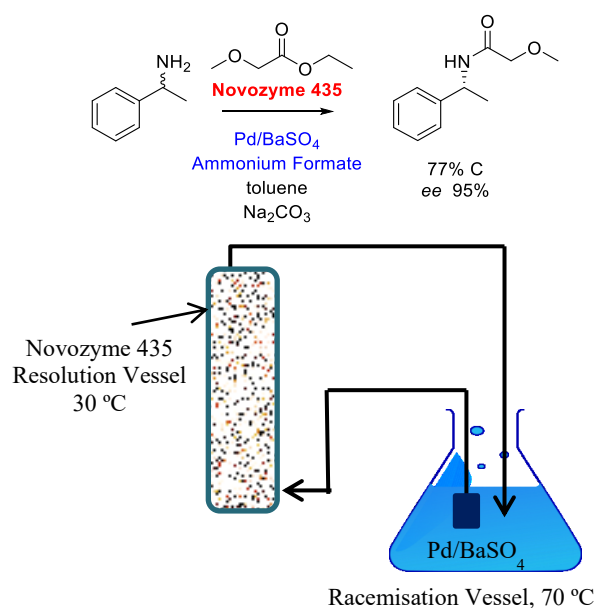


Figure 22. Schematic and reaction scheme of Miranda's semi-continuous process for the DKR of 1-phenylethylamine.^[288]

In this system a filter was used to exclude the Pd catalyst from the packed bed Novozyme 435 reactor, while a syringe pump was used to achieve the desired flow, and the two chambers were again at different temperatures (room temperature for the acylation, 70 °C for the racemisation). After ten hours, with 15 mol% of Pd catalyst, the amide was obtained in 77% yield and 95% *ee*, although only a 1% increase in conversion was observed in the last two hours. Interestingly, a one-pot DKR at 70 °C using these catalysts was also successful, with the amide obtained in 94% yield and 99% *ee*, albeit with a 30 mol% Pd catalyst loading.

Iborra *et al.* used ionic liquids to encapsulate and thus separate the acylation catalyst Novozyme 435 and racemisation catalyst zeolite CBV00 to achieve a DKR.^[289] By charging the two coated catalyst particles into a catalyst chamber, a flow system was developed with supercritical CO₂ as the carrier for the DKR of 1-phenylethanol (Figure 23).

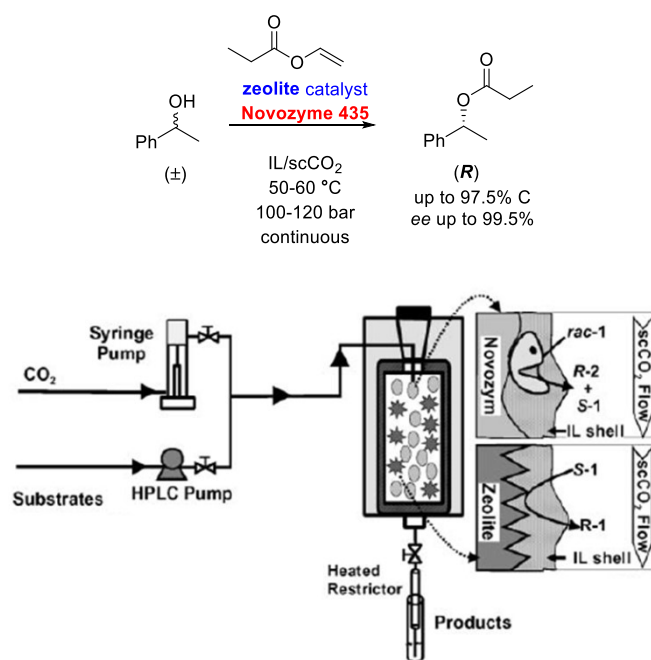


Figure 23. Iborra's continuous DKR of 1-phenylethanol using encapsulated zeolite and enzyme catalyst.^[289]

This process was operated for 9 days, with ester *ee* values up to 99.5% and conversion to the ester of up to 97.5%. To our knowledge this is the most successful example of a truly continuous chemoenzymatic acylative DKR process.

In 2005, Bornscheuer *et al.* developed a two-compartment process for the DKR of an α -hydroxy ketone.^[290] While they initially set out to develop a one-pot process, they found that the acidic resin (Amberlyst 15) they were using for the racemisation inhibited the activity of the acylation enzyme CAL-B as well as forming side-products with the vinyl butyrate acyl donor. As no compatible conditions could be found, they developed a two-pot process with a pump loop between the two systems, one vial containing the immobilised enzyme while the other contained the acidic resin (Figure 24).^[290]

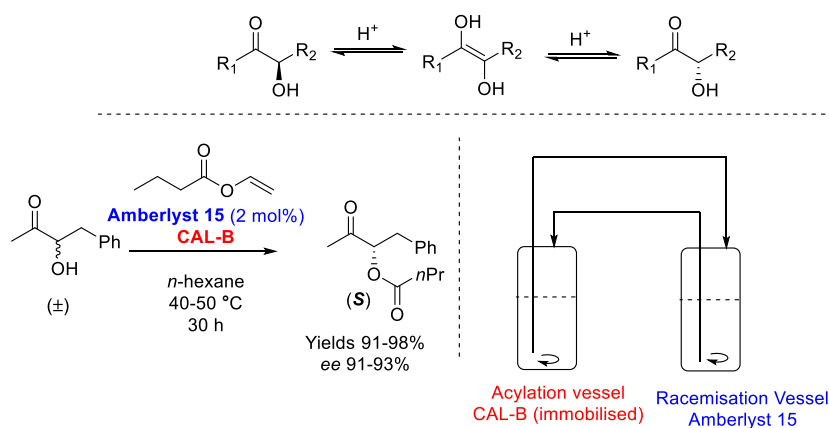
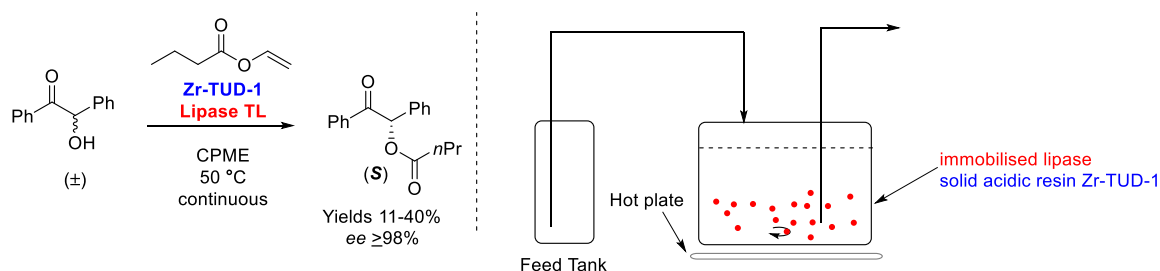


Figure 24. Bornscheuer's two-pot DKR of an α -hydroxy ketone.^[290]

The KR was run for 15 hours at 40 °C before starting the pumps to the racemisation vessel and increasing the temperature to 50 °C for a further 15 hours, providing excellent yields and *ees* of the α -hydroxy ester ketone in two different runs. This system also demonstrates the utility of a two-pot process in combining incompatible catalysts.

Based on their one-pot work for the DKR of benzoin,^[257] Ansorge-Schumacher and Kara have worked towards developing a continuous flow process.^[258] Desiring a more environmentally friendly solvent as compared to toluene and 2-MeTHF, CPME was found to give better results in a batch DKR of benzoin, and was therefore used in the continuous DKR (Scheme 61).

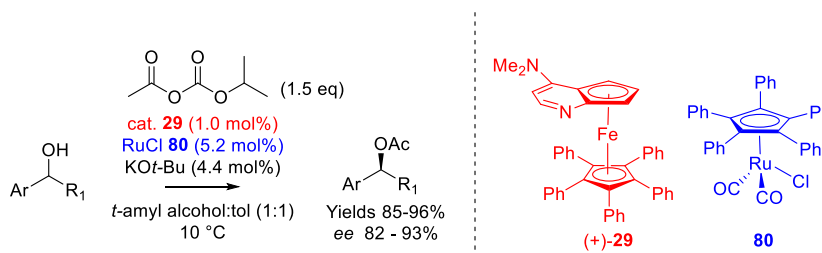


Scheme 61. Kara and Ansorge-Schumacher's continuous set-up for the DKR of benzoin.^[258]

They found that although a conversion of 40% was achieved after the first 2.5 hours, this gradually decreased over the next 74 hours to only 11% conversion at the end of the reactor, thus requiring further optimisation, although the *ee* of the ester was consistently high (>98% *ee*).

1.2.7 Non-enzymatic DKR of Amines and Alcohols

While the field of enzymatic acylative DKR of both amines and alcohols has expanded in recent years, to our knowledge there is only one example to date of a one-pot acylative *non-enzymatic* acylative alcohol DKR published by Fu *et al.* in 2012. To achieve this impressive feat, Fu used chiral 4-DMAP (+)-**29** in combination with Bäckvall's racemisation catalyst **80** which, following activation using KO*t*-Bu, effected *in situ* racemisation of the substrate *sec*-alcohols and allowed the resolved ester products to be obtained in isolated yields of 85-96% with *ees* of 82-93% (Scheme 62). The stereoconvergent acetylation of a diol was also demonstrated using this system.^[291]



Scheme 62. Fu's non-enzymatic acylative DKR of *sec*-alcohols using acylation catalyst **29** and racemisation pre-catalyst **80**.^[291]

It should be noted that, while the above is the only example to date of a non-enzymatic acylative DKR of alcohols, many other non-enzymatic dual-catalytic processes exist in the literature for the formation of enantioenriched products. Recent reviews by Macmillan^[292] and Shao^[293] highlight the wide variety of systems that are available, starting mostly from aldehydes/ketones, enones and imines; with chiral enamine formation or chiral hydrogen-bonding catalysis a common feature.

2 Previous Work

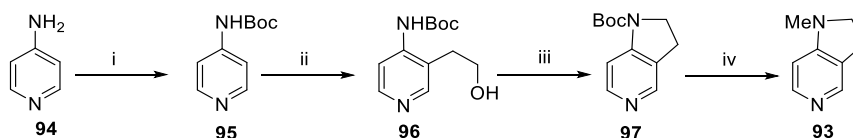
2.1 Alcohol KR

2.1.1 Development of Dibutylaminopyridine

2.1.1.1 Detailed Development and Synthesis of Atropisomeric Catalysts

Further to the brief mention above, the following is a summary of the development and synthesis of the Spivey atropisomeric catalysts for acylative KR. Many previous members of the group have worked on these compounds, including Tomasz Fekner,^[118–120,294] Stephen G. Davey,^[121,122] David P. Leese,^[118,122] Fujiang Zhu,^[121,122] Stellios Arseniyadis,^[118,295,296] Mahesh Mohan^[102,207,208] and Kerti Ausmees.^[297]

The Spivey approach to install chirality onto 4-DMAP-based catalysts is through the presence of restricted rotation around an aryl-aryl bond, positioned in the 5-position of the pyridine ring.^[119,120] Early efforts focused on azaindoline-based catalysts, as it was hypothesised that the restricted rotation around the C_{Ar}-N bond would contribute towards the barrier of rotation of the biaryl axis.^[120] The synthesis of the azaindoline core **93** began from commercially available aniline (Scheme 63).^[120]

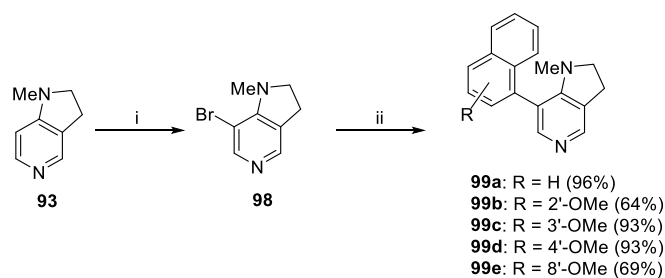


Scheme 63. Spivey's synthesis of *N*-methyl-1-azaindoline **93**.^[120]

Reagents and Conditions: (i) Boc_2O , DCM, rt, 45 min (99%); (ii) $t\text{-BuLi}$, THF, -78°C to rt, 2 h, $\text{Br}(\text{CH}_2)_2\text{OLi}$, -78°C to rt, 2 h (66%); (iii) MsCl , Et_3N , CH_2Cl_2 , -10°C to rt, 2 h (99%); (iv) DIBAL, DCM, 0°C to reflux, 20 h (55%).

Aniline **94** was Boc-protected, before deprotonation by *tert*-butyllithium and addition of 2-bromoethanol to form **96**. Functionalisation with mesityl chloride allowed for an *in situ* ring closure, before reduction of the Boc group to yield *N*-methyl -1-azaindoline **93**.

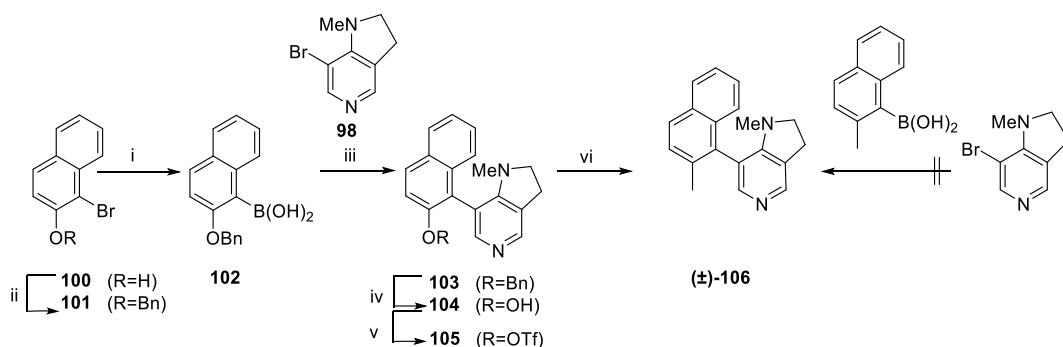
Bromination of azaindoline **93** followed by a cross-coupling with various aryl boronic acids yielded the first examples of atropisomeric azaindoline based catalysts **99a–99e** (Scheme 64).^[120]



Scheme 64. Spivey's synthesis of biaryls **99a–99e** using aryl boronic acids.^[120]

Reagents and Conditions: (i) NBS, DMF, 0°C , 90 min (81%); (ii) $\text{ArB}(\text{OH})_2$, Na_2CO_3 , $\text{Pd}(\text{PPh})_3$, toluene, H_2O , EtOH , reflux, 2–24 h.

Good yields were obtained for the less hindered substrates (**99a**, **99c** and **99d**) while for the more hindered boronic acids (**99b** and **99e**) higher loadings of both the catalyst and the boronic acid were required. Computer simulation however, showed that biaryl **99a** (R = H) had a half-life of only 1.9 minutes at 20 °C, which time scale does not allow for separation into enantiomers.^[120] In order to increase the barrier to rotation, a sterically more demanding naphthyl group (2-methyl-1-naphthalene-boronic acid) could be added to the azaindoline core (Scheme 65). However, all attempts to attach this sterically more hindered naphthyl group proved to be unsuccessful using previous conditions. A modified synthesis using a sterically less demanding 2-benzyloxynaphthyl group was thus employed. The benzyl ether could be cleaved *via* hydrogenolysis to yield the 2-naphthol and further elaborated to the 2-methylnaphthyl moiety (Scheme 65).^[120]

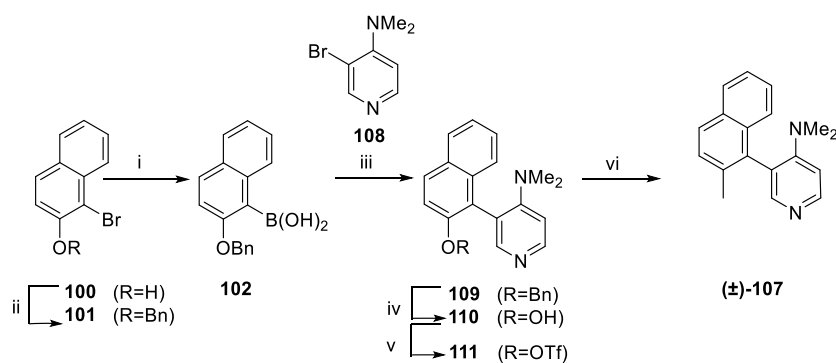


Scheme 65. Spivey's synthesis of atropisomeric biaryl (±)-**106**.^[120]

Reagents and Conditions: *BnBr*, K_2CO_3 , DMF; 60 °C, 5 h, (93%); (ii) *n*-BuLi, $B(OMe)_3$, Et_2O ; -78 °C $\rightarrow$ 0 °C, 17 h; (83%); (iii) $Pd(PPh_3)_4$, Na_2CO_3 , toluene, H_2O , $EtOH$, reflux, 24 h (82%); (iv) Pd/C , H_2 (1 atm), $EtOH$, rt, 5 h; (v) Tf_2O , pyridine; 0 °C, 90 min (93% over two steps); (vi) $MeMgBr$, $NiBr_2(PPh_3)_3$, Et_2O , reflux, 15 h (85%).

The boronic acid required (**102**) was formed easily in two steps from commercially available 1-bromo-2-naphthol *via* *O*-benzylation followed by a lithium-halogen exchange, quenching with trimethyl borate and acidic work-up. This could then be used with previously developed Suzuki cross-coupling conditions to attach the azaindoline core **98**. Removal of the benzyl group followed by triflation allowed for a Kumada-Corriu cross coupling to attach the methyl group yielding biaryl (±)-**106**.

Biaryl **106** proved to be much more stable to racemisation, and indeed it was calculated that only 1% of its optical purity would be lost over one year in solution at room temperature.^[119,120] In order to investigate the effect of the hindered rotation around the C_{Ar} -N bond on the rotational barrier around the biaryl axis, a dimethylaminopyridine analogue of **106** (**107**) was also synthesised starting from a known aryl bromide **108** (Scheme 66).^[120]



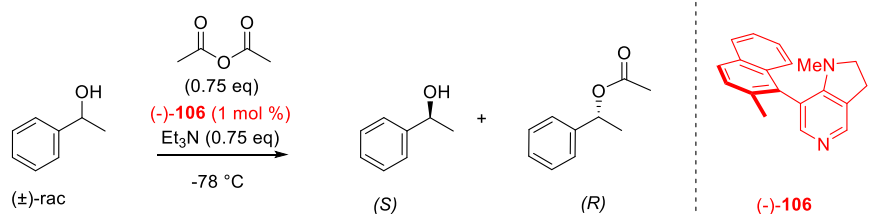
Scheme 66. Spivey's synthesis of atropisomeric biaryl (±)-**107**.^[120]

Reagents and Conditions: *BnBr*, K_2CO_3 , DMF; 60 °C, 5 h, (93%); (ii) *n*-BuLi, $B(OMe)_3$, Et_2O ; -78 °C → 0 °C, 17 h; (83%); (iii) $Pd(PPh_3)_4$, Na_2CO_3 , toluene, H_2O , $EtOH$, reflux, 24 h (13%); (iv) Pd/C , H_2 (1 atm), $EtOH$, rt, 5 h; (v) Tf_2O , pyridine; 0 °C, 90 min (93% over two steps); (vi) $MeMgBr$, $NiBr_2(PPh_3)_3$, Et_2O , reflux, 15 h (85%).

A low-yielding addition of the 5-bromo-4-dimethylaminopyridine **108** during the Suzuki-cross coupling and addition of the methyl group as before yielded (±)-**107**. In fact, it was found that the barrier to rotation for this compound was similar to that of the *N*-methyl-azaindoline biaryl **106**.

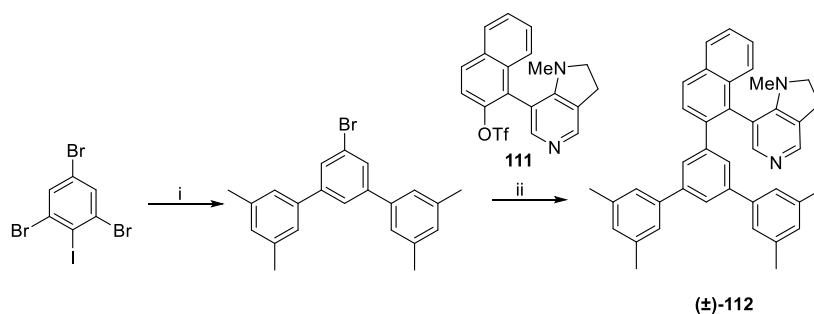
The catalytic activity and selectivity of catalyst **106** was then examined in a KR using 1-phenylethanol in various solvents (Table 10).^[101]

Table 10. Screen of solvents for selectivity with catalyst **106** as examined by Spivey.^[101]



Entry	Solvent	Time (h)	Conversion (%)	Selectivity
1	CH_2Cl_2	2	61	1.3
2	THF	7	33	1.4
3	toluene	8	60	1.5
4	Et_2O	8.4	45	1.3
5	EtOAc	8	44	1.4

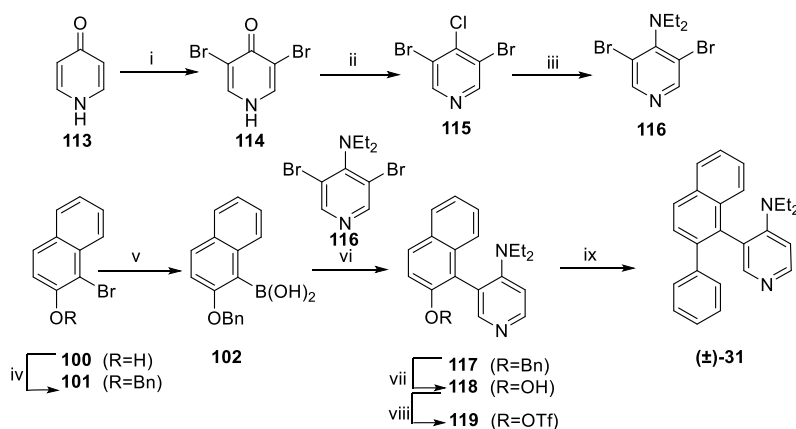
The selectivity however proved to be only 1.3-1.5 depending on the solvent, and therefore in an attempt to increase the selectivity, the terphenyl analogue **112** was synthesised (Scheme 67).^[101]



Scheme 67. Spivey's synthesis of terphenyl-azaindoline catalyst **(±)-112**.^[101]

Reagents and Conditions: (i) 3,5-dimethylphenyl-magnesium bromide, THF, reflux, 17 h (37%); (ii) (a) Mg, I₂, Et₂O, THF, rt to reflux, 30 min; (b) PdCl₂(dppp), Et₂O, THF, reflux, 15 h (19%).

Catalyst **112** was designed to increase the facial differentiation between the front and back faces of the pyridine ring, and this change was hypothesised to increase the selectivity. Catalyst **112** however also exhibited a low selectivity (*s* = 4.7 for 1-(1-naphthylethanol) using similar conditions^[101]). Diethylaminopyridine-based biaryl **31**, henceforth referred to as DEAP*, based on **107** was thus selected as the next catalyst candidate, as it was hypothesised that the diethylaminopyridine core would increase the 'left-from-right' differentiation on the pyridine ring. This was synthesised in a similar way to compound **107** (Scheme 66), albeit starting from 4-pyridone and further functionalisation to 3,5-dibromo-4-diethylaminopyridine before coupling with the boronic acid (Scheme 68).^[101]

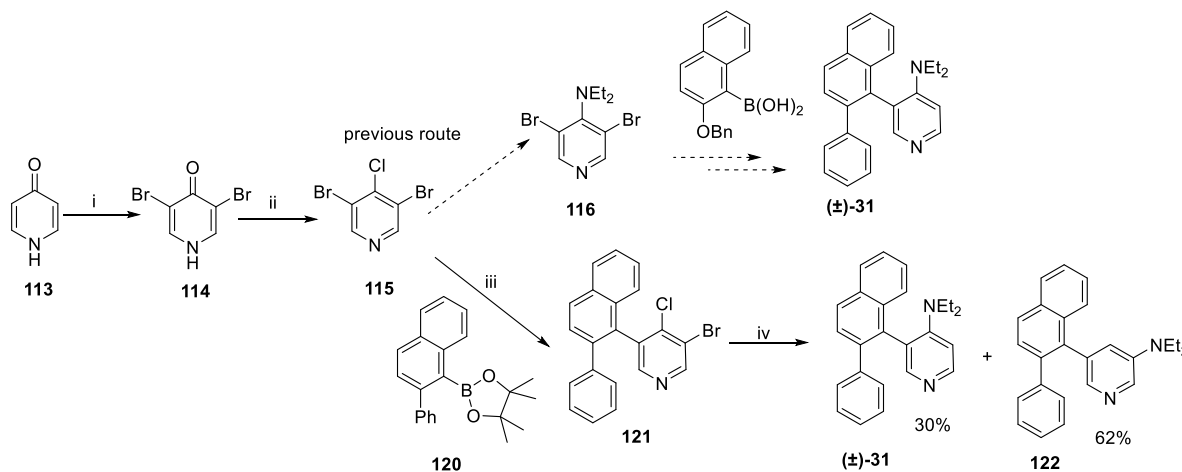


Scheme 68. Spivey's synthesis of diethylaminopyridine-phenyl catalyst **(±)-31**.^[101]

Reagents and Conditions: (i) Br₂, H₂O, 5 h (ii) PCl₅, 160 °C, 3 h (72% over two steps); (iii) Et₂NH, HCONEt₂, 170 °C, 20 h, (94%); (iv) BnBr, K₂CO₃, DMF; 60 °C, 5 h, (93%); (v) *n*-BuLi, B(OMe)₃; -78 °C → 0 °C, 17 h; (83%); (vi) Pd(PPh₃)₄, NaOH, toluene, H₂O, EtOH, reflux, 22 h (59%); (vii) Pd/C, H₂ (1 atm), EtOH, rt, 5 h; (viii) Tf₂O, pyridine; 0 °C, 90 min (76% over two steps); (ix) PhMgBr, PdCl₂(dppp), Et₂O, reflux, 22 h (93%).

Bromination of 4-pyridone **113** was followed by chlorodehydration using PCl₅ to give a 73% yield over two steps. The diethylamino group could then be installed *via* nucleophilic substitution to yield the desired aryl bromide **116**. The boronic acid **102** was synthesised as previously shown, and the cross-coupled product **117** was formed in 59% yield. Finally, removal of the protecting group and triflation was followed by a Kumada-Corriu cross coupling with phenyl magnesium bromide to give DEAP* **(±)-31**.

This catalyst did indeed prove to be much more selective than previous catalysts, and gave selectivity values of $s = 16$ at $-78\text{ }^{\circ}\text{C}$ for 1-(1-naphthylethanol) using *isobutyric* anhydride.^[101,102] An alternate, large-scale synthesis was next developed for this catalyst, including a classical resolution to separate the enantiomers – a highly desirable procedure as separation by CSP-HPLC is a tedious, expensive and time-consuming process.^[121] This route was developed as a large scale coupling of **102** and the **116** proved to be difficult to scale, and therefore the key coupling step was moved to earlier in the route (Scheme 69).^[121]

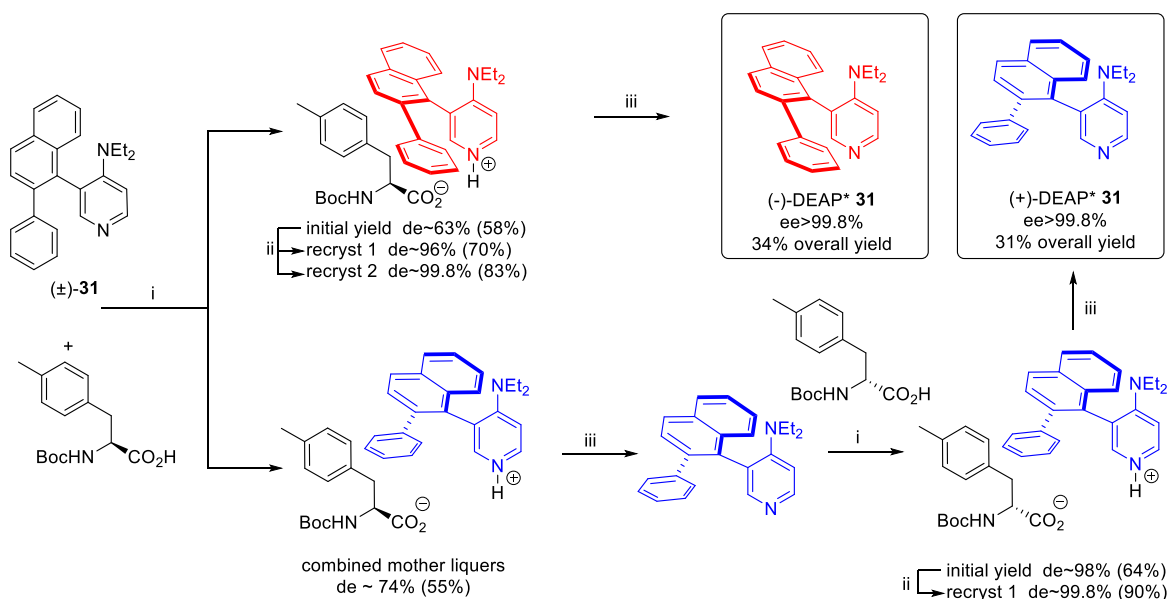


Scheme 69. Spivey's approaches to synthesis of catalyst (±)-**31**.^[121]

Reagents and Conditions: (i) Br_2 , H_2O , 5 h (ii) PCl_5 , $160\text{ }^{\circ}\text{C}$, 3 h (73% over two steps); (iii) Ag_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, benzene, $80\text{ }^{\circ}\text{C}$, 96 h, (80%); (iv) (a) *i*-PrMgCl then H_2O (99%), (b) Et_2NLi , Et_2NH , THF, $67\text{ }^{\circ}\text{C}$, 16 h (30%).

In this approach, a Suzuki cross-coupling was carried out on **115** with pinacolboronic ester **120**.^[121] Removal of the remaining bromine was achieved using *i*-Pr-MgCl and quenching with water, followed by addition of the diethylamino group to yield DEAP* (±)-**31**. This addition could not be achieved using the previously employed aromatic substitution reaction, hence an elimination-addition pathway was used, whereby treatment of debrominated-**121** with lithium diethylamide and diethylamine gave both 3- and 4-substituted products **122** and DEAP* (±)-**31**.

Guided by a software algorithm, Resolution Companion,^[298] an automated salt synthesis was carried out between (±)-**31** and 63 enantiomerically pure commercially available acids by a robot. Eutectic crystals were identified by DSC screening before optimisation of the crystallization procedure, to find that *N*-Boc-*O*-benzyl-(*S*)-tyrosine could be used to classically resolve catalyst **31**. The optimised procedure is shown below to yield 34% and 31% of the (–)- and (+)- enantiomers respectively (Scheme 70).^[121]



Scheme 70. Spivey's resolution of DEAP* catalyst **31**.^[121]

Reagents and Conditions: (i) *i*-PrOH, 75 °C, 30 minutes; (ii) recrystallisation from *i*-PrOH; (iii) CH₂Cl₂/Et₃N (10:1), SiO₂.

Initial salt formation with *N*-Boc-*O*-benzyl-(*S*)-tyrosine gave 58% of the (-)-**31** catalyst salt, with ~63% de. Two successive recrystallisations could increase the *de* to 99.8%, and “free-basing” of the salt provided DEAP* catalyst (-)-**31** in 34% total yield with >99.8% ee. Combining the mother liqueurs, free-basing and salt formation with *N*-Boc-*O*-benzyl-(*R*)-tyrosine thus provided the salt of (+)-**31**, which upon recrystallisation and free basing yielded DEAP* catalyst (+)-**31**, in a 31% total yield and >99.8% ee.

The large difference in selectivity observed between catalysts DEAP* and **106** were hypothesised to be due to the induced chiral conformation that the diethylamino group can adopt but the azaindoline cannot. Indeed, in the X-ray structure of DEAP* **31**, the two ethyl groups are angled in opposite directions (Figure 25).^[122]

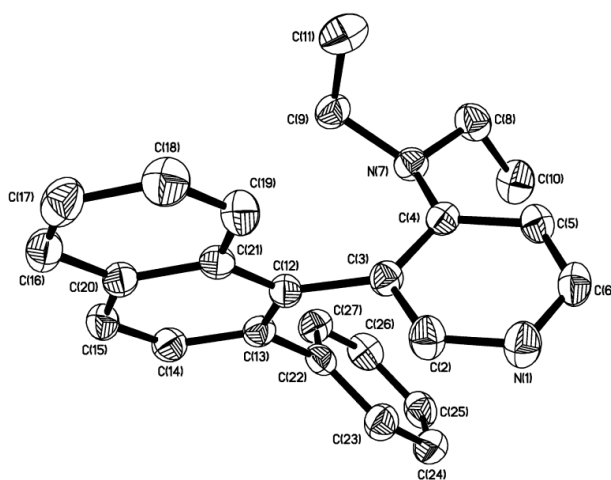
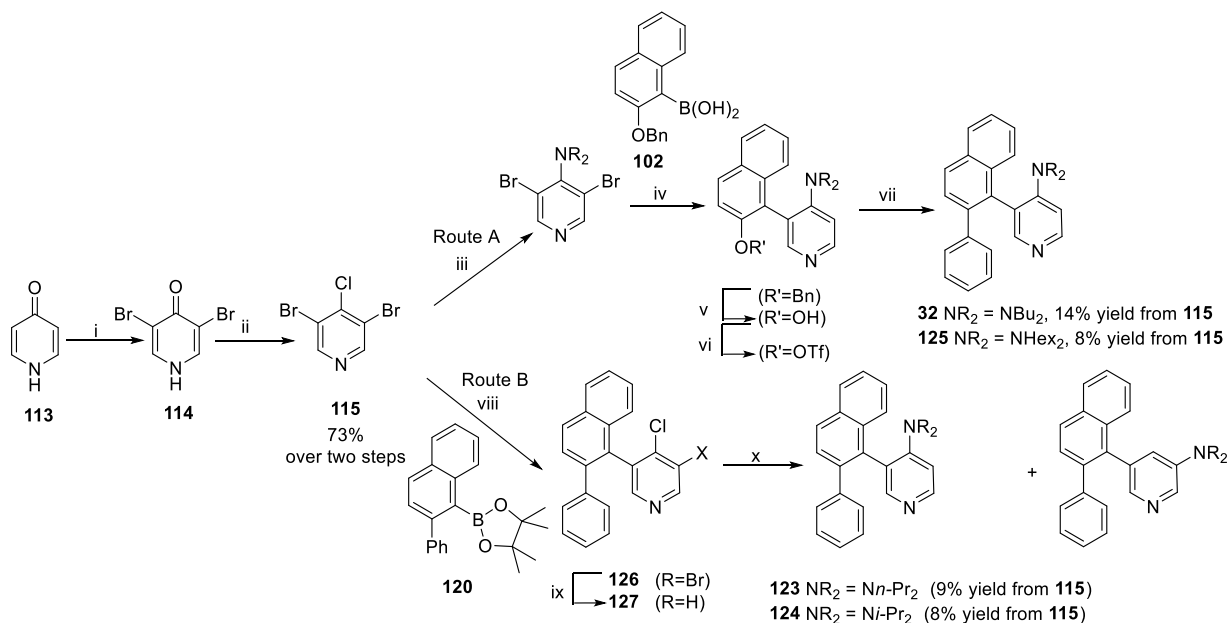


Figure 25. X-ray crystal structure of DEAP* (±)-**31** showing conformation adopted by the NEt₂ group.^[122]

In order to further investigate this hypothesis, a series of 4-dialkylaminopyridine catalysts were synthesised using one of the two routes above, including 4-di-*n*-propylamino- (**123**), 4-di*is*opropylamino-(**124**), 4-di-*n*-butylamino-(**32**) and 4-di-*n*-hexylaminopyridine (**125**)(Scheme 71).^[122]



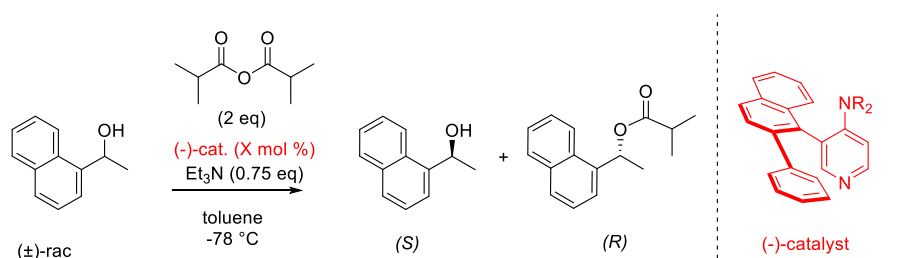
Scheme 71. Spivey's approach to synthesis of catalysts **32** and **123-125**.^[295]

Reagents and Conditions: (i) Br_2 , H_2O , 5 h (ii) PCl_5 , 160°C , 3 h (73% over two steps); **Route a:** (iii) NR_2H , DMF, 170°C ; **NBu**₂: 24 h (50%), **NHex**₂: 48 h (65%); (iv) 2-benzyloxy-1-naphthaleneboronic acid **102**, $\text{Pd}(\text{PPh}_3)_4$, aq. KOH, toluene, EtOH, 100°C , 20 h, **NBu**₂: (50%), **NHex**₂: (26%); (v) Pd/C , H_2 (1 atm), EtOH, rt, **NBu**₂: 18 h (78%), **NHex**₂: 20 h (97%); (vi) TiF_2O , pyridine; 0°C , 4 h, **NBu**₂: (50%), **NHex**₂: (26%); (vii) PhMgBr , $\text{PdCl}_2(\text{dppp})$, Et_2O , reflux, 20 h, **NBu**₂: (77%), **NHex**₂: (69%). **Route B** (viii) Ag_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, benzene, 80°C , 96 h, (80%); (ix) *i*-PrMgCl then H_2O (99%), (x) NR_2H , PhLi, THF, 67°C , **Nn-Pr**₂: 30 h (11% **123**, 46% **3-substituted**), **Ni-Pr**₂: 20 h (10% **124**, 37% **3-substituted**).

Catalysts **123** and **124** were prepared by Route B, as with compound **124**, no reaction was observed between diisopropylamine and the trihalopyridine **115**. In the final addition/elimination reaction of **127**, the ^1H NMR analysis of the crude reaction mixture showed the ratio of the 4 to 3 substituted products to be 1:5.0 for **123** and 1:4.5 for **124**.^[122] Catalyst **32** and **125** were synthesised using Route A, replacing the previously used diethylamine with dibutylamine and dihexylamine respectively in step iii, and all four new catalysts were separated into their enantiomers by semi-preparative CSP-HPLC.

These catalysts were then tested under standard conditions in the *isobutyration* of 1-(1-naphthyl)ethanol (Table 11).^[122]

Table 11. Variation of dialkylamino group on atropisomeric catalysts and effect on selectivity in acylative alcohol KR as examined by Spivey.^[122]

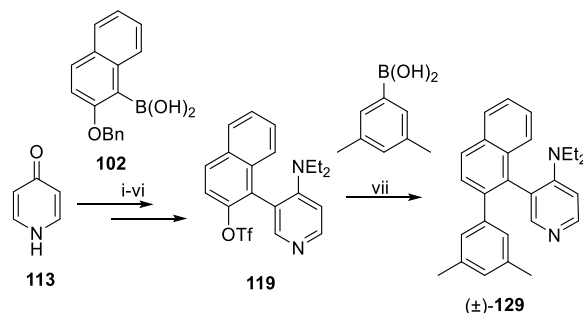


Entry	Catalyst (NR ₂)	Time (h)	Conversion (%)	Selectivity
1	NEt ₂ , 1 mol %	9	45	16
2	N <i>n</i> -Pr ₂ , 0.5 mol%	9	50	25 ^a
3	Ni-Pr ₂ , 0.5 mol%	9	50	15
4	NBu ₂ , 1 mol %	9	59	31 ^b
5	NHex ₂ , 1 mol%	14.2	37	39 ^c

^aDextrorotatory enantiomer of catalyst used giving enantiomeric products to those shown, ^b Reaction at -78 °C, *s* = 36 when run at -93 °C, ^cReaction run at -93 °C

Although the nature of the dialkylamino group evidently has a significant effect on the selectivity, there is no clear trend in these values with regards to either chain length or steric bulk, with the more hindered diisopropyl variant **124** showing lower selectivity than the dibutylaminopyridine catalyst **32**, which gave selectivities of *s* = 31 at -78 °C (entry 3 and entry 4). The dibutylaminopyridine catalyst **32** nevertheless gave good levels of selectivity with the highest conversion after 9 hours.

Further attempts to improve the selectivity were aimed at modifying the blocking phenyl ring.^[118] While the diethylamino-terphenyl analogue **128** was found to slightly improve selectivity compared to DEAP* catalyst **31**,^[118] the rate of reaction was significantly slower. A series of DFT calculations carried out showed that using a 3,5-dimethylphenyl (xylyl) group instead could increase the selectivity compared to DEAP* catalyst **31**.^[102] Synthesis of this modified catalyst (±)-**129** using the known route and a final Suzuki coupling was carried out as shown below (Scheme 72).^[102]

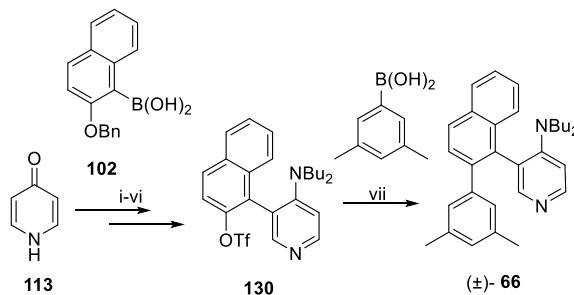


Scheme 72. Spivey's approach to synthesis of catalyst (±)-**129**.

Reagents and Conditions: (i)-(vi) see Scheme 68, (~26% over 6 steps); (vii) K₃PO₄, SPhos, Pd₂(dba)₃·CHCl₃, toluene, THF, 90 °C, 22 h (95%).

Catalyst **129** exhibited selectivity of $s = 27$ in conditions similar to Table 11, albeit using only one equivalent of *isobutyric* anhydride.

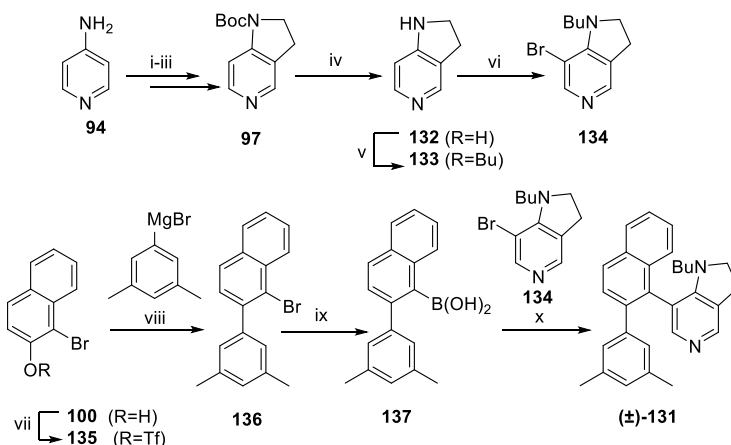
The nature therefore of both the blocking phenyl group and the dialkylamino group has a significant effect on the selectivity of these catalysts. Combination of these two effects, namely synthesis of the atropisomeric dibutylaminopyridine-xylyl catalyst **66**, henceforth referred to as DBAP* catalyst **66**, was therefore expected to further increase the selectivity. This catalyst was thus synthesised using the combination of the previously reported conditions (Scheme 73).^[208]



Scheme 73. Spivey's synthesis of DBAP* catalyst (±)-**66**.^[208]

Reagents and Conditions: (i)-(vi) see Scheme 71, Route A, (~13% over 6 steps); (vii) K_3PO_4 , SPhos, $Pd_2(dba)_3$, $CHCl_3$, toluene, THF, 90 °C, 22 h (64%).

These key changes to the amino group and blocking ring were then applied to the azaindoline-based catalyst series, to determine whether the improvement in selectivity could be translated to this series. The *N*-butyl-xylyl catalyst **131** (5-Azy*) was synthesised as shown below by Mohan and Ausmees, with the development of a key coupling step between the azaindoline moiety and the xylyl-naphthaleneboronic acid, negating the need to form the 2-benzoyloxynaphthyl intermediate (Scheme 74).^[297]



Scheme 74. Spivey's synthesis of 5-Azy* catalyst (±)-**131**.^[297]

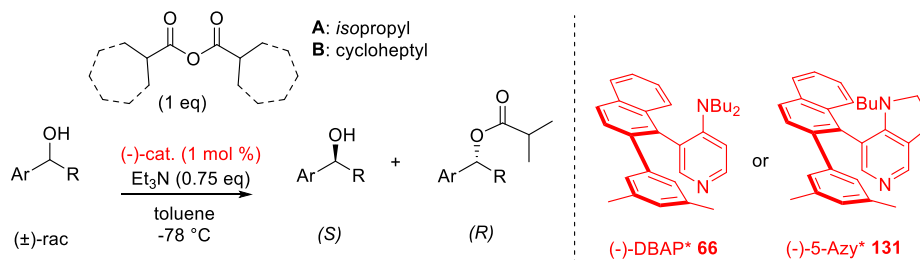
Reagents and Conditions: (i)-(iii) see Scheme 63, (~65% over three steps); (iv) $LiAlH_4$, THF, 0 °C → 66 °C, 6.5 h (66%) (v) $BuBr$, NaH, 15-crown-5, TBAI, 40 °C, 3 h (49%); (vi) NBS, CH_2Cl_2 , -1 °C, 24 h (83%); (vii) Tf_2O , 4-DMAP, pyridine, 0 °C, 2.5 h (95%); (viii) 3,5-dimethylphenyl-magnesium bromide, $PdCl_2(dppp)$, Et_2O , 40 °C, 2.5 h (76%); (ix) $n-BuLi$, $B(OMe)_3$, -78 °C → 0 °C, 17 h; (57%); (x) PEPPSI-*i*-Pr, KOH, toluene, uW 76 °C → 180 °C, 65 min (70%).

Compound **97** was synthesised using the previously shown route (Scheme 74). Reduction of the Boc group with LiAlH₄ yielded *N*-H-indoline **132**, and alkylation with butyl bromide followed by bromination yielded *N*-butyl-bromoazaindoline **133**. Kumada-Corriu cross coupling of naphthyl triflate **135** yielded bromide **136**, and synthesis of the boronic acid **137** was achieved using the standard conditions in 57% yield. The final cross-coupling conditions were initially developed by Ausmees between boronic acid **137** and **98**. A number of conditions were tested, varying the catalyst, ligand, base, solvent and temperature. All conditions resulted in a low yield apart from when PEPPSI-*i*-Pr was used in combination with a large excess of KOH (12 equiv.) and the boronic acid (3 equiv.) in toluene, giving an 88% conversion. Changing to the butyl bromide **134** gave conversions of up to 82% when heating in a microwave, with an optimised yield of 70% for the formation of (±)-**131**.^[297]

2.1.2 Optimised Catalysts – Scope and Selectivity

The results achieved by Ausmees and Mohan with these two most promising catalyst candidates are presented below. Overall DBAP* catalyst **66** was found to be the most selective catalyst developed in the Spivey group to date, while the azaindoline-based catalyst 5-Azy* **131** was found to give acceptable levels selectivity with notably fast rates of reaction: between 1.7 and 5× faster than DBAP* catalyst **66** over 8 hours. It was hypothesised that the longer butyl alkyl chain on both catalysts increases the solubility of the acyl pyridinium salt, which helps to increase the rate of reaction, while the xylyl group increases the facial discrimination between the top and bottom faces of the catalyst, thus increasing the selectivity for both compared to the parent catalysts **32** and **112**.^[208] The table below represents the results achieved with these catalysts for a variety of substrates, using both *isobutyric* anhydride, and the more selective system dicycloheptane carboxylic anhydride (Table 12).^[208,297]

Table 12. Substrate scope for catalysts DBAP* catalyst **66** and 5-Azy* catalyst **131** as examined by Ausmees and Mohan.^[208,297]



Entry	Substrate	Catalyst	Acyl Donor	Time (h)	Conversion	Selectivity
1		(-)-DBAP* 66	A	8	48	44
2		(-)-5-Azy* 131	A	2	61	12
3		(-)-DBAP* 66	A	8	21	11
4		(-)-5-Azy* 131	A	8	64	3.9
5		(-)-DBAP* 66	A	8	35	33
6		(-)-5-Azy* 131	A	2	50	16
7		(-)-DBAP* 66	A	8	6.4	4.8
8		(-)-5-Azy* 131	A	8	35	3.4
9		(-)-DBAP* 66	A	8	25	17
10		(-)-5-Azy* 131	A	2	42	5.2
11		(-)-DBAP* 66	A	8	19	5.5
12		(-)-5-Azy* 131	A	2	32	2.9
13		(-)-DBAP* 66	A	8	32	2.7
14		(-)-5-Azy* 131	B	8	41	3.5
15		(-)-DBAP* 66	A	8	28	38
16		(-)-5-Azy* 131	B	8	46	59
17		(-)-DBAP* 66	A	8	10	63
18		(-)-5-Azy* 131	B	8	30	19
19		(-)-5-Azy* 131	B	8	49	12
20		(-)-DBAP* 66	A	8	29	91
21		(-)-5-Azy* 131	B	8	45	65

DBAP* catalyst **66** is more selective when directly compared to 5-Azy* catalyst **131** (entries 1-12), although the selectivity of 5-Azy* catalyst **131** can be increased when using dicycloheptane carboxylic anhydride, which was found to give slightly higher selectivities than *isobutyric* anhydride with this catalyst, presumably as the larger group helps to differentiate the approaches to the pyridinium salt. Interestingly, while the

phenyl-*tert*-butylethanol (entries 17 and 18) gave very good selectivities for both catalysts, the naphthyl analogue (entries 7 and 8) gave very poor selectivity. The best selectivity of $s = 91$ was achieved with 1-(9-anthracenyl)ethanol (entry 20).

2.2 Amine KR

Acylative amine KR is a less developed field than the corresponding acylative alcohol KR as discussed in section 1.2.5. Efforts in the group have focused on achieving amine KR with a variety of different substrates, including aryl alkyl amines and α -amino acid esters (Figure 26).^[3,207] The initial substrate of choice for the development of amine KR within the Spivey group was α -methylbenzylamine **138**, as this is a commonly used substrate for developing amine KR,^[299–301] and is also very similar to the common *sec*-benzylic alcohols used as substrates for alcohol KR.

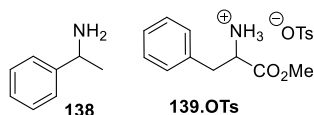
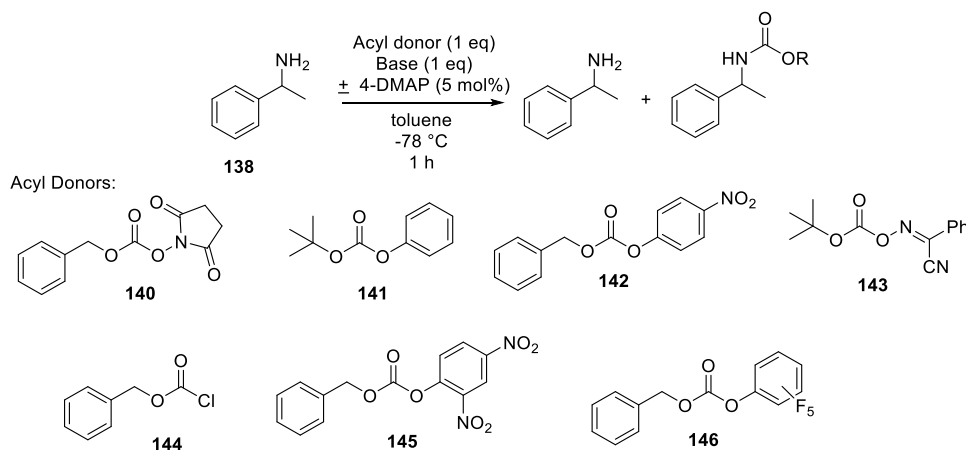


Figure 26. Structures of potential amine substrates **138** and **139.OTs** as surveyed by Davey.^[3]

Studies by Davey^[3] first focused on choosing a suitable acyl donor, as the anhydrides typically used for alcohol KR react readily with amines in an uncatalysed background reaction due to the increased nucleophilicity of amines compared to alcohols. The screen of acylating agents therefore aimed to find a reagent that would give significant conversion when catalysed by 4-DMAP, while having only a minimal background reaction present. Carbonates were chosen as suitable acylating agents, as these are less reactive than anhydrides and also have the added benefit of producing carbamates as the product, which can be deprotected under milder conditions than amides to regenerate the starting amine (Table 13).^[3]

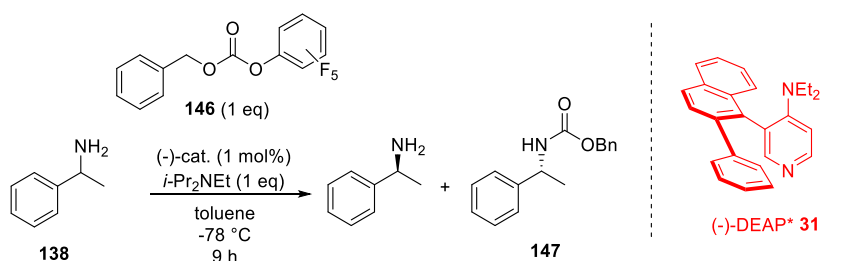
Table 13. Screen of potential acylating agents for amine KR as examined by Davey.^[3]



Entry	Acyl Donor	Base	Background Conversion (%)	Catalysed Conversion (%)
1	140	Et ₃ N	60	60
2	141	Et ₃ N	0*	0
3	142	Et ₃ N	0	0
4	143	Et ₃ N	0	0
5	144	Et ₃ N	75	75
6	145	Et ₃ N	15	75
7	146	Et ₃ N	10	55
8	146	<i>i</i> -Pr ₂ NEt	5	55
9	146	-	5	50

*no quench

A number of commercial carbonates (entries 1 to 5) gave no differential between the catalysed and background reactions. On the other hand, two highly activated carbonates with electron deficient groups (entries 6 and 7) gave a significant differential (5.5× and 5× respectively). Changing the base from triethylamine to Hünig's base further increased this differential, as this is more hindered and is less likely to be acting as a base catalyst (entry 8).^[302,303] This differential was deemed by Davey to be sufficient to warrant attempting a KR experiment, and so the catalyst was changed to enantiopure DEAP* (Scheme 75), the best catalyst developed in the group at the time^[118,121].



Scheme 75. Davey's first attempt at KR of α-methylbenzylamine (stereochemistry randomly assigned).^[3]

The rate of acylation however was significantly slower with catalyst DEAP* 31 relative to 4-DMAP, and delivered only 20% conversion after 9 hours. The selectivity was also disappointing, with $s = 1.75 \pm 0.25$.

These results prompted a move towards the more deactivated substrate, phenylalanine methyl ester tosylate salt **139.OTs**.

Davey anticipated that the electron withdrawing ester group would deactivate the amine relative to α -methylbenzylamine, while still representing a useful class of substrate. Initially used as the HCl salt, the tosylate salt was found to give slightly higher rates of reaction and was used in a KR experiment with the previously developed pentafluorophenyl benzyl carbonate **146** with a PPY-based catalyst **148** (Table 14).^[3,122]

Table 14. Davey's attempted KR of phenylalanine methyl ester tosylate salt **139.OTs**.^[3]

Entry	Catalyst (mol%)	Time (h)	Conversion (%)	Selectivity
1	4-DMAP (1 mol%)	9	40	-
2	-	9	0	-
3	(-)-PPY 148 (10 mol%)	16	<5	1.5±0.5 ^a

^a stereochemistry randomly assigned

Unfortunately, catalyst **148** proved to be even more unreactive under these conditions, with <5% conversion after 16 hours with low selectivity ($s=1.5 \pm 0.5$), and the reaction was too slow to give an acceptable KR. Evidently, although 4-DMAP had been used to test the reactivity of the substrates and the differential between the catalysed and background reaction, the chiral catalysts used were not reactive enough to achieve useful levels of conversion.

Work at this point moved towards developing a solid supported chiral catalyst, and attempts to improve the KR with the above substrates were suspended by Davey.

3 Aims and Objectives

Following directly from the work of Mohan,^[208,297] Ausmees,^[297] Davey^[3] and Livingston,^[286] the aims and objectives at the outset for this thesis work were as follows:

Amine KR

To develop a non-enzymatic amine KR using racemisation-compatible acyl donors and the Spivey 5-Azy* catalyst **131**, based upon work by Davey on the KR of amino acid esters.

Alcohol KR

To modify current alcohol KR conditions developed by Mohan and others by using a racemisation-catalyst compatible acyl donor and to achieve maximum selectivity at room temperature using the Spivey DBAP* catalyst **66**.

Alcohol DKR

One-pot: To combine a room temperature alcohol KR procedure with a literature racemisation catalyst to achieve a one-pot DKR procedure.

Membrane – enhanced: To develop a membrane-enhanced alcohol DKR (MEDKR) based on previous work by Livingston. Work in the area of separated DKR has focused so far on enzymatic resolution catalysts, and/or immobilised and modified catalysts. Our aim was to develop the first example of a semi-continuous DKR with a small molecule non-enzymatic KR catalyst and a small molecule unmodified racemisation catalyst.

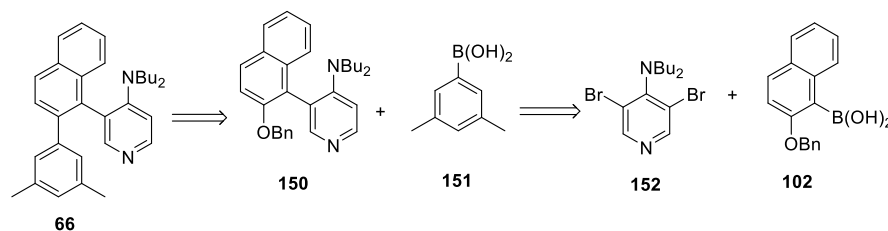
4 Results and Discussion

4.1 Synthesis of Catalysts

The first step in the project was to synthesise the chiral catalysts required. From previous work on alcohol KR catalyst development, the two most promising candidates were chosen for synthesis. These were the dibutylaminopyridine-xylyl catalyst **66** (DBAP*) and also the azaindoline-xylyl catalyst **131** (5-Azy*) as developed by Mohan and Ausmees.^[208,297] Although small scale syntheses of both had previously been carried out (*vide supra*), gram quantities of the catalysts would be required for the successful development of the MEDKR, and we hoped by the end of the synthesis to have ~10 g of each catalyst in hand. A first, small-scale synthesis was carried out for both catalysts while the large-scale synthesis was carried out during a four-month placement at the Eli Lilly laboratories in Windlesham, Surrey. Both scale syntheses are presented here concurrently.

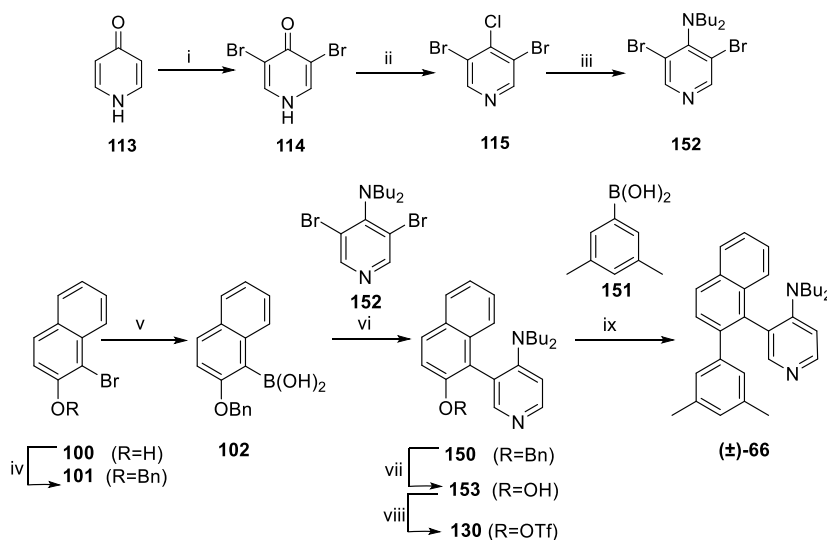
4.1.1 Synthesis of Atropisomeric Dibutylaminopyridine Catalyst DBAP*

A retrosynthetic analysis of DBAP* **66** is shown below (Scheme 76).



Scheme 76. Retrosynthetic analysis of atropisomeric dibutylaminopyridine-based catalyst **66**.

The key coupling step in this synthesis is the challenging formation of the pyridine-naphthyl bond, with maximum yields of 52% reported.^[208] The previous forward synthesis for **66** (Scheme 77) was carried out on a <1 g final scale by Mohan, with separation into enantiomers using a semi-preparative HPLC.



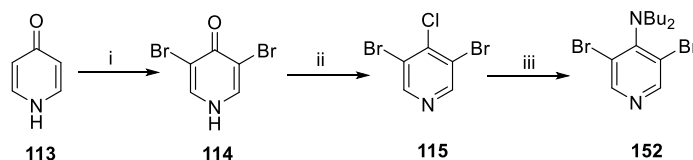
Scheme 77. Synthesis of DBAP* catalyst **66** as carried out by Mohan.

Reagents and Conditions: (i) Br_2 , H_2O (84%); (ii) PCl_5 ; $160\text{ }^\circ\text{C}$, 3 h (78%); (iii) NBu_2H , NMP; $170\text{ }^\circ\text{C}$, 20 h (81%); (iv) BnBr , K_2CO_3 , DMF; $60\text{ }^\circ\text{C}$, 5 h (93%); (v) $n\text{-BuLi}$, B(OMe)_3 ; $-78\text{ }^\circ\text{C} \rightarrow 0\text{ }^\circ\text{C}$, 17 h (71%); (vi) $\text{Pd(PPh}_3)_4$, toluene, EtOH, $100\text{ }^\circ\text{C}$, 20 h (52%); (vii) Pd/C , EtOAc, EtOH, H_2 (1 atm), rt, 24 h (>99%); (viii) Tf_2O , 4-DMAP, pyridine; $0\text{ }^\circ\text{C}$, 3 h (90%); (ix) $\text{Pd}_2(\text{dba})_3$, CHCl_3 , SPhos, THF/toluene, K_3PO_4 ; reflux, 20 h (64%).

The results below summarise our efforts to complete and scale-up the above synthesis of DBAP* **66**.

4.1.1.1 Synthesis of 3,5-Dibromo-4-dibutylamino-pyridine **152**

The aryl bromide coupling partner **152** was synthesised in three steps starting from commercially available 4-pyridone (**113**) (Scheme 78).

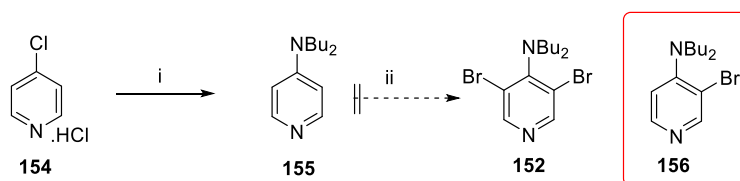


Scheme 78. Synthesis of **152** from commercial pyridone **113**.

Reagents and Conditions: (i) Br_2 , H_2O (84%); (ii) PCl_5 ; $160\text{ }^\circ\text{C}$, 3 h (78%); (iii) NBu_2H , NMP; $170\text{ }^\circ\text{C}$, 20 h (81%).

The small scale synthesis of **152** was carried out without problems initially starting from 5 g of previously prepared **114** to yield 3.65 g of **152** (51% over two steps).

On a larger scale, with the hope of making ~ 10 g of DBAP* catalyst **66**, we wanted to avoid the use of bromine in the synthesis, to which end alternative routes were investigated, where the bromination would be achieved using NBS (Scheme 79).



Scheme 79. Potential alternative routes to **152** investigated.

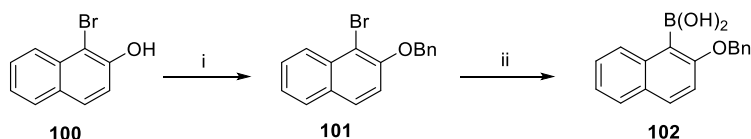
Reagents and Conditions: (i) NBu_2H , DMSO, $170\text{ }^\circ\text{C}$, 3 h (54%) (ii) NBS, CH_2Cl_2 ; $0\text{ }^\circ\text{C}$ to rt, >48 h.

After a quick solvent screen for the amination reaction between DMF, DMSO, H_2O and NMP, identifying DMSO as the solvent of choice; it was found that the formation of the dibutylaminopyridine from 4-chloropyridine **154** was only partially successful (54% yield on 2 g), while the subsequent bromination with NBS proved challenging. The reaction was initially run at $0\text{ }^\circ\text{C}$, but due to low conversions was left overnight at room temperature, which resulted in a large number of by-products. A further attempt at $0\text{ }^\circ\text{C}$ showed that although mono-bromination proceeded cleanly to ~50% conversion, dibromination and reaction completion did not occur. It was previously found that the dibromo compound is essential for a high-yielding subsequent Suzuki coupling^[120] and therefore the original route using bromine was scaled up.

The bromination of 4-pyridone **113** (Scheme 78) was run on successively larger scales, from 0.2 g to 10 g to 40 g, with the yield ranging from 58% to 87% to 84% respectively and the material taken through crude without purification to the next step. The chlorination of **114** (Scheme 78, step ii), which had proved to be successful at smaller scales (5 g gave 73% yield), provided some difficulties at larger scale. The reaction is run neat with no solvent at very high temperatures, and requires all of the materials to melt, while also producing very large volumes of HCl gas. A NaOH (aq) bubbler was therefore used to quench the HCl formed in the reaction, and on large scale (62 g) gave yields of 78%. The product was recrystallised once from dichloromethane and taken through to the amination. The substitution (Scheme 78, step iii) worked very well and was straightforward to scale, with no need to use dry solvents. The final amination reaction was run at a 40 g scale with an 81% isolated yield after purification by flash column chromatography, in addition to some impure fractions. It is worth noting that only one step required purification by column chromatography up to compound **152**, a significant advantage on such large scales.

4.1.1.2 Synthesis of Boronic Acid **102**

The second partner for the coupling step was prepared from commercially available 1-bromo-2-naphthol **100**, with protection of the hydroxyl group followed by formation of the boronic acid (Scheme 80).



Scheme 80. Synthesis of boronic acid **102** from commercially available **100**.

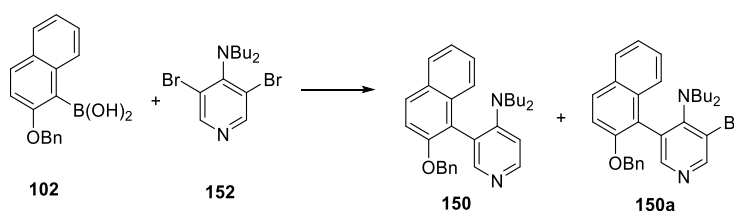
Reagents and Conditions: (i) BnBr , K_2CO_3 , CH_3CN ; $60\text{ }^\circ\text{C}$, 5 h (93%); (ii) $n\text{-BuLi}$, B(OMe)_3 ; $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 17 h (89%).

To start the large scale synthesis, it was investigated whether the DMF previously used as a solvent for the benzyl protection could be replaced with a more benign solvent, and it was found that acetonitrile gave very similar results. Synthesis of **101** was then carried out on increasing scales with the final reaction performed on 150 g of the naphthol **100**. It was found that 150 g of **101** could be isolated by recrystallisation, while the remaining 100 g of crude material was purified by column chromatography to yield 59.1 g, an overall yield of 99%. Formation of the boronic acid **102** followed previously reported procedures, initially using diethyl ether as the solvent of choice, with a large scale reaction run using 60 g of **101**, yielding 89% of **102**. The boronic acid **102** could be isolated by filtration from Et₂O, and after solvent removal the filtrate was recrystallised from CH₂Cl₂. It should be noted that again no column chromatography steps are required for purification up to boronic acid **102**.

Diethyl ether however, is not a suitable solvent to scaling up to a >100 g scale due to its low flash point. Therefore the reaction was tried in THF, *tert*-butyl methyl ether (TBME) and also cyclopentyl methyl ether (CPME). THF gave none of the desired product, while both the ether solvents gave reduced yields (~50% vs 89% for diethyl ether). The product obtained from cyclopentyl methyl ether contained fewer impurities, and therefore this was the solvent of choice for the scale up. A reaction was run on 20 g with CPME and gave a 61% yield. Unfortunately, due to time constraints this reaction was not repeated on a larger scale.

4.1.1.3 Suzuki Coupling Step of Boronic Acid **102** and Dibutylaminopyridine **152**

The next step was the Suzuki coupling of the dibromopyridine and naphthyl boronic acid components to give biaryl **150**. This step is the most challenging in the sequence of steps required to synthesise DBAP* **66** (Scheme 81). Originally reported with a 52% yield,^[208] efforts were concentrated to improve this key coupling step.



Scheme 81. Suzuki coupling of aryl bromide **152** and boronic acid **102** to form **150** and **150a**.

Reagents and Conditions: (i) Pd(PPh₃)₄, KOH, dioxane, H₂O, 110 °C, 20 h (65%).

An initial attempt at the coupling was carried out following a procedure from Mohan^[208] with Pd(PPh₃)₄, KOH, toluene, and water as the solvent, yielding only 37% conversion to the desired product **150**, while the remaining aryl bromide was recovered as the mono-brominated moiety.

The use of an alternative catalyst, PdCl₂(PPh₃)₂ was attempted, as this is a less air-sensitive analogue of Pd(PPh₃)₄. Bases and boronic acids are commonly used to reduce the Pd^{II} species *in situ* to the desired Pd⁰ catalysts.^[304–306] However, this reaction only gave a 10% yield, with most of the starting material degrading

quickly to the completely debrominated dibutylaminopyridine. A catalyst screen was therefore carried out using the original conditions combining KOH, toluene and water (Figure 27).

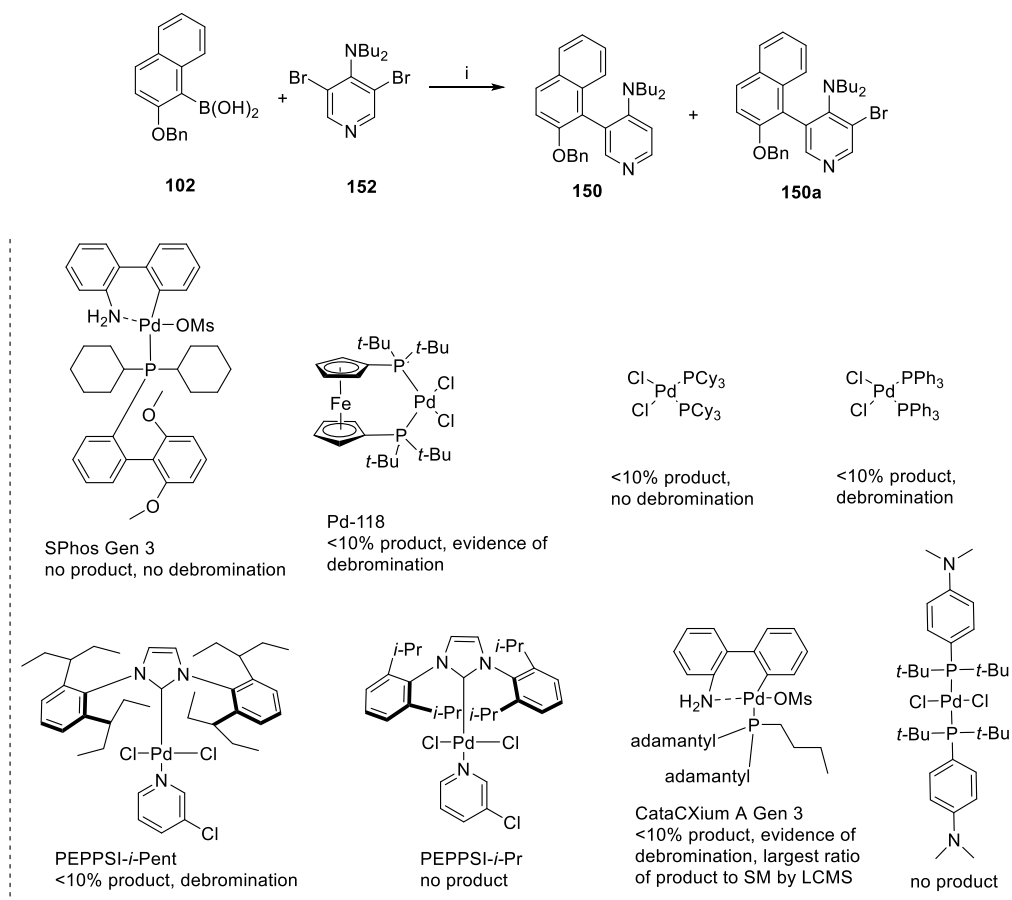


Figure 27. Catalysts screened for Suzuki coupling of **102** and **152**, using toluene, EtOH and KOH as the base.

Reagents and Conditions: (i) Pd catalyst (5 mol%), KOH, toluene, H₂O, 100 °C, 6 h.

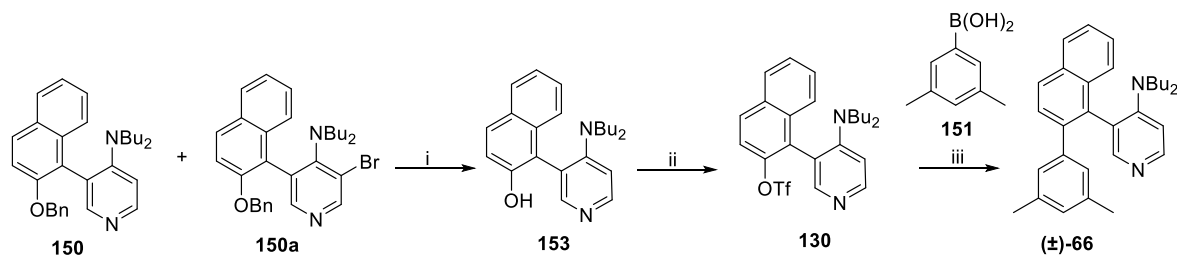
None of the catalysts screened gave increased yields, with CataCXium showing the most product formation and also the least amount of debrominated starting material. This catalyst was screened with three different solvents and four bases (dioxane, THF and toluene, K₃PO₄, Na₂CO₃, K₂CO₃, Cs₂CO₃). Unfortunately, none of these gave any product, as the boronic acid was unstable under these conditions, and no debromination of the aryl halide was observed, indicating that the catalyst was not reactive enough under these conditions.

It was then decided to re-evaluate Pd(PPh₃)₄ as a catalyst while changing the conditions. We found that while the original conditions using toluene and 65 equivalents of water still only gave 37% conversion, changing to dioxane as the solvent increased the conversion to 61% by ¹H NMR analysis, and adding only 20 equivalents of water increased the yield to 63% with a mixture of the brominated and debrominated products **150** and **150a**. The reaction was scaled from the original 50 mg to 500 mg, giving a similar conversion (61%) on the larger scale. Interestingly, it was found that most of the reaction occurred in the first 2½ hours with no trace of the boronic acid by LCMS, and that after this, even when more boronic acid was added to the reaction the conversion stayed within 10% of the value after 2½ hours, indicating rapid decomposition of the catalyst in

the reaction mixture. Doubling the concentration of the reaction on 500 mg had no negative effect on the conversion (C = 63% by ^1H NMR analysis), and further increasing the scale to 1 g also had no large effect (C = 58% by ^1H NMR). Further scaling to 5 g and then finally to a 20 g reaction was successful, with a 65% combined isolated yield for the 20 g reaction, of which 57% was the brominated product **150a** and 8.5% the debrominated product **150**. Although the $\text{Pd}(\text{PPh}_3)_4$ required weighing out in a glove box, solvent addition and reaction could be carried out in a fume hood. Coupled products **150** and **150a** were purified by flash column chromatography. The increased yield to 65%, as well as the successful scaling of the reaction was an extremely positive result, as previously this coupling had been the most limiting step in the synthesis.

4.1.1.4 Hydrogenation and Final Steps Towards DBAP* **66**

The final steps in the synthesis were the hydrogenation of both the brominated and de-brominated products obtained from the Suzuki coupling, followed by triflation and a final Suzuki coupling of the xylyl moiety (Scheme 82).



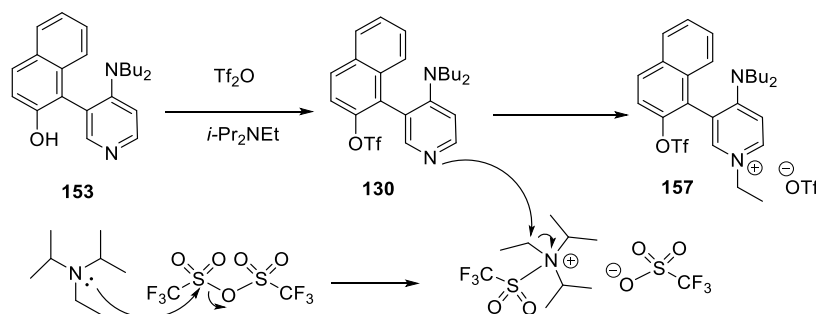
Scheme 82. Final steps towards (±)-DBAP* catalyst **66**.

Reagents and Conditions: (i) Pd/C , $i\text{-Pr}_3\text{NEt}$, EtOAc , EtOH , H_2 (60 atm), rt, 24 h (>99%); (ii) Trf_2O , pyridine, CH_2Cl_2 , 0 °C, 3 h (85%); (iii) $\text{Pd}_2(\text{dba})_3$, SPhos , THF/toluene , K_3PO_4 , reflux, 20 h (90% C by ^1H NMR).

The brominated and debrominated products **150** and **150a** could be easily combined in a hydrogenation carried out in a Parr shaker with Hünig's base and 5% Pd/C to give quantitative conversion to the debrominated naphthol. The largest scale for this reaction was 18.1 g, limited by vessel size of the Parr shaker, although the reaction time was extended on this scale to 48 hours. Successive hydrogenations were carried out on an 8 g scale, with a 22 hour reaction time.

This was followed by triflation of the naphthol **153**. There are two published procedures,^[102] one using 4-DMAP and pyridine as the solvent, and one using 4-DMAP, Hünig's base and dichloromethane. As the use of pyridine on such large scales was undesirable, the second procedure using dichloromethane was chosen. Initial attempts at this worked well, and gave 90% conversion by ^1H NMR analysis on a 0.5 g scale. When increasing the scale to 18 g of the crude hydrogenated mixture (traces of Hünig's base still present) the reaction did not go to completion and stayed at the same conversion over 3 hours (66% by LCMS), and so another 0.5 equivalents of triflic anhydride was added. Very soon after this the LCMS showed two new peaks, at MW of SM+28 and P+28. Work-up of the reaction as usual gave only 30% of the desired triflate product **130**, and a methanol wash of the column to remove any remaining naphthol **153** also gave one other

major product (12 g) by LCMS which had a MW of P+28. ^1H NMR analysis of this material after purification by HPLC showed two new peaks, a triplet and a quartet, while the alkyl peaks for the NBu_2 moiety became very broad. Mass spectrometry, ^1H NMR and ^{19}F NMR analysis of the compound together showed that this material was in fact the *N*-ethyl pyridinium triflate salt **157**, with a possible mechanism of formation shown below (Scheme 83).^[307]



Scheme 83. Possible mechanism for formation of *N*-ethyl pyridinium triflate salt **157**.^[307]

Evidence for the triflate acting as the anion comes from a ^{19}F NMR spectrum, showing the presence of two different fluorine environments in the purified salt. Due to time constraints no attempts were made to recover and dealkylate this product. In further reactions, Hünig's base was replaced by pyridine in the reaction and 4-DMAP was omitted in the new conditions. On a 1.6 g scale these conditions gave 85% conversion to triflate **130** by ^1H NMR analysis, while on a 5.8 g scale only 54% of **130** was recovered and on a 6 g scale the yield was only 47% of isolated material, with the rest of the material recovered as the impure naphthol **153**. Due to time constraints these conditions were not optimised, and the material was taken on to the final reaction; a further Suzuki coupling with a stable commercially available boronic acid. These results highlight the challenges arising on scale-up of reactions, as reactions that work well on small scales can have unexpected results on larger scales. We therefore recommend that the triflation step should be run in pyridine in future reactions.

The final Suzuki reaction had a reported yield of 93% on a small scale (<500 mg), and was initially tried on a 100 mg scale. Following the published procedure^[102,308] resulted in only 15% conversion to the desired product **66**, as well as 40% hydrolysis of the triflate **130** to the naphthol **153**. A second attempt was made using the original Buchwald conditions,^[308] using only toluene as the solvent and not pre-stirring the catalyst and ligand. This resulted in 94% conversion to the product by LCMS, and so these conditions were used for the next reaction, which was carried out on 1 g. The LCMS and ^1H NMR of the crude reaction mixture both looked promising, showing 85% C by LCMS, and a combined isolated yield of the two reactions was 68% (0.67 g). A 5 g reaction was attempted next, but unfortunately even after 3 days the conversion was only 20% with 25% hydrolysed starting material present. After purification by flash column chromatography, 0.62 g of DBAP* **66** and 3.65 g of the triflate **130** was recovered. The triflate was re-subjected to the reaction conditions, and gave 94% conversion by LCMS overnight. Purification by column chromatography of this

reaction mixture was hampered by the fact that two different fractions had the same MW as desired product, and after ¹H NMR analysis it was found that the higher-running spot was in fact a product from a 1,4-palladium migration and C-H activation – compound **158**. Formation of this product is possibly *via* one of the mechanisms shown below which have been adapted from an analogous aryl-iodide 1,4-palladium migration reported by Larock (Scheme 84 and Scheme 85) :^[309,310]

Scheme 84. Larock's 1,4-palladium migration in Suzuki coupling.^[309]

Scheme 85. Possible mechanisms for formation of 1,4-palladium migration product 158.^[309,310]

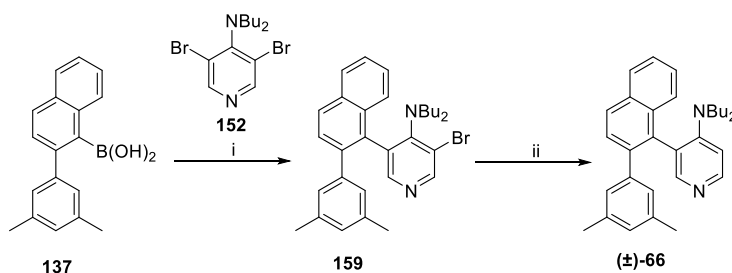
desired product by LCMS and ^1H NMR. Attempts to purify by chiral chromatography proved to be problematic as the product co-eluted with the boronic acid and other by-products and could not be effectively purified.

A final coupling was attempted on a 5.3 g scale using the same conditions as for the successful 3 g reaction. However, after leaving the reaction overnight, only 31% conversion was seen by LCMS, with 10% hydrolysis of the starting material. Filtering the reaction mixture, re-adding the base, solvent and catalyst/ligand mixture as before also did not help, with only a 53% conversion after 18 hours. The product obtained from this reaction was combined with the previous 3 g reaction to purify. Small impurities co-eluted with the product, however 6.2 g was recovered in 74% purity, and it was deemed clean enough for chiral separation. The overall yield for the final two reactions (3 g + 5.3 g of **130**) was 60%.

The total yield of the desired product ($\pm$)-**66** was 1.3 g from the initial batches, with a further 6.2 g from later batches. Scaling up of the final steps, the triflation and final Suzuki coupling, proved to be extremely problematic, and more time needs to be committed to this in order to improve these steps on a large scale. Nevertheless, >30 g of the coupled deprotected naphthol product **153** was synthesised successfully, and large amounts of precursors are now available for further development of the synthesis.

4.1.1.4.1 Alternative Procedure Towards DBAP* catalyst **66**

As the final two steps in the synthesis had proved to be so challenging, we were interested to see if our improved $\text{Pd}(\text{PPh}_3)_4$ coupling conditions could be applied to the coupling of the more hindered xylyl-naphthyl boronic acid **137** with the dibromo-dibutylaminopyridine coupling partner **152**. The reaction was attempted on a small scale (50 mg) using the optimal conditions for the coupling (Scheme 86).



Scheme 86. Alternative synthesis of ($\pm$)-DBAP* catalyst **66** via late stage coupling and hydrogenation.

Reagents and Conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, KOH, dioxane, H_2O , 110°C , 5 days (22%); (ii) Pd/C, *i*-Pr₂NEt, EtOAc, EtOH, H_2 (1 atm); rt, 4 days, (75%).

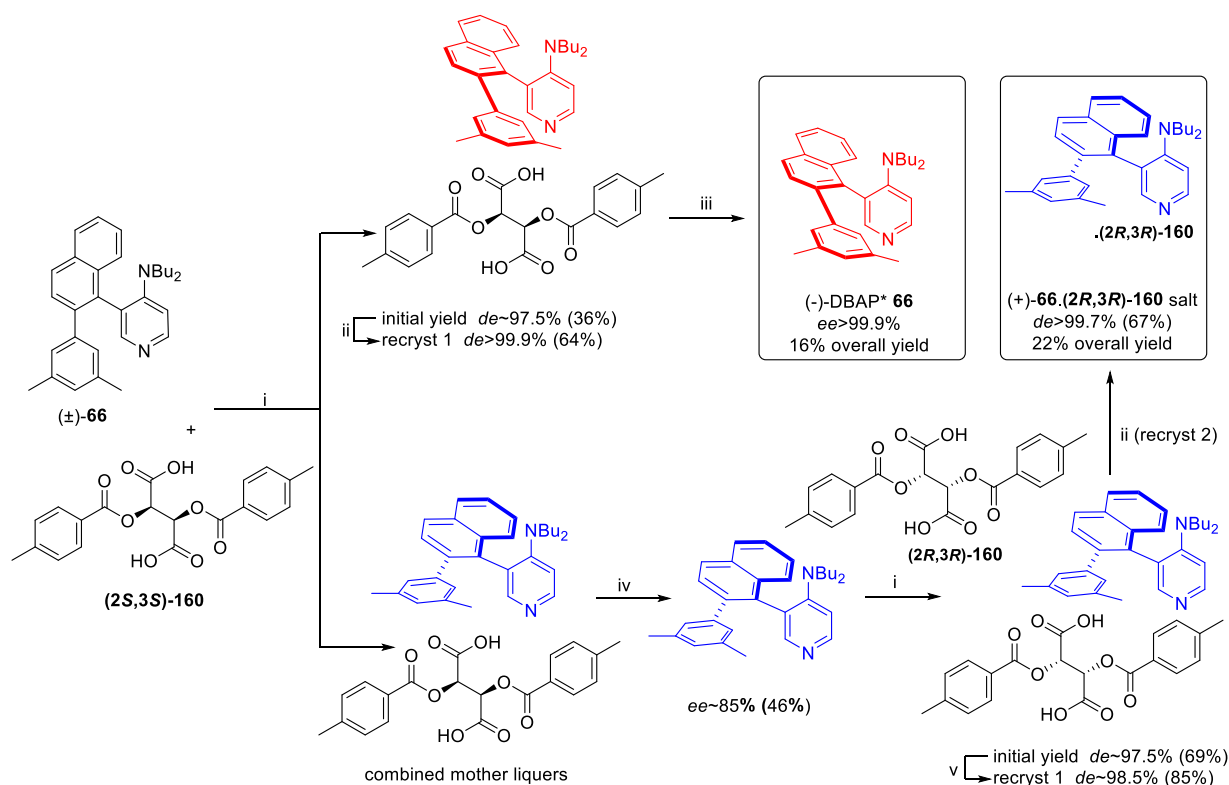
We were delighted to see that ~35% conversion was observed by ^1H NMR analysis of the reaction mixture, albeit mostly to the mono-brominated coupled product **159**, which we anticipated could be reduced by hydrogenation to the desired product. Not having any water in the reaction had a detrimental effect ($\text{C}<30\%$), while increasing the number of boronic acid equivalents increased the conversion relative to **152** (50% conversion by ^1H NMR analysis). Purification of the reaction proved challenging, and on a 50 mg reaction at

58% conversion only 17% of the brominated product could be recovered after column chromatography. The procedure was attempted on 0.5 g to determine the reproducibility of the reaction on this scale, and while again 50% conversion was observed, the isolated yield was only 22% based on the **152**. Nevertheless, 47% of the boronic acid was recovered and a further 20% of **152** was recovered.

To remove the uncoupled bromide, a one-pot procedure was initially attempted, adding ethanol to the coupling reaction after 48 hours. While this was successful on a small scale, on the 0.5 g reaction no change occurred after ethanol addition, even when more catalyst was added to the reaction. We presume this to be due to fast deactivation of the catalyst within the reaction mixture, also explaining the recovery of the boronic acid. A separate hydrogenation using 10% Pd/C and Hünig's base in EtOAc and ethanol was carried out on the aryl-bromide **159**, which proceeded in quantitative conversion and 95% product recovery on a small scale (14 mg) and 75% yield on a larger scale (150 mg) due to extended reaction times.

4.1.1.5 Resolution

The chiral DBAP* catalyst **66** prepared in the above work was racemic. Its separation into its constituent enantiomers has previously been achieved using semi-preparative chiral HPLC; an arduous and time-consuming process that is not suitable for large scale separation. It was therefore highly desirable to find another method to resolve this compound using classical resolution with an appropriate homochiral acid. Our collaborators at Eli Lilly carried out a screening of commercially available homochiral acids, and successfully identified 4-methyldibenzoyl-(2*S*,3*S*)-(-)-tartaric acid ((2*S*,3*S*)-**160**) as being able to resolve DBAP* **66** (Scheme 87). The initial separation of the enantiomers by Richardson at Eli Lilly, as well as further recrystallisations and purification in our laboratory are described below.



Scheme 87. Resolution of DBAP* catalyst **66** as developed by Eli Lilly.

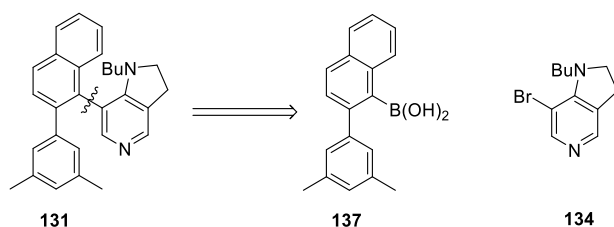
Reagents and Conditions: (i)(a) *i*-PrOH, rt, 5 minutes, solvent removed (89%) (b) recrystallisation from 4-methyl-2-pentanone; (ii)recrystallisation from *i*-PrOH; (iii) $\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$ (10:1), SiO_2 (iv) SCX column (v) recrystallisation from 4-methyl-2-pentanone.

As described by Richardson, formation of the salt proceeded in 89% yield (74% by mass) from 6.2 g of the impure DBAP* **66** (74% by mass). Recrystallisation of the salt from 4-methyl-2-pentanone gave a 36% yield (2.8 g, 3.4 mmol) of the single enantiomer **(-)-DBAP*. (2S,3S)-160** salt in 97.5% *de*. Recrystallisation and formation of the enantioenriched salt also rejected most of the impurities, which were collected in the filtrate. We found that the *de* of the salt could be increased to >99.9% *de* by a further recrystallisation from isopropanol (*de*>99.9%, 64%). Recovery of the “free-based” DBAP* **66** was carried out as previously described for DEAP* **31**,^[121] stirring the salt in a solution of $\text{CH}_2\text{Cl}_2:\text{Et}_3\text{N}$ overnight, followed by evaporation of this mixture and passing the residue dissolved in EtOAc through a short plug of silica. The filtrate from the original recrystallisation was collected by Richardson and “free-based” using an SCX column to provide 61% yield (3.2 g, 79% by mass, 5.8 mmol) of the **(+)-DBAP* catalyst 66**. Purification of this mixture by flash column chromatography at Imperial College yielded 1.99 g of the **(+)-DBAP* 66** (48% yield from original salt formation, minor impurities still present). The *ee* of this mixture was around 85%, as analysed by chiral HPLC at Imperial College, although the impurities could have effected this value This was resolved following the procedure from Richardson with the opposite enantiomer of the acid, 4-methyldibenzoyl-**(2R,3R)-(+)-tartaric acid ((2R,3R)-160)**, allowing for isolation of 69% of the **(+)-DBAP*. (2R,3R)-160** salt in 97.5% *de*, before two further recrystallisations (one from 4-methyl-2-pentanone (85%, 98.5% *de*), one from *i*-PrOH (67%, 99.7% *de*)) to provide the **(+)-DBAP*. (2R,3R)-160** salt. In this case again initial salt

formation again rejected most of the impurities, while collecting the mother liqueurs and one further recrystallisation from *i*-PrOH gave an additional 300 mg of the (+)-DBAP*.*(2R,3R)*-**160** salt (300 mg, 14% yield, 99.7% *de*). Overall, (+)-DBAP*.*(2R,3R)*-**160** was formed in 22% yield from the initial salt formation, in >99.7% *de*. As the salt is more stable and easier to handle than the free catalyst it was decided to keep it in this form and to “free-base” small quantities only when required.

4.1.2 Synthesis of Atropisomeric Catalyst 5-Azy*

The second catalyst we wanted to synthesise was the atropisomeric azaindoline based catalyst 5-Azy* **131**, which was shown by Ausmees and Mohan to be moderately selective while providing increased levels of reactivity compared to DBAP* catalyst **66** (*vide supra*). A retrosynthetic analysis of 5-Azy* catalyst **131** is shown below (Scheme 88).

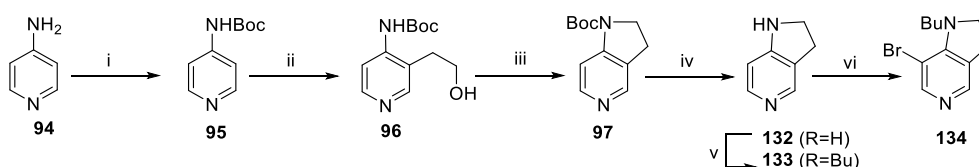


Scheme 88. Retrosynthetic analysis of atropisomeric azaindoline based catalyst 5-Azy* **131**.

The key coupling step in this synthesis is again the challenging formation of the pyridine-naphthyl bond, although with this catalyst this coupling step has been achieved with the xylyl-group already attached, presumably as the azaindoline moiety is slightly less hindered than the dibutylaminopyridine analogue. An extensive catalyst and parameter screen was carried out by Ausmees in order to develop conditions for this coupling. The previously published synthesis for compound **131** (Scheme 74) was carried by Ausmees and Mohan, with separation into enantiomers on a semi-preparative HPLC.^[297]

4.1.2.1 Synthesis of *N*-butyl-5-bromo-1-azaindoline **134**

To start the synthesis, the aryl bromide coupling partner **134** was synthesised in six steps following the previous route as shown below (Scheme 89).

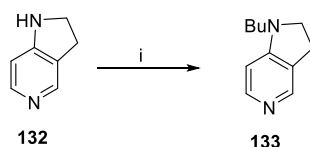


Scheme 89. Synthesis of *N*-butyl-5-bromo-1-azaindoline **134**.

Reagents and Conditions: (i) Boc_2O , DCM, rt, 45 min (previously synthesised); (ii) $t\text{-BuLi}$, THF, $-78\text{ }^\circ\text{C}$ to rt, 2 h, $\text{Br}(\text{CH}_2)_2\text{OLi}$, $-78\text{ }^\circ\text{C}$ to rt, 2 h (72%); (iii) MsCl , Et_3N , CH_2Cl_2 , $-10\text{ }^\circ\text{C}$ to rt, 2 h (92%); (iv) LiAlH_4 , THF, $0\text{ }^\circ\text{C}$ $\rightarrow$ $66\text{ }^\circ\text{C}$, 6.5 h (66%); (v) BuBr , NaH , 15-crown-5, TBAI, $40\text{ }^\circ\text{C}$, 3 h (64%); (vi) NBS , CH_2Cl_2 , $-1\text{ }^\circ\text{C}$, 24 h (75%).

The initial steps were carried out on a small scale as described by Fekner,^[120] starting from **95** which had been synthesised in larger scales by previous group members. Initial addition of bromoethanol in step (ii) resulted in only a 39% yield, which reaction upon scaling to 2 g gave a 72% yield. The following cyclization step with mesityl chloride proceeded cleanly on scales up to 1.21 g (92% yield). Finally removal of the Boc group by LiAlH₄ proceeded with a 66% yield when using a fresh bottle of LiAlH₄ to give compound **132**. Due to the dangers associated with using *tert*-butyllithium, 100 g of compound **132** was ordered by custom synthesis by our collaborators at Eli Lilly from Sphinx Scientific Laboratory Corp for the large scale synthesis of 5-Azy* catalyst **131**.

The rest of the synthesis was carried out as described by Ausmees.^[297] On a small scale of up to 0.7 g, the alkylation proceeded smoothly with a 64% yield, while the bromination with NBS proceeded with a 75% yield on a 0.5 g scale. For scaling up, an alternative reductive amination was developed to avoid the use of sodium hydride and 15-crown-5 (Scheme 90).

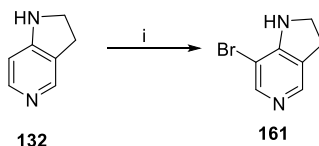


Scheme 90. Alternative route to *N*-butyl-azaindoline **133** by reductive amination.

Reagents and Conditions: (i) butyraldehyde, AcOH, NaBH(OAc)₃, THF, rt, 3 h (93%).

This reaction proceeded well on small scales (<5 g) to give a 78 % yield, while on larger scales (20 g) the yield was 93%. The addition of acetic acid was found to be crucial in this reaction, as otherwise the imine was the main product observed by LCMS. The final bromination step with NBS was also scaled up, with small scale yields quantitative, and the largest scale reaction carried out on 20 g. This large scale reaction showed 100% conversion by LCMS and ¹H NMR analysis, although the crude yield was only 64%. Purification also proved difficult, with only 30% material (10 g) recovered after purification by flash column chromatography.

In order to have increased tunability within the synthesis, the bromide was also added to **132** before the alkylation step, so that the alkyl group can be easily varied in the future (Scheme 91).



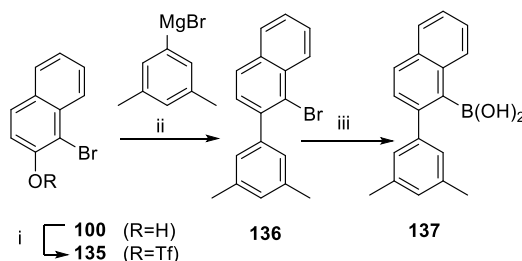
Scheme 91. Bromination of **132** before alkylation to yield **161**.

Reagents and Conditions: (i) NBS, CH₂Cl₂, 0 °C, 2 h (42%).

Although the reaction was complete by LCMS, after an aqueous wash, only 42% of the product was recovered even with basification of the aqueous layer, albeit in 98% purity. Altogether ~6 g of **161** was synthesised.

4.1.2.2 Synthesis of Boronic Acid **137**

The synthesis of the boronic acid **137** was carried out as described by Ausmees, starting from commercially available 1-bromo-2-naphthol **100** (Scheme 92).^[297]

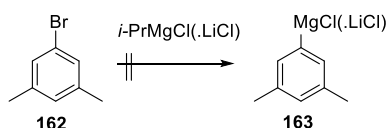


Scheme 92. Synthesis of the boronic acid **137** starting from commercially available 1-bromo-2-naphthol.^[297]

Reagents and Conditions: (i) $\text{ Tf}_2\text{O}$, pyridine, CH_2Cl_2 , 0 °C, 2.5 h (>99%); (ii) 3,5-dimethylphenyl-magnesium bromide, $\text{PdCl}_2(\text{dppp})$, Et_2O , 40 °C, 2.5 h (70%); (iii) $n\text{-BuLi}$, B(OMe)_3 ; -78 °C $\rightarrow$ 0 °C, 17 h (69%).

The triflation proceeded smoothly on scales up to 6.6 g in the laboratory with yields of up to 96%, including purification by column chromatography. On scaling of this reaction, the solvent was changed from pyridine to CH_2Cl_2 and pyridine used instead of 4-DMAP to catalyse the reaction. Upon removal of the solvent and the pyridine, the products from these reactions were clean by ^1H NMR analysis and could be taken straight through to the Kumada coupling. The largest scale reaction for the triflation was 50 g, with an overall quantitative yield. The following Kumada-Corriu coupling proved to be more problematic, as initially several attempts were needed to successfully form the Grignard reagent, and it was found that a large amount of magnesium was still left after the Grignard reagent formation. A second attempt at the reaction (3.92 g) was more successful, as 1.2 equiv. of the 3,5-dimethylphenylbromide was employed relative to the magnesium, resulting in a yield of 70% for the coupling.

However, increasing the scale of this reaction much further (>20 g) would have been problematic. The formation of Grignard reagents on large scale is a relatively difficult process, as the initiation for the Grignard reagent formation is difficult to follow or predict, and large, difficult to control exotherms can be observed once the reaction has initiated.^[311,312] *iso*Propyl magnesium bromide and also the turbo Grignard $i\text{-PrMgCl}\cdot\text{LiCl}$ developed by Knochel are well known to form Grignard reagents by halogen-metal exchange.^[313,314] This was tested on the bromo-3,5-dimethylphenyl **162** to avoid the need to make Grignard reagents on large scale using magnesium (Scheme 93).



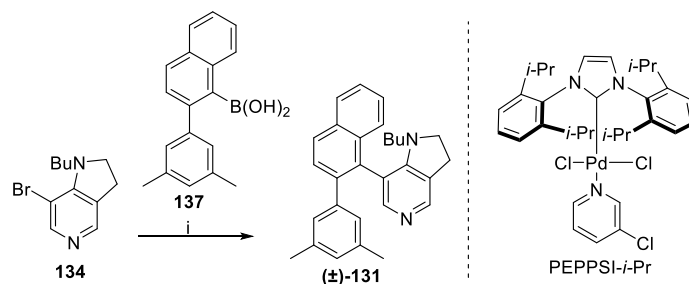
Scheme 93. Attempted formation of Grignard reagent for coupling through reaction with turbo Grignard reagent.

However, all attempts at this failed, with a maximum of 40% conversion to the desired Grignard reagent even after heating and long reaction times. Finally, the Grignard reagent 3,5-dimethylphenyl magnesium bromide was bought from commercial sources. This was used in the previously developed Kumada coupling conditions, changing to THF as the solvent instead of diethyl ether due to the low flash point of diethyl ether. The largest scale attempted for this reaction was on 30 g of the crude triflate, with an overall yield of 64% over two steps from the naphthol.

Synthesis of the boronic acid **137** (Scheme 92, step iii) was carried out as previously described for the 2-benzyloxy analogue in the synthesis of DBAP* **66**. On a small scale (2.28 g) the reaction yielded 69% of the boronic acid, while on a larger scale (5 g) the reaction was less successful, with a yield of 40%. The purification of **137** was less facile than for the 2-benzyloxy analogue **102**, as recrystallisation from CH₂Cl₂ yielded only 24-40% of the desired boronic acid, and flash column chromatography was required to recover the remaining material. No alternative solvents were tried for this process.

4.1.2.3 Palladium Catalysed Suzuki Coupling

A Suzuki coupling was used for the final step in the synthesis of the 5-Azy* catalyst **131** (Scheme 94). This reaction was optimised in the group,^[297] with PEPPSI-*i*-Pr being the catalyst of choice.



Scheme 94. Suzuki coupling for synthesis of (±)-**131**.

Reagents and Conditions: (i) PEPPSI-*i*-Pr, KOH, xylene, μ W 76 °C $\rightarrow$ 180 °C, 65 min OR conventional heating, 180 °C, 2 h (62%).

On a small scale, this reaction proved to be very sensitive to the presence of moisture, and the reaction only proceeded if the dry reagents were first desiccated over phosphorus pentoxide. Changing solvent from toluene to xylene allowed for smooth heating, as previously cracking of the microwave vials during reaction had been observed. With these conditions, the reaction proceeded to >70% conversion on a 70 mg scale, with a 62% isolated yield, and 55% yield on a 300 mg scale. Conventional heating at 180 °C for 2 hours was also successful instead of using microwave conditions, essential for larger scale syntheses as the largest microwave vial is only 20 mL in volume. On a larger scale (0.6 g), the reaction was carried out using conventional heating, also reducing the number of equivalents of boronic acid from 4 to 2.5. This reaction proceeded well, with a 61% conversion by ¹H NMR analysis and good recovery of the product after purification (0.57 g, 60 %).

Separation into enantiomers for use in KR was carried out by CSP-HPLC.

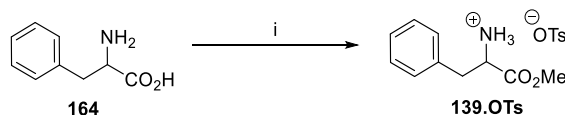
4.1.3 Conclusions and Future Work

The syntheses for the two lead catalysts DBAP* **66** and 5-Azy* catalyst **131** were both optimised and the catalysts synthesised successfully. A large scale procedure was developed for the first seven steps of the synthesis of DBAP* **66** containing only four column chromatography purifications over nine steps. In addition, our collaborators at Eli Lilly developed a method for the classical resolution of DBAP* **66**, which significantly increases the desirability and practicality of this catalyst. A large scale procedure has also been developed up to the final coupling step for 5-Azy* catalyst **131**. Further work is required either to optimise the final steps for the synthesis of DBAP* **66** in the original route without the formation of by-products, or to further develop the direct coupling procedure between boronic acid **137** and dibutylaminopyridine **152** to achieve higher yields and efficient in-situ debromination, as this would decrease the total number of steps. Further scaling of the final coupling step for the 5-Azy* catalyst **131** is also required, while also the yield for the formation of the boronic acid **137** needs to be increased. Finally development of conditions for classical resolution of the 5-Azy* catalyst **131** would be desirable.

4.2 Towards Amine KR

4.2.1 New Catalyst and Background Reactivity Screen

Since the work on amine KR by Davey,^[3] more selective and more reactive analogues of the atropisomeric 4-DMAP catalyst series have been developed in the group, specifically, DBAP* **66** and 5-Azy* catalyst **131**.^[102,208] This work, as well as the recently developed alcohol DKR by Fu^[291] prompted us to start our work by developing an amine KR before moving onto a membrane-enhanced amine DKR, as we believed this would have significantly greater impact than developing an alcohol DKR. The work by Davey on phenylalanine methyl ester salts as substrates for an amine KR was considered an appropriate starting point. As the main hindrance in the previous work had been the unreactivity and low selectivity of the catalysts, it was hoped that the new catalysts would perform better. The tosylate salt of racemic phenylalanine methyl ester was therefore prepared using conditions developed by Davey (Scheme 95).^[3]

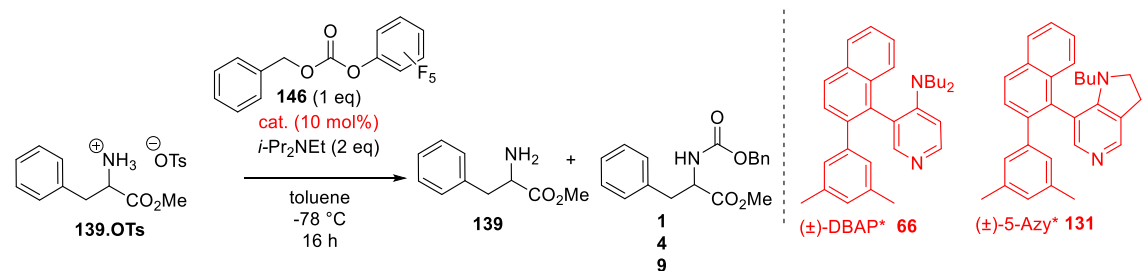


Scheme 95. Preparation of phenylalanine methyl ester tosylate salt **139.OTs** according to the route of Davey.^[3]

Reagents and Conditions: (i) TsOH, MeOH, benzene, reflux, 16 h, (80%).

With the substrate in hand, the background reaction was initially tested, as well as the catalysed rates with 10 mol% of either 4-DMAP or each of the two most promising racemic catalyst candidates using conditions similar to those reported by Davey (16 hour vs 9 hour reaction time) (Table 15).

Table 15. Evaluation of reaction conversions of phenylalanine methyl ester tosylate salt **139.OTs** after 16 hours.



Entry	Temperature (°C)	Catalyst (10 mol%)	Background Conversion (%)	Conversion (%)
1	-78→-60 ^a	DBAP* 66	18	27
2	-78→-60 ^a	4-DMAP	18	74
3	-78	5-Azy* 131	13	74
4	-78	4-DMAP	13	66

^aVarying temperature due to problems with cryostat.

While temperature control problems were initially observed due to cryostat malfunction, the high background reactivity and the small differential of $\times 1.5$ between the catalysed and background reaction for DBAP* catalyst **66** was clearly observed (Table 15, entry 1) and demonstrated that DBAP* catalyst **66** is significantly less reactive than 4-DMAP itself at least for this particular transformation (entry 2), and that for future kinetic studies it would be inadvisable to use 4-DMAP to map the reactivity of catalyst **66**.

It was then decided to test the 5-Azy* catalyst **131**, which had in previous alcohol KR studies been shown to be the more reactive of the two asymmetric catalysts.^[297] Using 10 mol% of the 5-Azy* catalyst **131** gave 74% conversion after 16 hours (Table 15, entry 3), while 4-DMAP itself as a catalyst gave 66% conversion (entry 4). The background conversion was 13% over 16 hours (entries 3 and 4). This was a positive result, with catalyst **131** giving a higher final conversion than 4-DMAP itself for this reaction. Although over this time period the difference in final conversions between the catalysed and the background reaction was not suitable for achieving an efficient KR, it was nevertheless anticipated that stopping the reaction earlier might maximise the catalysed reaction while minimising the impact from the background if the initial rate of catalysed reaction was fast.

We next decided to investigate the effect of having a salt as the starting substrate. One main factor when using a salt is the need to include a base in the reaction to “free-base” the salt. Previous studies by Davey had shown that triethylamine can catalyse the reaction,^[3] which is why Hünig’s base was used in all the reactions above. Although Hünig’s base is unlikely to act as a nucleophile, it could possibly still have an effect on the reaction through a base-catalysed acylation. Indeed, Litvinenko proposes that for the reaction of primary amines with acyl donors, 4-DMAP acts as a general base.^[315]

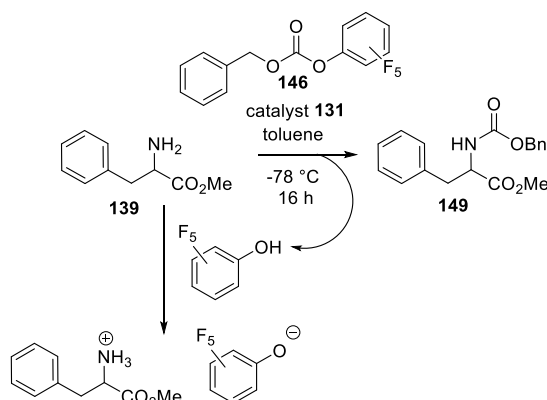
To this end, a series of experiments were run where the starting material was “free-based” by shaking with *aq.* K₂CO₃, extracting into ethyl acetate, drying over sodium sulfate and removing the ethyl acetate *in vacuo* immediately prior to the reaction (Table 16).

Table 16. Effect of base and catalyst on the conversion of the carbamylation of amino acid ester **139**.

Entry	Catalyst	Base	Conversion (%)
1	5-Azy* 131	✓	66
2	-	✓	24
3	5-Azy* 131	-	44
4	-	-	15
5	4-DMAP	-	51

The use of both the base and the 5-Azy* catalyst **131** gave a 66% conversion after 16 hours (entry 1), the use of 2 equivalents of the base gave 24% conversion (entry 2), while 10 mol% of the catalyst gave 44 % conversion (entry 3). The background reaction, with neither base nor catalyst added gave 15% background conversion (entry 4). The use of 4-DMAP as a catalyst with no base present gave a 51% conversion after 16 hours (entry 5).

Interestingly, the maximum conversion reached even with 4-DMAP with no base present was 50%; previously it has been suggested that without a base present in the reaction, the phenol produced as a side-product by the acylation would protonate the remaining starting material, effectively stopping the reaction at 50% conversion and this did indeed seem to be the case (Scheme 96).



Scheme 96. Proposed deactivation of amine substrate by pentafluorophenol side-product of carbamylation.

5-Azy* catalyst **131** and 4-DMAP gave very similar conversions, demonstrating that 5-Azy* catalyst **131** is a very reactive asymmetric catalyst. Nevertheless, the background reaction was also very high, and the overall conversion with 5-Azy* catalyst **131** was only three times as high as the background reaction after 16 hours, which is not a large enough differential for a useful KR.

As the reaction stopped at 50% conversion, we thought it was possible that the catalysed reaction proceeds quickly to ~ 50% conversion before stopping due to deactivation, while the background was much slower. If this were true, it would mean that the catalysed reaction could be stopped after a matter of hours with 50% conversion, and a minimal background reaction. Previous results by Davey also support this hypothesis, as he reported 0% conversion after 9 hours for the background reaction, and 40% conversion with 4-DMAP after 9 hours in the reaction with the tosylate salt.^[3] Therefore, kinetic studies were required to see how rapidly the catalysed reaction proceeded to completion (50% conversion in this case), and to confirm that the background reaction did not also have the same fast initial reaction rate. Work by Seidel also prompted us to also look at the difference that the concentration can have on the reaction^[299] (Table 17).

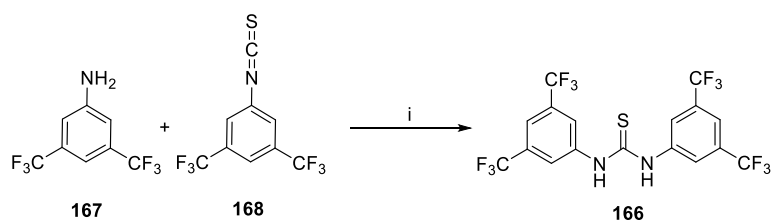
Table 17. Evaluation of reaction parameters after 1 hour for carbamylation of “free-based” phenylalanine methyl ester.

Entry	Concentration (M)	4 Å MS	Acyl donor	Conversion (%)
1	0.5	-	146	4
2	0.5	✓	165	3 ^a
3	0.01	✓	165	0 ^a

^aMolecular sieves added to reaction

After 1 hour at -78 °C, 4% conversion was observed by ¹H NMR when using phenylalanine methyl ester, with the fluorinated carbonate acyl donor **146** (entry 1). Using benzoic anhydride **165** as the acyl donor as employed by Seidel, 3% conversion was obtained after 1 hour (entry 2). Using a 0.01 M concentration with benzoic anhydride gave no observable conversion by ¹H NMR spectroscopy (entry 3), indicating the effect of the concentration on reducing conversion. This low concentration did however make the reaction impractical.

Work by Seidel also prompted us to evaluate the effect of hydrogen bond donors in the KR, as he reported a large increase in conversion upon use of a chiral hydrogen bond donor.^[299] Potentially, employing an achiral hydrogen bond donor in tandem with our 5-Azy* catalyst **131** could increase the reactivity of the catalysed system. To test this hypothesis, a commonly used achiral HB donor **166** was selected and synthesised (Scheme 97).^[316]

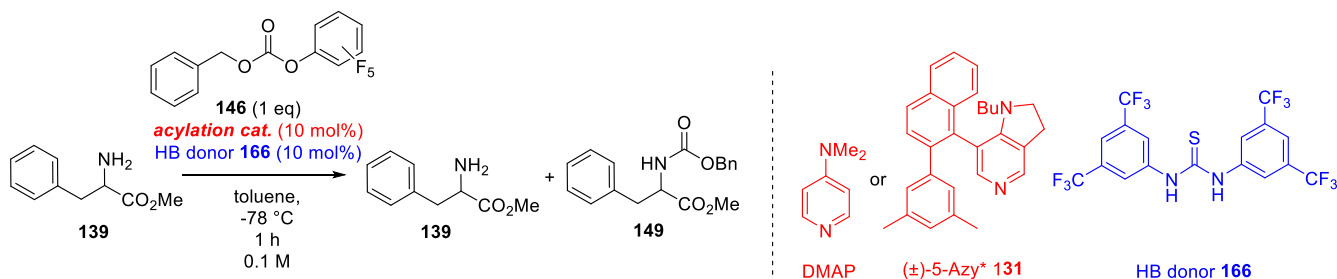


Scheme 97. Synthesis of (3,5-trifluoromethyl)thiourea **166** according to the method of Mukherjee.^[316]

Reagents and Conditions: (i) THF, 50 °C, 80 h, (>99%).

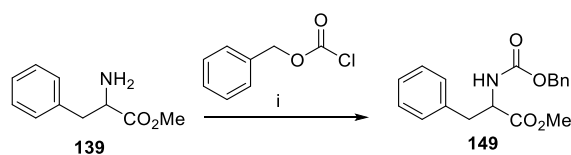
The acylation was also carried out with a 5× reduction in concentration to minimise the background reaction, while still retaining the practicality of the reaction (Table 18).

Table 18. Effect of HB donor **166** on KR of phenylalanine methyl ester **139**.



Entry	HB catalyst 166	Carbamylation Cat.	Conversion (%)
1	-	-	0
2	-	4-DMAP	43
3	✓	-	0
4	✓	4-DMAP	37
5	-	5-Azy* 131	24

The HB donor **166** (entries 1 and 3) had absolutely no effect on the conversion after 1 hour at -78 °C. However, for the first time, no background conversion was observed in the absence of a catalyst (entry 1), while 4-DMAP itself catalysed the reaction to 43% after 1 hour (entry 2). This was a promising result, and encouraged us to also test the racemic catalyst 5-Azy* **131** for reactivity. This catalyst gave good levels of conversion (24% C after 1 hour, entry 5), prompting us to attempt a KR using the conditions shown at 0.1 M concentration. In order to enable the product identification, authentic racemic Cbz protected phenylalanine methyl ester **149** was synthesised as shown below (Scheme 98).



Scheme 98. Synthesis of Cbz-protected phenylalanine methyl ester **149**.

Reagents and Conditions: (i) CH₂Cl₂, rt, 16 h (60%).

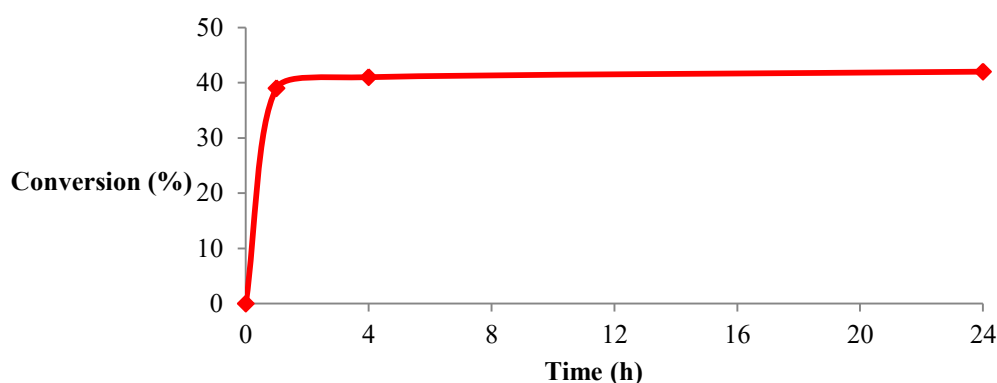
As we planned to run the reaction at -78 °C, quenching removed aliquots of a reaction was anticipated to be extremely difficult to achieve without any warming taking place, which would in turn influence both conversion and possibly selectivity. Consequently, three separate reactions were set up from stock solutions, which were stopped after 1 hour, 4 hours and 24 hours respectively, and the conversions and *ee* measured by chiral HPLC (Table 19).

Table 19. KR of phenylalanine methyl ester **139** with pentafluorophenyl benzyl carbonate **146** at -78 °C, catalysed by 5-Azy* catalyst **131**.

Reaction scheme: **139** + **146** (1 eq, cat. 10 mol%) in toluene at -78 °C, 0.1 M, yields **139** and **149**. Catalyst: **(-)-5-Azy* 131**.

Time (h)	<i>ee</i> of amine	<i>ee</i> of carbamate	Conversion (%)	<i>S</i> ^a
1	19	26	42	2.04
4	18	28	39	2.09
24	20	28	41	2.14

^a stereochemistry randomly assigned



The conversion was ~42% after the first hour, and remained at this level for the next 23 hours. Presumably, this was due to substrate deactivation by the pentafluorophenol by-product (Scheme 96). The results also showed a selectivity of *s* = 2.1. This first result for a KR was disappointing, as although the reactivity of the catalyst was increased as hoped and the selectivity was marginally higher, it still remained too low for a viable KR.

4.2.2 Acylating Agent and New Substrate Screen

Further improvements were clearly required to increase the selectivity of this system. However, discussions with colleagues in Chemical Engineering about developing this work into a MEDKR alerted us to the

challenges associated with using membranes at $-78\text{ }^{\circ}\text{C}$ as they have not previously been tested at such low temperatures. Also, the system would require significant amounts of energy to cool the solvent flow from $90\text{ }^{\circ}\text{C}$ (required for a racemisation) to $-78\text{ }^{\circ}\text{C}$ in the MEDKR system. Consequently, we decided to evaluate a further set of deactivated primary amines for their viability in a KR at $0\text{ }^{\circ}\text{C}$ or room temperature using three different acyl donors with varying reactivity (Figure 28).

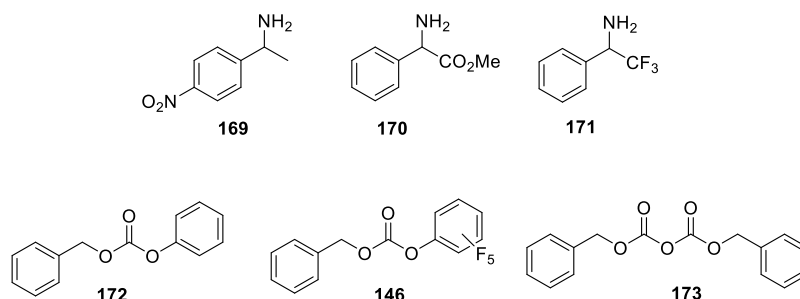
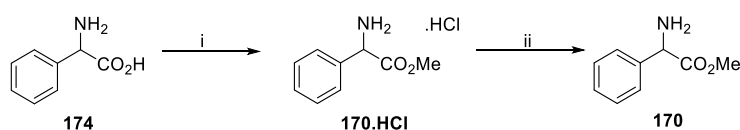


Figure 28. Screen of potential deactivated amines **169**, **170** and **171** and acyl donors **172**, **146** and **173** for KR development.

None of the chosen substrates were commercially available at a reasonable price and were therefore synthesised using literature procedures. The acyl donor **146** was synthesised as previously described.^{[216][3]} Compounds **172** and **173** were commercially available.

Phenylglycine methyl ester **170** was prepared using the following route (Scheme 99).^[317]

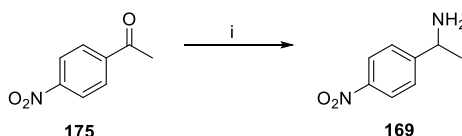


Scheme 99. Synthesis of phenylglycine methyl ester **170** via methylation and subsequent “free-basing”^[317]

Reagents and Conditions: (i) SOCl_2 , MeOH, reflux, 2.5 h (>99%); (ii) aq. K_2CO_3 , extraction into EtOAc (60%).

The phenylglycine methyl ester hydrochloride salt **170.HCl** was obtained in quantitative a yield, and was free-based prior to use in a 60% yield.

The 1-(*para*-nitrophenyl)ethanamine **169** was prepared using a reductive amination method (Scheme 100).^[318]



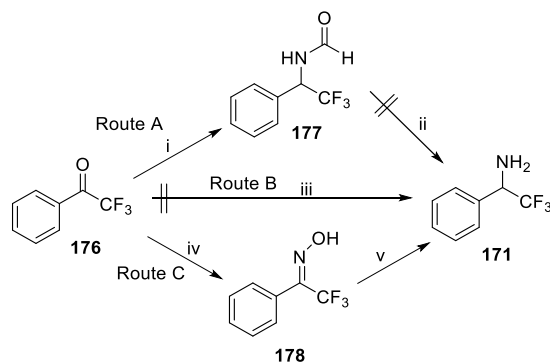
Scheme 100. Synthesis of 1-(*para*-nitrophenyl)ethanamine **169**.^[318]

Reagents and Conditions: (i) $\text{NH}_4\text{CO}_2\text{Me}$, NaCNBH_3 , MeOH, rt, 48 h (33%).

The yield of the 1-(*para*-nitrophenyl)ethanamine **169** was only 33% yield after aqueous work-up, albeit with no need for further purification. At a second attempt, a large number of by-products were observed in the ^1H

NMR of the crude product, with the most significant being the 1-(*para*-nitrophenyl)ethanol. However, enough of this amine was synthesised for initial testing of the KR.

The trifluoromethylated compound **171** proved difficult to obtain. The initial route explored, starting with trifluoromethylacetophenone **176**, involved the use of ammonium formate both as the amine source and as the reducing agent to give formamide **177** which would then be hydrolysed (Scheme 101, Route A).^[319]



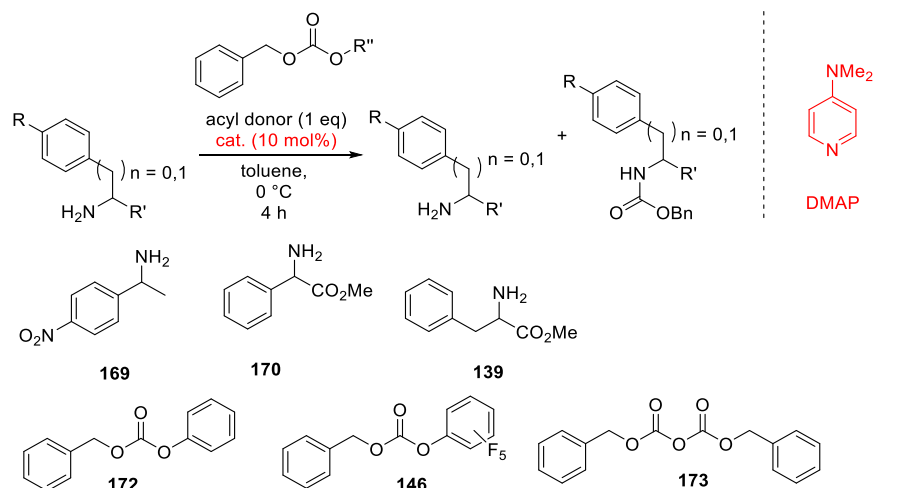
Scheme 101. Attempted routes towards the synthesis of α -trifluoromethylbenzylamine **171**.^[318–320]

Reagents and Conditions: Route A (i) $\text{NH}_4\text{CO}_2\text{H}$, 120 °C, 6 h (>99%) (ii) NaOH(aq) , MeOH, 60 °C, 3 h (0%) Route B (iii) $\text{NH}_4\text{CO}_2\text{Me}$, NaCNBH_3 , MeOH, rt (0%) Route C (iv) $\text{NH}_2\text{OH.HCl}$, NaOAc, H_2O , EtOH, 85 °C, 16 h (>99%) (v) Pd/C , H_2 (1 atm), AcOH, Et_2O , rt, 16 h, (70%).

The first step worked well and gave the formamide **177** in quantitative yield, but the hydrolysis did not occur, even when heating at reflux at 100 °C for 4 hours. The second attempt used the same procedure as had been successful for the 1-(*para*-nitrophenyl)ethylamine (Scheme 101, Route B).^[318] However, this reaction also gave a complex mixture of products with no evidence for the desired product by ^1H NMR analysis of the reaction mixture. A final procedure was attempted which converted the starting ketone to oxime **178**, followed by hydrogenation to the amine (Scheme 101, Route C).^[320] The oxime **178** was obtained in quantitative yield, and the following hydrogenation product was purified by distillation, to give a 70% yield over two steps.

Reactions were then performed at 0 °C with the new amine substrates and acyl donors, using 4-DMAP to map the reactivity of 5-Azy* catalyst **131** with the substrates (Table 20).

Table 20. Background and catalysed reactions of deactivated amines **169**, **170** and **139** with acyl donors **172**, **146** and **173**.



Entry	Amine	Acyl Donor	Catalysed	Background
1	169	172	0	0
2	170	146	0	0
3	169	146	46	13
4	170	146	45	25
5	139	146	53	26
6	169	173	100 ^a	100
7	170	173	100	100

^aDimerisation to form a urea compound also observed through 4-DMAP activation^[7]

Benzyl phenyl carbonate **172** proved to be too unreactive (entry 1), even when the reaction temperature was increased to 50 °C, indicating that the pyridinium salt is not formed. Dibenzyl dicarbonate **173** proved to be too reactive under the conditions tested (entries 6 and 7). Pentafluorophenyl benzyl carbonate **146** did however provide different levels of catalysed and uncatalysed reaction for the substrates. The greatest difference in background and catalysed reactivity was with the 1-(*para*-nitrophenyl)ethylamine **169**, with a 3.5 fold differential between the background and the catalysed conversion. The two amino acid derivatives showed a two-fold differential between the background and the catalysed conversion.

A further set of carbonate acyl donors was then evaluated, with reactivities anticipated to lie between that of benzyl phenyl carbonate **172** (unreactive) and pentafluorophenyl benzyl carbonate **146** (high background reaction). In order to find compounds in this reactivity range, we used the pK_a of the phenol as being indicative of reactivity/leaving group ability (Figure 29).

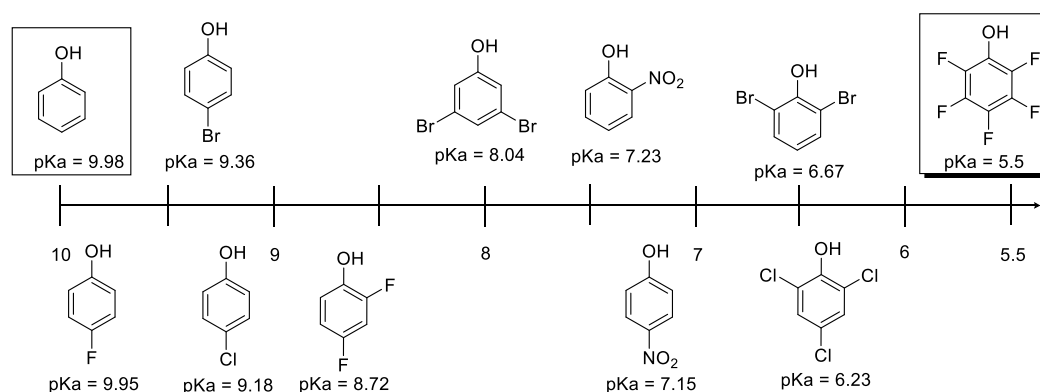
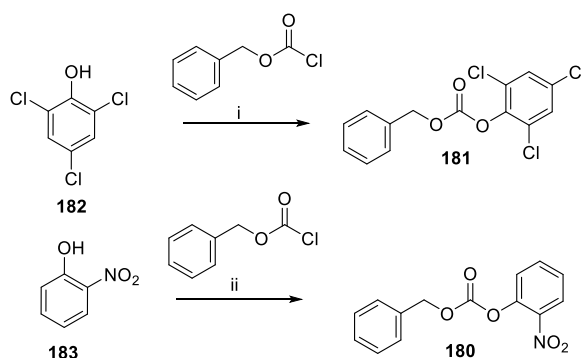


Figure 29. pK_a values for a series of phenols for potential incorporation into mixed carbonates to be used in KR reactions.

Previous studies by Davey^[3] showed that *p*-nitrophenyl benzyl carbonate did not react with 4-DMAP at -78 °C, and so the relevant range of pK_a values was between 5.5 and 7.15. Trichlorophenol was chosen as a test substrate as this had a pK_a value of 6.23 which was in the desired range, and was also readily available. It was also decided to test the commercially available *p*-nitrophenyl benzyl carbonate **179** at 0 °C, and the *o*-nitrophenyl benzyl carbonate **180**, as an interesting study by Brunelle^[321] indicated that *o*-nitrophenyl carbonate showed remarkable activity towards 4-DMAP compared to the *para* isomer.

The trichlorophenyl benzyl carbonate **181** was synthesised using the previous procedure for carbonate synthesis (Scheme 102).^[3]



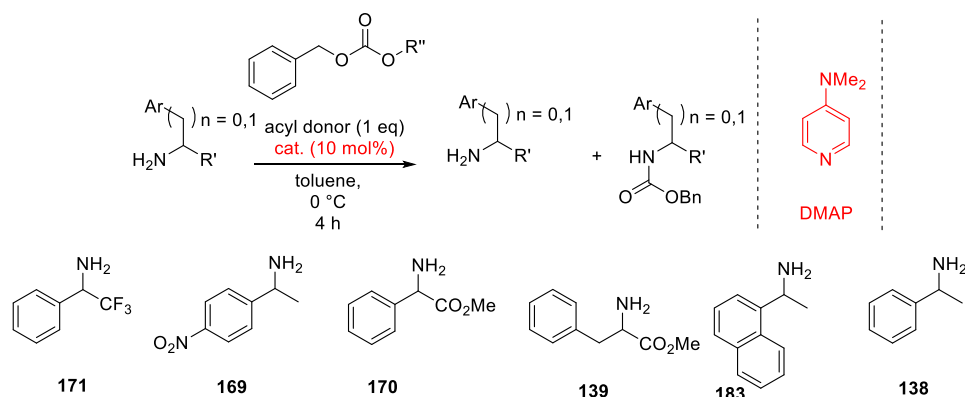
Scheme 102. Synthesis of trichlorophenyl benzyl carbonate **181**^[3] and *o*-nitrophenyl benzyl carbonate **180**.^[322]

Reagents and Conditions: (i) quinoline, CH_2Cl_2 , rt, 72 h (72%) (ii) *i*-Pr₂NEt, THF, rt, 17 h (46%).

The synthesis of **181** proceeded in 72% yield following a procedure from Davey for the corresponding pentafluorophenyl carbonate. The *o*-nitrophenyl benzyl carbonate **180** was synthesised in a moderate yield using a literature procedure (Scheme 102).^[322]

The combined results for all the acyl donors and amine substrates tested are shown below. The reactivity of the amines increases from **171**→**169**→**170**→**139**→**183**→**138**.

Table 21. Assessment of background and catalysed reactions for new amine substrates **138-139**, **169-171** and **183** with carbonates **146**, **172-173** and **179-181**.



Entry	Amine	Acyl Donor (R =)	Catalysed	Background
1	171	C_6F_5	0	0
2	169	C_6H_5	0	0
3	169	C_6F_5	46	13
4	169	$\text{CH}_2\text{C}_6\text{H}_5$	100	100
5	170	C_6H_5	0	0
6	170	$o\text{-NO}_2\text{C}_6\text{H}_4$	13	0
7	170	$p\text{-NO}_2\text{C}_6\text{H}_4$	11	0
8	170	$2,4,6\text{-C}_6\text{H}_2\text{Cl}_3$	8	0
9	170	C_6F_5	45	25
10	170	$\text{CH}_2\text{C}_6\text{H}_5$	100	100
11	139	$2,4,6\text{-C}_6\text{H}_2\text{Cl}_3$	20	<2
12	139	C_6F_5	53	26
13	183	C_6F_5	50	31
14	138	C_6F_5	50	50

The trifluoromethylated amine **171** did not show any reaction in the presence of 4-DMAP (entry 1), indicating that it was too deactivated to react under these conditions, even when the temperature was increased to 50°C . Of the new acyl donors tested **172**, **179**, **180** and **181** gave 0% background reaction at 0°C with phenylglycine methyl ester **170** (entries 5-9), while **179**, **180** and **181** still showed some activity when 4-DMAP was present (entries 6-9). However, the conversions were very low even with 4-DMAP. Changing the amine to phenylalanine methyl ester **139** (entry 11) almost doubled the conversions obtained in the 4-DMAP catalysed reaction, while also giving a slightly faster background reaction. α -Methylbenzylamine **138** (entry 14) proved too reactive under the conditions tested, giving 50% background conversion with pentafluorophenyl benzyl carbonate. Naphthyl amine **183** (entry 13) did give some differential between the catalysed and the uncatalysed reaction, although not enough to be useful for KR. The reactions of phenylalanine methyl ester and phenylglycine methyl ester with trichlorophenyl benzyl carbonate (entries 8 and 11) were deemed to show the most promise for optimisation and so the rates of

conversion in these reactions were monitored at both 0 °C and room temperature. This required multiple samples to be taken over a 24 hour period (Figure 30).

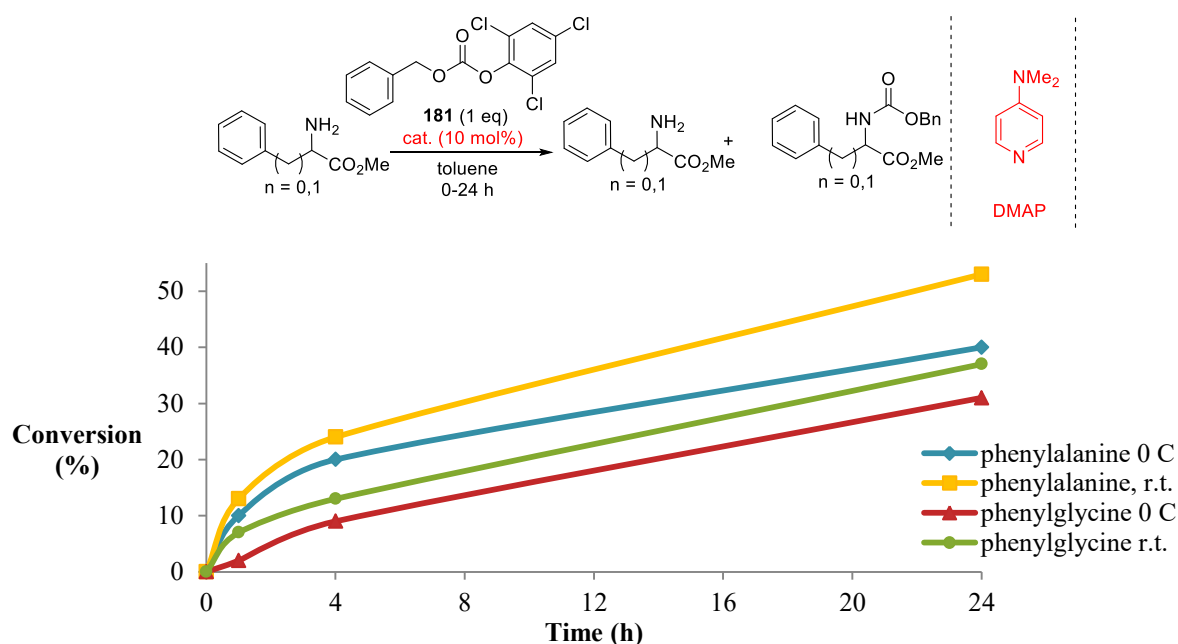


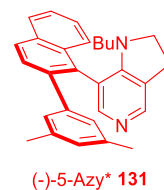
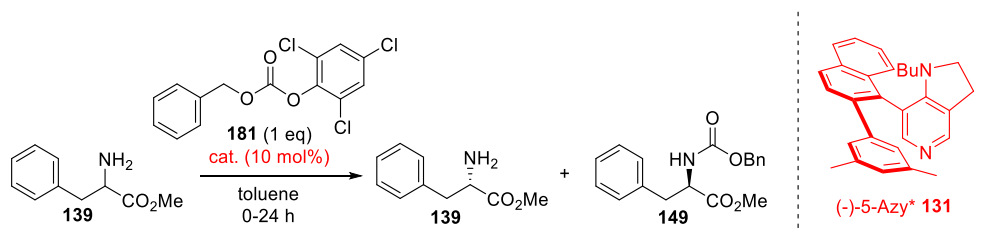
Figure 30. 4-DMAP-catalysed conversion for phenylalanine methyl ester **139** and phenylglycine methyl ester **170** at rt and 0 °C.

The table below also gives the background conversion compared to the catalysed conversion for the reactions above (Table 22).

Table 22. Catalysed and background reactions for reactions of phenylalanine methyl ester **139** and phenylglycine methyl ester **170** with trichlorophenyl benzyl carbonate **181** at 0 °C and at room temperature.

Entry	Amine	Temperature	Catalyst	Conversion (%)		
				1 h	4 h	24 h
1	170	rt	-	0	<1	5
2	170	rt	✓	7	13	37
3	170	0	-	0	0	<2
4	170	0	✓	2	9	31
5	139	rt	-	0	<2	10
6	139	rt	✓	13	24	53
7	139	0	-	0	<2	5
8	139	0	✓	10	20	40

Although the background conversion for **139** was higher than for **170** (entries 1 and 3 vs entries 5 and 7), the higher catalysed conversion was still advantageous for measuring the *ee* of the product and starting material during a KR (entries 2, 4, 6 and 8). These conditions were therefore chosen to test a KR with an enantiomerically pure catalyst. During the KR, aliquots were taken every 30 minutes for four hours. Control reactions containing no catalyst and 4-DMAP were also performed in parallel (Figure 31).



*Stereochemistry randomly assigned

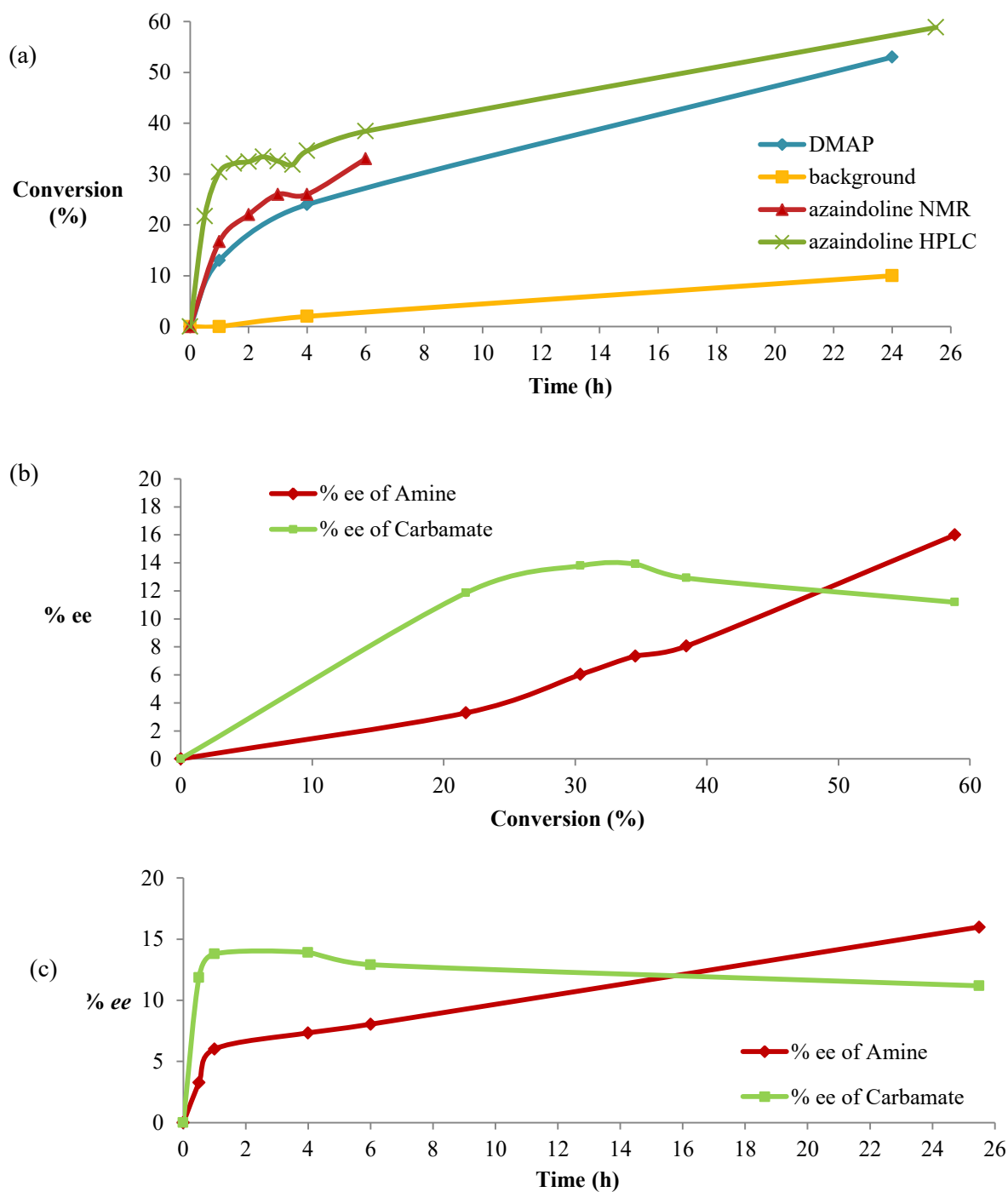


Figure 31. KR of phenylalanine **139** at rt (a) % conversion of reaction vs time. (b) % ee of reagents vs % conversion. (c) % ee of reagents vs time.

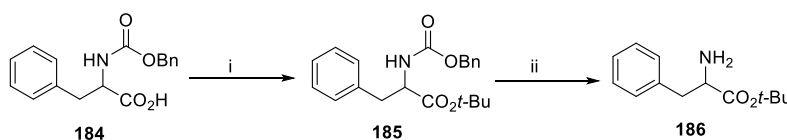
It was found that 5-Azy* catalyst **131** is very reactive, with conversions by ^1H NMR higher than with 4-DMAP under these conditions (Figure 31(a)). There is a discrepancy between conversions calculated from ^1H NMR data on the crude samples, and those calculated from HPLC trace analysis, therefore the HPLC conversions were used to calculate selectivity as these were expected to be more accurate. Each sample was run through the HPLC three times and the mean value of conversion plotted for each time point. It is apparent from inspection of the graphs showing % *ee* vs. either conversion or time (Figure 31 (b) and (c)) that the reaction proceeds rapidly to about 30% conversion (*i.e.* in about 40 min) but then slows significantly. A selectivity value of $s \sim 1.5$ could be calculated consistently for each time point, indicating that while the catalyst does exhibit some enantiodiscrimination, it is not selective enough to form the basis of a practically useful KR procedure.^[42] The selectivity is also lower than that found at $-78\text{ }^\circ\text{C}$. This is presumably due to the higher background rate of reaction under these conditions.

Previous results had shown that DBAP* catalyst **66** was significantly less reactive than both 4-DMAP and the 5-Azy* catalyst **131** used above.^[297] However, as in alcohol KR studies it had been shown to be very selective,^[297] this catalyst was also tested under analogous reaction conditions, *i.e.* over 24 hours at $-78\text{ }^\circ\text{C}$, and over 4 hours at rt.

The poor catalytic activity of DBAP* **66** under both conditions was evidenced by the low conversions observed: $C = 2\%$, $s = 1.14$ after 4 hours at rt, and $C = 8\%$, $s = 1.8$ after 24 hours at $-78\text{ }^\circ\text{C}$. As the selectivities were also very disappointing, even when compared to the 5-Azy* catalyst **131**, the DBAP* **66** catalyst was not used in further studies towards amine KR.

4.2.3 Increasing Substrate Bulk

In order to increase the selectivity in these reactions, one possible option was to change the nature of the ester ‘protecting group’ on the α -amino acid so as to tune the steric differentiation between the two groups attached to the stereogenic centre. To this end, the *tert*-butyl ester of phenylalanine was selected for attempted KR. This compound was synthesised using the route shown below (Scheme 103).^[323,324]



Scheme 103. Synthesis of phenylalanine *tert*-butyl ester **186**.^[325]

Reagents and Conditions: (i) $(\text{Boc})_2\text{O}$, 4-DMAP, *t*-BuOH, rt, 3.5 h (84%) (ii) Pd/C, H_2 , EtOAc, rt, 24 h (90%).^[323,324]

In addition to looking at the effect of changing the ester group, the addition of both a base, LiBr and 18-crown-6 was also tested in the KR, as previously Fu^[2] had shown that the addition of LiBr and 18-crown-6 increased the selectivity in his related KR studies, and we were interested to see the effect of the base on the selectivity. The results with the *tert*-butyl ester **186** are summarised below (Table 23).

Table 23. KR of phenylalanine *tert*-butyl ester at -78 °C.

Entry	Base	LiBr	Time (h)	C (%)	<i>S</i> ^a
1	-	-	4	43	2.9
2	✓	-	4	98	1.05
3	✓	-	0.3	24	3.2
4	-	✓	4	25	2.3
5	-	✓ + 18-crown-6	1	25	3.2

^a stereochemistry randomly assigned

We were pleased to see an increase in selectivity in these reactions to $s = 2.9$ (*cf.* $s = 2.1$ for the methyl ester, see Table 19) when no further additives were included at -78 °C (entry 1). The effect of adding a tertiary amine ancillary base was, as expected, to allow these reactions to proceed beyond 50% conversion; indeed, the effect that the base had on the selectivity could not be accurately confirmed due to the high conversion achieved in the first experiment attempted ($C = 98\%$ after 4 hours, entry 2). A second attempt, in which the reaction duration was restricted to just 20 minutes however showed that the addition of 2 equivalents of base increased the selectivity from 2.9 to 3.2 (entry 3). The addition of LiBr did not increase the selectivity, and the conversion was also reduced (entry 4), while the combination of LiBr and 18-crown-6 also increased the selectivity to 3.2 (entry 5).

As the *tert*-butyl ester was found to have a positive effect on the selectivity, other bulky phenylalanine esters were also investigated: diphenylmethyl ester **187** and adamantyl ester **188**.

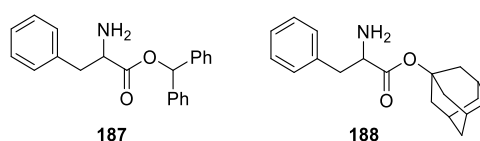
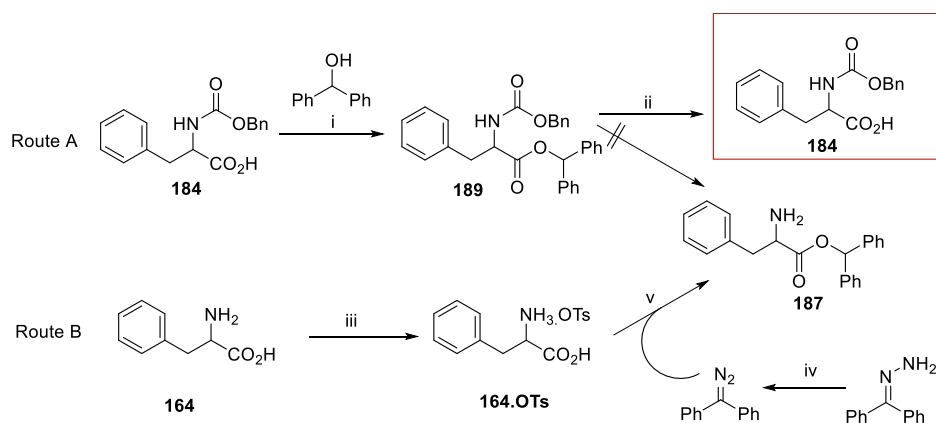


Figure 32. Phenylalanine diphenylmethyl ester **187** and phenylalanine adamantyl ester **188**.

Initial attempts to prepare diphenylmethyl ester **187** started from *N*-Cbz protected phenylalanine (Scheme 104, Route A).^[326]



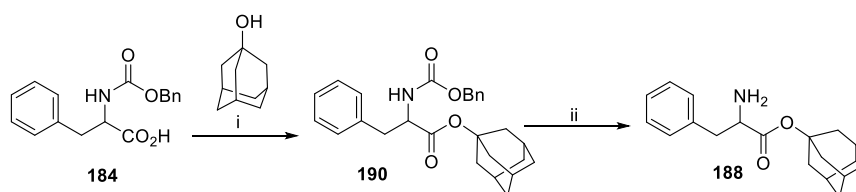
Scheme 104. Attempted synthesis of phenylalanine diphenylmethyl ester **187**.

Reagents and Conditions: Route A (i) DCC, 4-DMAP, CH_2Cl_2 , rt, 3 h (95%) (ii) Pd/C, H_2 , EtOAc, rt, 3 h (0% of desired product) Route B (iii) $\text{TsOH} \cdot \text{H}_2\text{O}$, H_2O , 60 °C, 1 h (54%) (iv) Ag_2O , MgSO_4 , pet. ether, rt, 30 min (formed *in situ*) (v) DMF, 50 °C, 10 min (73%).

Although the esterification with diphenylmethanol proceeded to complete conversion (by ^1H NMR analysis), the subsequent hydrogenolysis to remove the carbamate protecting group was unsuccessful, as the ester was deprotected preferentially. Careful monitoring by TLC showed that the reaction was complete after 3 hours and no trace of the desired product was formed during that period.

An alternative route started from the phenylalanine **164** itself. The tosylate salt of this α -amino acid was formed and then reacted with diphenyldiazomethane to give the ester **187** in an overall yield of 39% (Scheme 104, Route B).^[325] The diphenyldiazomethane was formed *in situ* from benzophenone hydrazone using silver oxide as the oxidant,^[327] and was used without purification for the esterification.

The adamantyl ester **188** was synthesised by coupling *N*-Cbz phenylalanine with 1-adamantol using DCC followed by hydrogenolysis of the carbamate protecting group (Scheme 105).^[326]

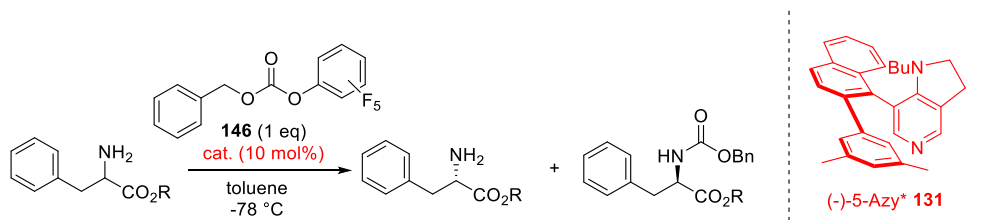


Scheme 105. Synthesis of phenylalanine adamantyl ester **188**.^[326]

Reagents and Conditions: (i) 4-DMAP, DCC, CH_2Cl_2 , rt, 16 h (54%) (ii) Pd/C, H_2 , EtOAc, rt, 16 h (77%).

The esterification proceeded in 54% yield, while the hydrogenolysis, employing 10% Pd/C and an atmosphere of H_2 gas, gave the product in 77% yield. The results of KR reactions with these new substrates are shown below (Table 24).

Table 24. KR with phenylalanine diphenylmethyl and adamantyl esters at -78 °C



Entry	R	C (%) ^a	S ^b
1	CHPh ₂	28	1.6
2	adamantyl	12	1.9

^aConversion calculated by ¹H NMR analysis of the crude reaction mixture ^b stereochemistry randomly assigned

Disappointingly, further increasing the steric bulk of the ester protecting group from the *tert*-butyl to the diphenylmethyl or adamantyl esters in fact reduced selectivity in the reaction from *s* = 2.9 to 1.6 and 1.9 respectively.

Despite their superficial structural homology with *sec*-alcohols, it was becoming apparent that α -chiral primary amines present different challenges when trying to achieve good discrimination between their enantiomers for KR using atropisomeric 5-Azy* catalyst **131**. Clearly, we needed to establish which features were responsible for the differences. Previously, a transition state model for the acylative KR of *sec*-alcohols using atropisomeric DEAP* catalyst **31** had been developed and shown to account for the sense of selectivity and be broadly consistent with the levels of selectivity achieved experimentally.^[121] This model, which has also been corroborated computationally,^[126] invokes the approach of the alcohol from the face of the acyl pyridinium intermediate opposite to that blocked by the 2-phenyl substituent on the naphthyl ring. The conformation of the acyl group is such that the carbonyl bond is parallel to the biaryl axis and then the reactive enantiomer of the *sec*-alcohol is the one that can orientate itself such that the hydrogen substituent points toward the *peri* hydrogen of the naphthyl ring, the smallest of the two substituents lies under the acyl group and the largest one points away from the complex mainly for steric reasons. The carboxylate counter anion is envisaged to be located on the reactive face of the pyridinium ring and participate as a general base aiding deprotonation of the alcohol as it approaches the carbonyl carbon (Figure 33a).

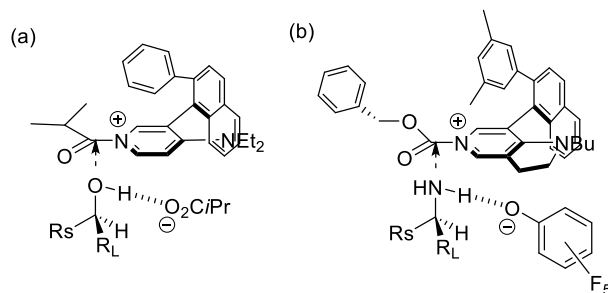


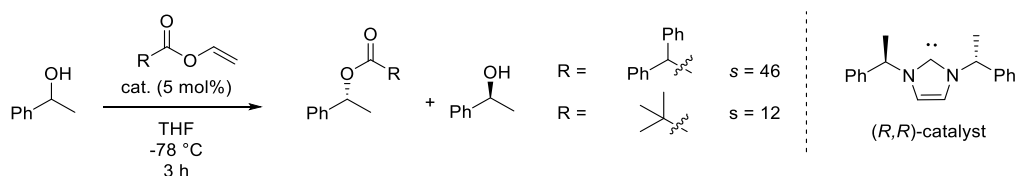
Figure 33. Proposed transition state models: (a) for *sec*-alcohol acylative KR catalysed by chiral catalysts DEAP* **31**, and (b) for amine carbamylative KR catalysed by chiral 5-Azy* catalyst **131**.

If an analogous transition state applied in the case of α -chiral primary amines (Figure 33b), then it is possible that increasing the size of the ester group meant that this substituent became more similar in size to the benzyl group and hence that the catalyst could not effectively differentiate between the two groups. However, it is also quite probable that the transition state for amine carbamoylation with a carbonate differs significantly from that for alcohol acylation with an anhydride. Although the gross features are likely to be similar, we questioned whether the conformation of the carbonyl would be similarly controlled and whether there would be any participation of phenolate counter anion in attack of the amine at the carbonyl. Moreover, we did not have a directly comparable *sec*-alcohol to our phenylalanine esters with which to compare selectivity data directly and we knew that although many *sec*-benzylic alcohols gave excellent selectivity values ($s > 50$ in some cases,^[297] albeit with the DEAP* **31** catalyst) *sec*-alcohols having alkyl and benzyl substituents are generally less selective substrates for KR.^[150]

In an attempt to improve the selectivity with our amine substrates, we first identified some key differences between these and the *sec*-benzylic alcohols that we knew to be good substrates:

- An extra methylene group between the amine and the aryl group in phenylalanine.
- The presence of the ester instead of an alkyl group as R_S .
- A carbonate as the acyl donor instead of an anhydride. This changes both the counter-ion and the electrophilic centre on the pyridinium salt.

All three of these differences could be having a large effect on the selectivity. For example in the proposed model above (Figure 33) for the Cbz-catalyst adduct, the steric bulk of the acyl group is further away from the electrophilic carbonyl centre than with the anhydride. As the steric bulk of the anhydride was found to have a significant impact on selectivity for alcohols (*e.g.* *isobutyric* anhydride compared to *acetic* anhydride), this could also be having an effect here. Indeed, previously published work by Maruoka^[328] and Shiina^[165] also shows that the bulk of the acyl donor has a large effect on selectivity in KRs, with one example from Maruoka showing a four-fold increase in selectivity from $s = 12$ to 46 when a *tert*-butyl group was exchanged for a diphenylmethyl group (Scheme 106).^[328]



Scheme 106. Maruoka's alcohol KR showing large change in selectivity depending on bulk of acyl donor.^[328]

Achieving improved selectivity by changing the acyl donor as opposed to the substrate has clear advantages in terms of the versatility of the process developed and so in order to evaluate these role of the structure of

the acyl donor in determining the selectivity of amine KR, it was decided to try to prepare the following new acyl donors (Figure 34).

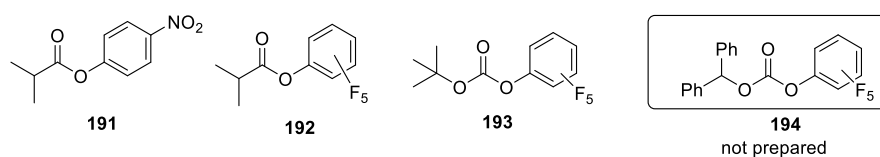
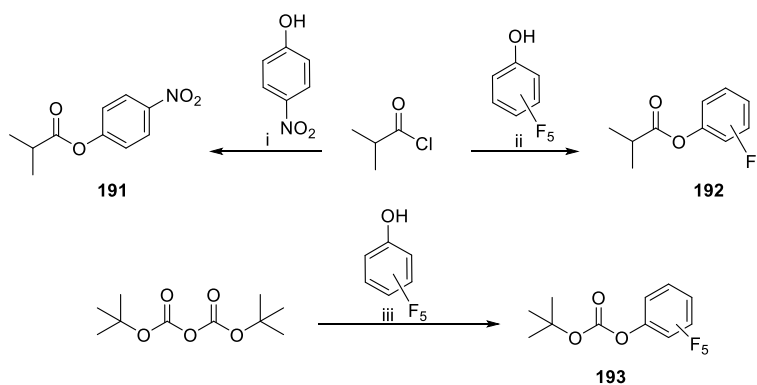


Figure 34. New acyl donors **191-193** prepared for amine KR.

Acyl donors **191** and **192** were prepared to allow us to evaluate the effect of the change of counter anion in acylative KR reactions (cf. the use of *isobutyric* anhydride). Acyl donor **193** allowed us to evaluate whether the switch from benzyl to *tert*-butyl carbonate strongly affects selectivity in these reactions. Synthesis of compounds **191**, **192** and **193** were carried out using the routes shown below (Scheme 107).^[3,329]

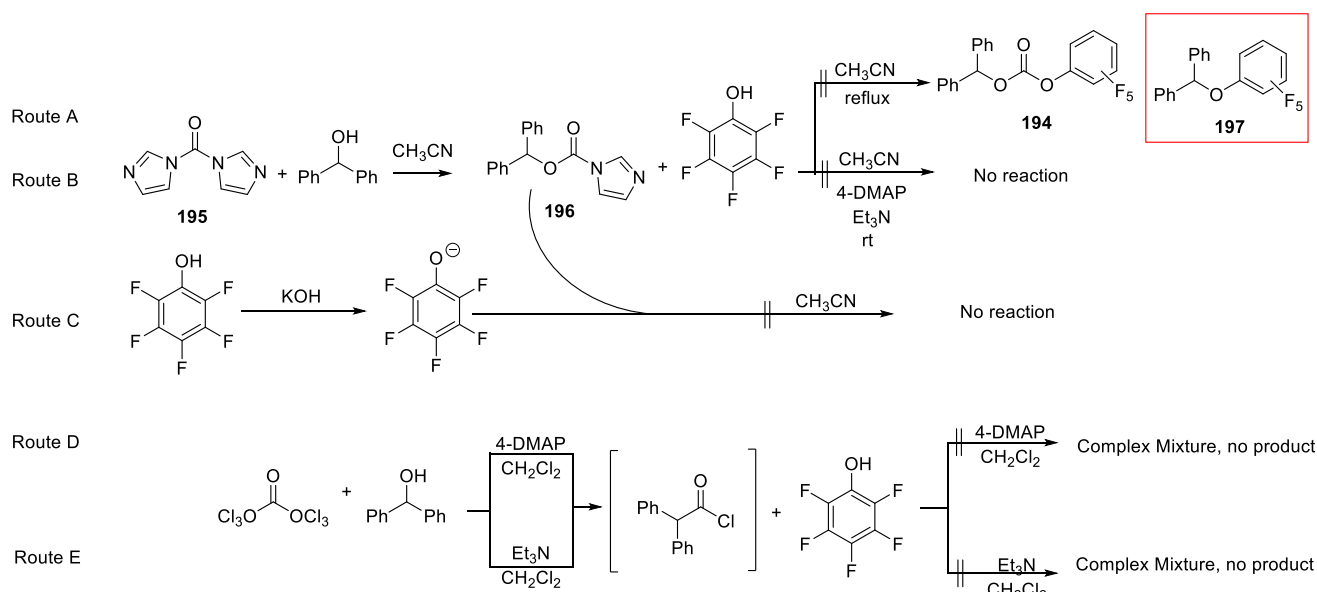


Scheme 107. Synthesis of acyl donors **191**, **192** and **193**.^[3,329]

Reagents and Conditions: (i) Et_3N , CH_2Cl_2 , rt, 3 h (79%) (ii) Et_3N , CH_2Cl_2 , rt, 3 h (15%); (iii) 4-DMAP, CH_2Cl_2 , rt, 5 h (75%).

Compounds **191** and **193** were made in yields of 79% and 75% respectively, while **192** was prepared in just 15% yield due its volatility.

Synthesis of carbonate **194** was also attempted, in order to evaluate the selectivity using the diphenylmethyl group. Unfortunately, all attempts at the synthesis of pentafluorophenyl diphenylmethyl carbonate **194** failed (Scheme 108).^[330]

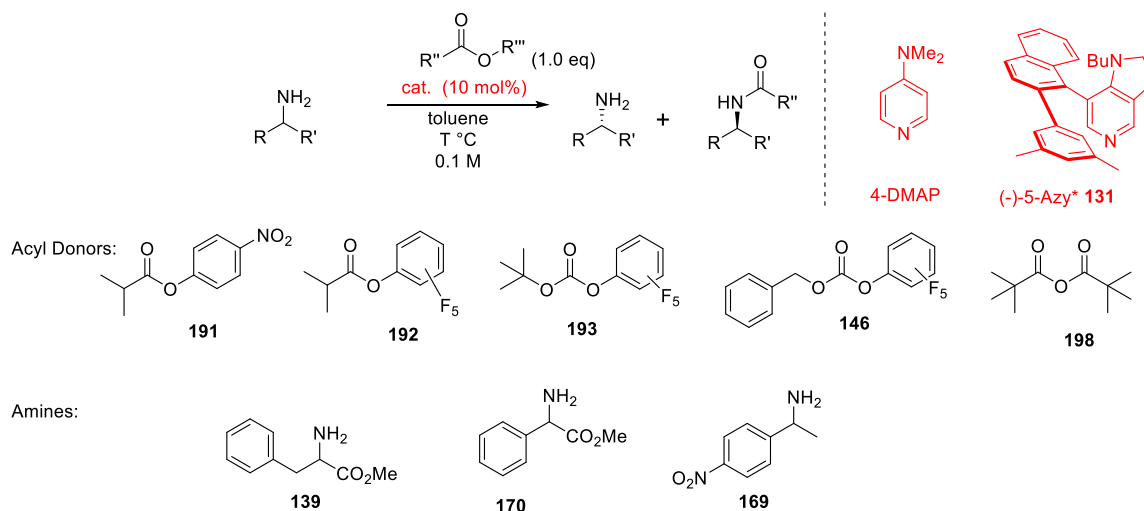


Scheme 108. Attempted syntheses of pentafluorophenyl diphenylmethyl carbonate **194**.

The first intermediate (**196**) in Route A was recrystallised from ethanol with a 50% yield, but the following reaction with pentafluorophenol in acetonitrile at reflux was unsuccessful, instead forming ether **197** via decarboxylation. Adding 4-DMAP and triethylamine (Route B) did not yield any product, while using the phenolate anion also did not yield the desired product (Route C). The use of triphosgene was also unsuccessful, as both conditions used (Routes D and E) yielded only a complex mixture of materials, with no product detected by ^1H NMR analysis of the crude reaction mixture.

The following reactions were then carried out using these new acyl donors. In each case, background reactions and 4-DMAP-catalysed reactions were run to test reactivity.

Table 25. Evaluation of factors affecting selectivity in amine KR: reactions with amines **139**, **170** and **169** and comparison with new acyl donors **191**, **192**, **193**, **146** and **198**.



Entry	Amine	Acyl Donor	Catalyst	Temperature (°C)	Time (h)	Conversion (%)	<i>S</i> ^b
1	139	191	4-DMAP	0	4	0	-
2	139	192	-	-78	4	0	-
3	139	192	4-DMAP	-78	4	10	-
4	139	192	131	-78	24	24	3.3
5	139	193	4-DMAP	-78	4	0	-
6	139	198	4-DMAP	0	4	0 ^a	-
7	170	146	131	-78	4	34	1.36
8	169	146	131	0	5	50	1.15

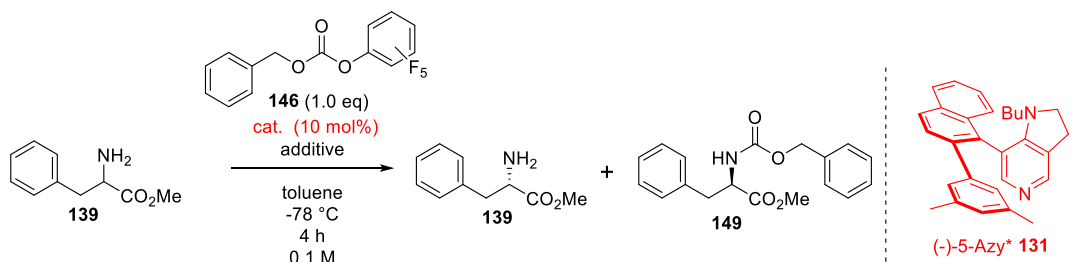
^aNo quench was observed with this acyl donor ^bstereochemistry randomly assigned

The acyl donors **191**, **193** and **198** were found to be too unreactive under the conditions tested, even with 4-DMAP as a catalyst (entries 1, 5 and 6). Acyl donor **192** was found to give no background reaction (entry 2), and only 10% conversion using 4-DMAP as the catalyst after 4 hours at -78 °C (entry 3). 5-Azy* catalyst **131** gave a selectivity value of $s = 3.3$ using acyl donor **192** (entry 4), which compares favourably to the selectivity of $s = 2.1$ obtained using **146** (Table 19). Although this was the highest selectivity yet observed it was still not high enough for a viable KR ($s > 7$ required).

Substrates **170** and **169** reacted with lower levels of selectivity as compared with substrate **139** (entries 7 and 8). As compound **170** was run under exactly the same conditions as compound **139**, it can be determined that the extra methylene group in phenylalanine is not detrimental to the selectivity. The KR with substrate **169** was performed under slightly different conditions. It was hypothesised that a slow addition of the acyl donor would slow down the background reaction, and therefore the acyl donor was added slowly over 4 hours, and the reaction stirred for an extra hour before being quenched. The low selectivity obtained even for this substrate, which does not contain an ester moiety, may indicate that the presence of an ester is not decisive in determining the level of selectivity achieved in this type of KR.

Finally, a number of salts were evaluated as additives in these reactions, as other groups including those of Fu and Cossey have used these to positive effect in their amine KR procedures.^[209,296] In their reactions, the increases in selectivity that they reported when using salt additives was postulated to be due to *in situ* counter-ion exchange of key intermediates (Table 26).

Table 26. The effect of additives on the KR of phenylalanine methyl ester.



Entry	Additive	Conversion (%)	<i>S</i> ^a
1	NBu ₄ Br	30	2.1
2	NBu ₄ CO ₂ <i>i</i> -Pr	60	1.2
3	HCO ₂ <i>i</i> -Pr	14	3.2
4	HCO ₂ <i>i</i> -Pr + <i>i</i> -Pr ₂ NEt	25	3.4

^astereochemistry randomly assigned

The addition of tetrabutylammonium bromide (entry 1) and of tetrabutylammonium *isobutyrate* (entry 2) did not increase the selectivity, while the addition of *isobutyric acid*, alone or in combination with Hünig's base (entries 3 and 4) did seem to marginally increase the selectivity. Nevertheless, these selectivity values remained too low to form the basis for a synthetically useful KR system.

4.2.4 Conclusions and Future Work

In conclusion, the carbamylative KR of phenylalanine esters and related α -chiral primary amines catalysed by atropisomeric chiral 5-Azy* catalyst **131** have been explored. Unfortunately, and despite considerable experimentation, the levels of enantioselectivity achieved have been rather modest. Although they were improved from $s = 2$ to $s = 3.4$ during these studies, even the highest levels of selectivity achieved were considered insufficiently promising to warrant further development into a DKR process. Clearly, improved conditions need to be found to improve selectivity within this system before this will be a viable objective and in the context of the current research, the decision was taken to cease work in this area and instead to switch focus to that of developing a DKR of *sec*-alcohols, for which the basic KR process was better developed (*i.e.* much more selective).

4.3 Development of Alcohol DKR

4.3.1 Development of Conditions for Alcohol KR which are Potentially Compatible with a One-pot DKR

As our work on the development of amine KR for use in a DKR process had not resulted in the development of a suitably selective system, it was decided to revisit alcohol KR and to develop a method for an acylative alcohol DKR using the Spivey catalysts as the non-enzymatic acylation catalyst. As the selectivity for alcohol KR with these catalysts was much higher than for amines ($s > 50$ at -78 °C), this was a much better starting point for the successful development of a DKR system.

4.3.1.1 Selection of Acyl Donor

Initial work in this area was carried out by Qian Wen Tan, a BSc student in the group.^[331] Our initial aim was to modify Fu's alcohol DKR procedure for use with the Spivey catalyst, and to develop a practical, room temperature procedure for this process. From Fu's work, it was clear that the anhydrides previously used for our KR systems were incompatible with the ruthenium racemisation catalyst^[291] and therefore focus first turned to ascertaining what selectivity could be obtained using Fu's acyl carbonate with DBAP* **66** at room temperature (Table 27).

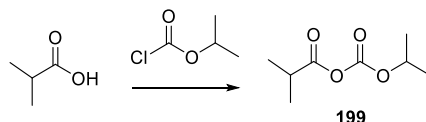
Table 27. Optimisation of room temperature KR process with varying acyl carbonates and bases with Spivey's DBAP* catalyst **66**.

$(\pm)\text{-26} + \text{acyl donor (1.0 eq)} \xrightarrow[\text{toluene}]{(-)\text{-cat. (1.0 mol \%)} + \text{Base (0.75 eq)}} (\text{S})\text{-26} + (\text{R})\text{-26}$

Entry	R	R'	Additive	Temperature (°C)	Time (h)	C (%)	s
1 ^a	Me	O <i>i</i> -Pr	-	rt	6	87	2.7
2 ^a	<i>i</i> -Pr	<i>i</i> -Pr	Et ₃ N	rt	0.5	60	9.3
3	<i>i</i> -Pr	<i>i</i> -Pr	Et ₃ N	-78	8	41	64 ^b
4 ^a	<i>i</i> -Pr	O <i>i</i> -Pr	-	rt	0.5	78(67 ^c)	6.6(7.5 ^c)
5	<i>i</i> -Pr	O <i>i</i> -Pr	-	-78	6	62	16
6	<i>i</i> -Pr	O <i>i</i> -Pr	Et ₃ N	-78	6	61	20
7	<i>i</i> -Pr	O <i>i</i> -Pr	Et ₃ N	rt	0.5	60	8.5
8	<i>i</i> -Pr	O <i>i</i> -Pr	<i>i</i> -Pr ₂ NEt	rt	0.5	61	8.5
9	<i>i</i> -Pr	O <i>i</i> -Pr	PMP	rt	0.5	57	8.6
10	<i>i</i> -Pr	O <i>i</i> -Pr	2,6-di- <i>tert</i> -butylpyridine	rt	0.5	60	7.7
11	<i>i</i> -Pr	O <i>i</i> -Pr	K ₃ PO ₄	rt	0.5	70	7.6
12	<i>i</i> -Pr	O <i>i</i> -Pr	K ₂ CO ₃	rt	0.5	70	7.8
13	cycloheptyl	O <i>i</i> -Pr	Et ₃ N	rt	0.5	64	10.5±1.0 ^c

^a Entries 1, 2 and 4 carried out by Qian Wen Tan^[331] ^b Repeat reactions confirm result as increase from original value of $s = 44$ found by Ausmees ^c Duplicate run

At room temperature, it was found that Fu's acetyl *isopropyl* carbonate gave a selectivity of only $s = 2.7$ (Table 27, entry 1) compared to the optimised conditions ($-78\text{ }^{\circ}\text{C}$, *isobutyric* anhydride, entry 3, $s = 64$). In an attempt to determine whether the low selectivity was due to the change in nature of the acyl donor or the increase in temperature from $-78\text{ }^{\circ}\text{C}$ to room temperature, Qian Wen also looked at the selectivity of *isobutyric* anhydride at room temperature (entry 2). The selectivity for this substrate was also greatly diminished compared to that found at $-78\text{ }^{\circ}\text{C}$ (entry 3). In the hope of increasing the selectivity, she synthesised the *isobutyryl isopropyl* carbonate using Fu's procedure^[291] (Scheme 109) to increase the bulk of the acyl donor (Table 27, entry 4).



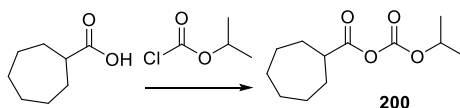
Scheme 109. Synthesis of *isobutyryl isopropyl* carbonate **199** as carried out by Qian Wen Tan.^[331]

Reagents and Conditions: (i) Et_3N , Et_2O , $0\text{ }^{\circ}\text{C}$, 2 h (65%).

While this acyl donor did increase the selectivity ($s = 7.0 \pm 0.5$), selectivities of over 10 are desirable for a DKR to ensure high *ee* of the product, and this selectivity was also lower than that found with *isobutyric* anhydride. Evidently, the *isopropyl* carbonate ($i\text{-PrOCO}_2^-$) counter-ion reduced the selectivity of the reaction compared to the *isobutyrate* ($i\text{-PrCO}_2^-$) counter-ion, both at room temperature and at $-78\text{ }^{\circ}\text{C}$, even though the acyl transfer group remained the same.

As Fu had not added a base to his DKR reactions, it was necessary to see whether the presence of the base would affect the selectivity. Pleasingly, the addition of 0.75 equivalents of Et_3N did in fact increase the selectivity both at $-78\text{ }^{\circ}\text{C}$ and at room temperature (Table 27, entries 6 and 7). A quick base screen revealed that no other base gave significantly better results, while inorganic bases did not change the selectivity (entries 8-12).

In a final attempt to increase the selectivity, cycloheptyl *isopropyl* carbonate **200** was synthesised (Scheme 110).



Scheme 110. Synthesis of *cycloheptyl isopropyl* carbonate **200**.^[291]

Reagents and Conditions: (i) Et_3N , Et_2O , rt, 4 h (60%).

As indicated previously, dicycloheptane carboxylic anhydride had been found to increase selectivity relative to *isobutyric* anhydride for the KR of *sec*-benzylic alcohols (Table 12).^[297] Satisfactorily, the selectivity with this acyl donor increased to $s = 10.5 \pm 1.0$ (Table 27, entry 13). Consequently, this acyl carbonate was used in subsequent studies.

4.3.1.2 Catalyst Loading

Kinetic studies were then carried out with the optimised acyl donor **200**, with a decrease of the catalyst loading to 0.5 mol%, under the assumption that the rate of racemisation would be the limiting rate for the DKR (Figure 35).

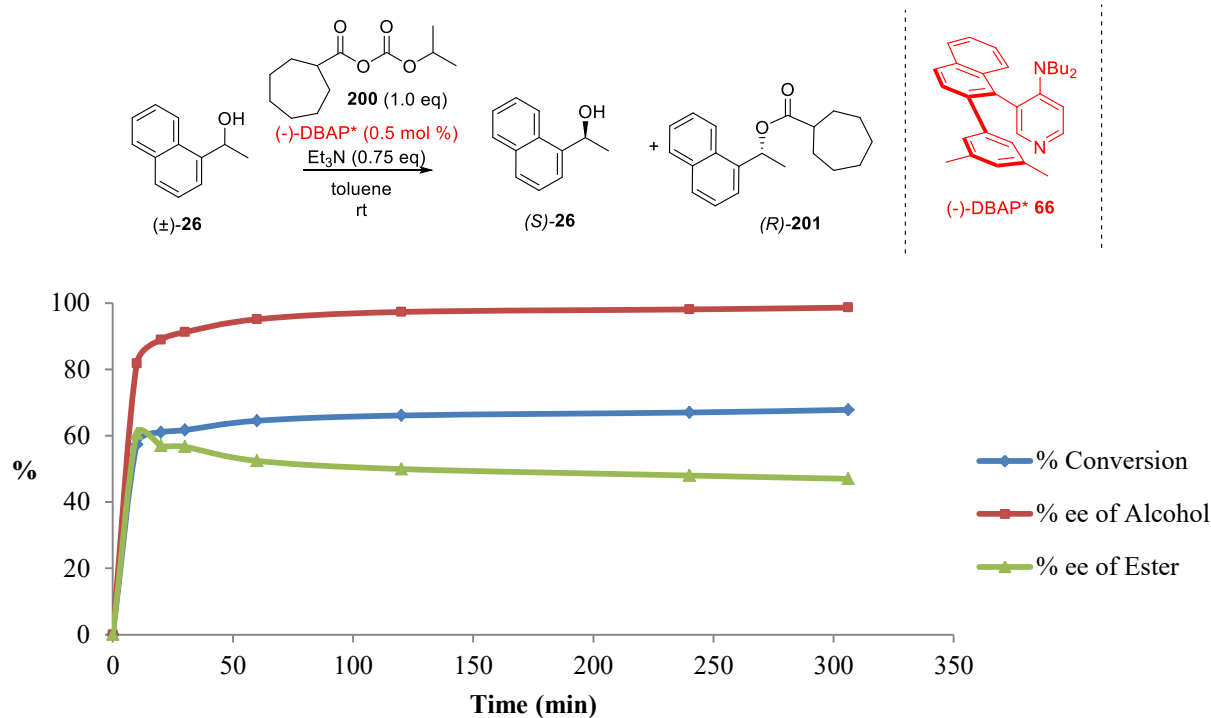


Figure 35. Progression of KR of 1-(1-naphthyl)ethanol **26** using 0.5 mol% DBAP* catalyst **66**, showing change in % conversion, and % ee of the alcohol and ester.

Interestingly, the reaction went to almost 60% conversion within the first five minutes, and then stayed at a very similar conversion throughout the remainder of the reaction, with the *ee* of both the starting material and product relatively unchanged. An initial selectivity of $s = 10$ was calculated from the first time point, and this increased to 12 as the reaction progressed, with an average selectivity of 11.3. The average selectivity can be found by plotting the nominator against the denominator for Kagan's equation for selectivity (equation 5), and the slope of the line is the average selectivity.

$$s = \frac{\ln(1-C)(1-ee)}{\ln[(1-C)(1+ee)]} \quad (5)$$

Initially no obvious explanation could be found for the conversion limit of 60%, as there was theoretically enough of the acylating agent to allow complete conversion and 0.75 equivalents of the base. Although it is known that KR reactions can effectively stop around 50% conversion when the selectivity is very high due to the slow rate of reaction of the slow-reacting enantiomer, it was not anticipated that this effect was responsible given the modest selectivity of our system.

A second kinetic study was carried out using 0.1 mol% of catalyst, to further slow down the reaction to be compatible with a potentially slow racemisation. This time, one equivalent of base was added to ensure this was not the cause of the conversion limit (Figure 36).

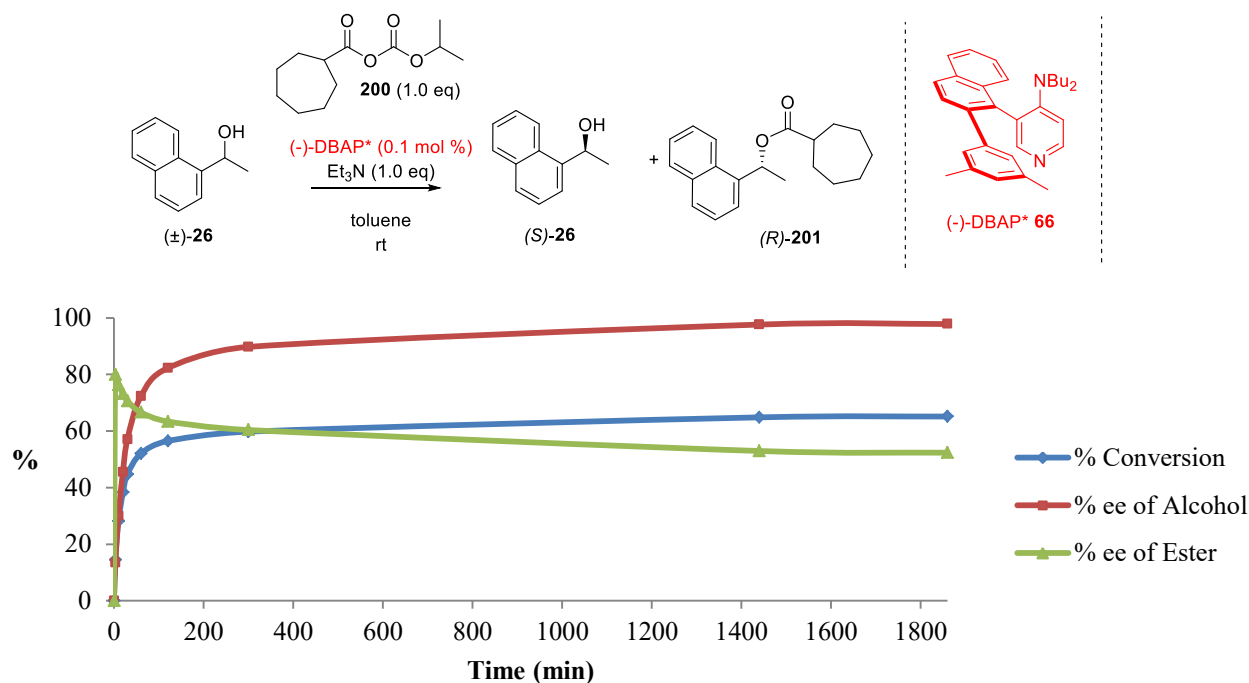


Figure 36. Progression of KR of 1-(1-naphthyl)ethanol **26** using 0.1 mol% DBAP* catalyst **66**, showing change in % conversion, and % ee of the alcohol and ester.

Again, the maximum conversion reached was around 65%, with an average selectivity of $s = 11.5$. At this point it was decided that the selectivity and low catalyst loading would be suitable to develop the DKR process. The maximum *ee* of the product that could be expected from these reactions is ~83% with the current selectivity of $s \sim 11.5 \pm 1.5$.

4.3.2 Development of Racemisation Catalyst

Many different racemisation catalysts have been reported in the literature in combination with an enzyme for the enzymatic DKR of alcohols. One of these is Bäckvall's commercially available pentaphenylcyclopentadienyl ruthenium(II) catalyst **80**, also used by Fu in his DKR procedure. Initial efforts focused on determining the rate of racemisation using this catalyst in the presence of acyl donors **199** and **200**.

4.3.2.1 Bäckvall Catalyst Studies

Racemisation with catalyst **80** was attempted with *isobutyryl isopropyl carbonate*. As triethylamine was also used in our optimised KR system, this was included in one of the racemisation reactions. The results with

both (*S*)-1-(1-naphthyl)ethanol (obtained from a KR) and (*S*)-1-phenylethanol (commercial) are shown below (Figure 37).

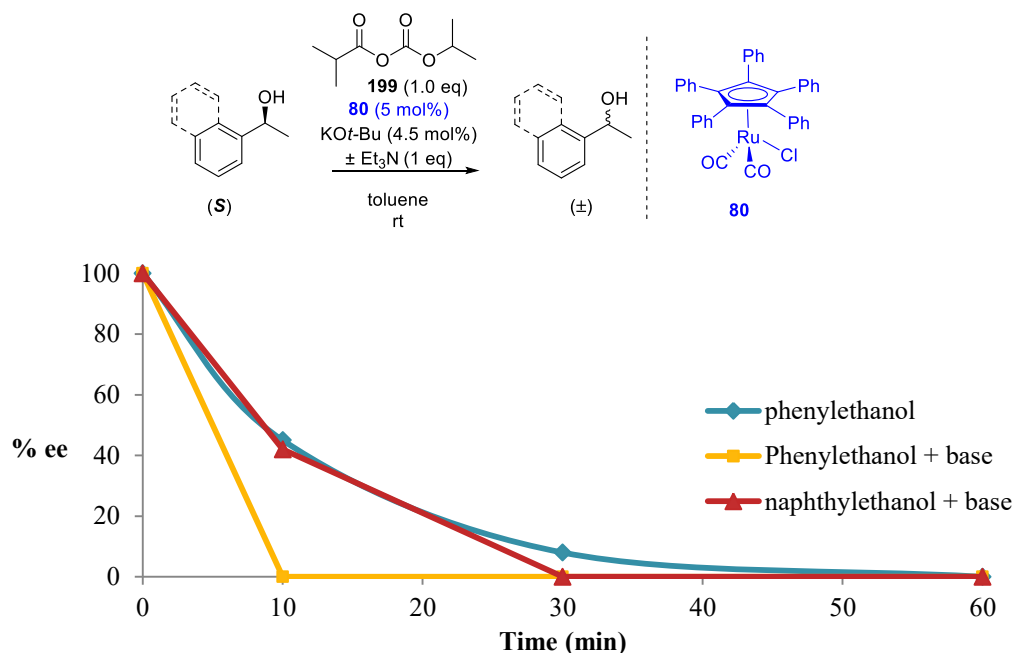


Figure 37. Racemisation of alcohols in the presence of isobutyryl isopropyl carbonate **199**.

Using 5 mol% of **80**, (*S*)-1-phenylethanol was racemised completely in 1 hour even in the presence of the acyl carbonate **199**, while addition of the base increased the rate of racemisation so that it was complete within ten minutes. The racemisation of (*S*)-1-(1-naphthyl)ethanol was also attempted, and complete racemisation in the presence of Et₃N occurred within 30 minutes.

4.3.2.2 Alternate Catalyst Search

Although Bäckvall's catalyst **80** seemingly tolerated the KR conditions, it was reported to be air-sensitive, and indeed Fu's DKR procedure is set-up in a glove box. In addition, although tolerating the acyl carbonate, the rate of racemisation is still much reduced in comparison to the acyl donor free racemisation (0% ee within 30 minutes at 1/10th of tested catalyst loading). It was therefore decided to evaluate a number of other catalysts reported in the literature as possible alternatives, hoping to find either a more air-stable and/or more acyl carbonate tolerant catalyst. Six catalysts were identified, all of which had been used in alcohol DKR reactions and shown to be active at room temperature (Figure 38).

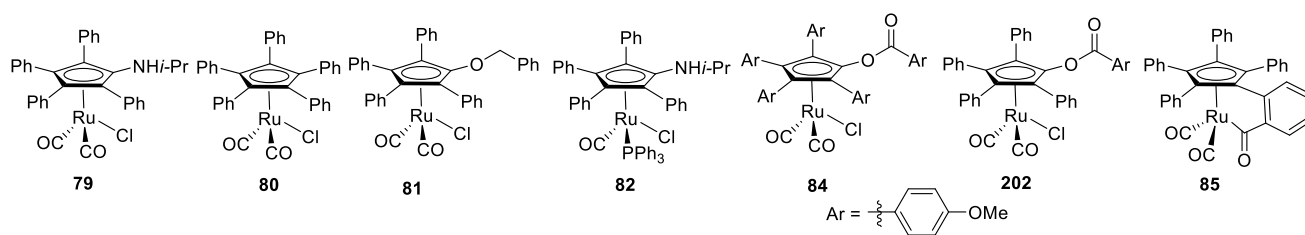


Figure 38. Potential ruthenium racemisation catalysts for alcohol DKR.^[232–234,236,244]

Catalysts **81**, **82**, **84** and **202** are reported to be air-stable, while the Park catalyst **79** is commercially available. According to published rate constants, the relative rates of reaction for the racemisation of (*S*)-1-phenylethanol by these catalysts should be as indicated as shown below (Figure 39). It should be noted however that some of the literature rate constants refer to different catalyst loadings and for **79** the substrate is in fact (*S*)-4-phenyl-2-butanol, which usually has a slower rate of racemisation than (*S*)-1-phenylethanol.

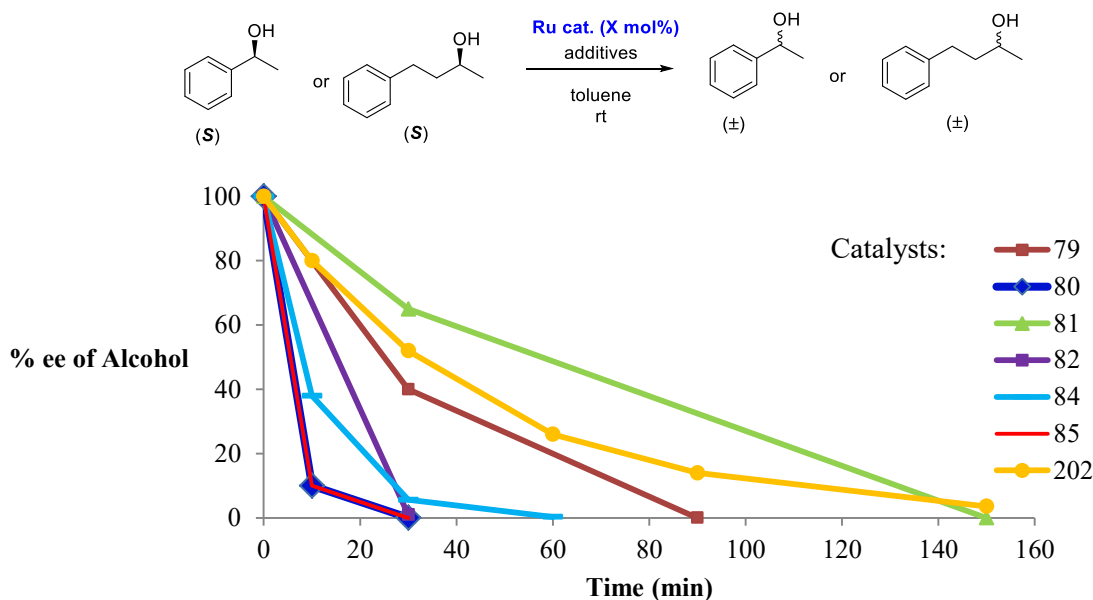
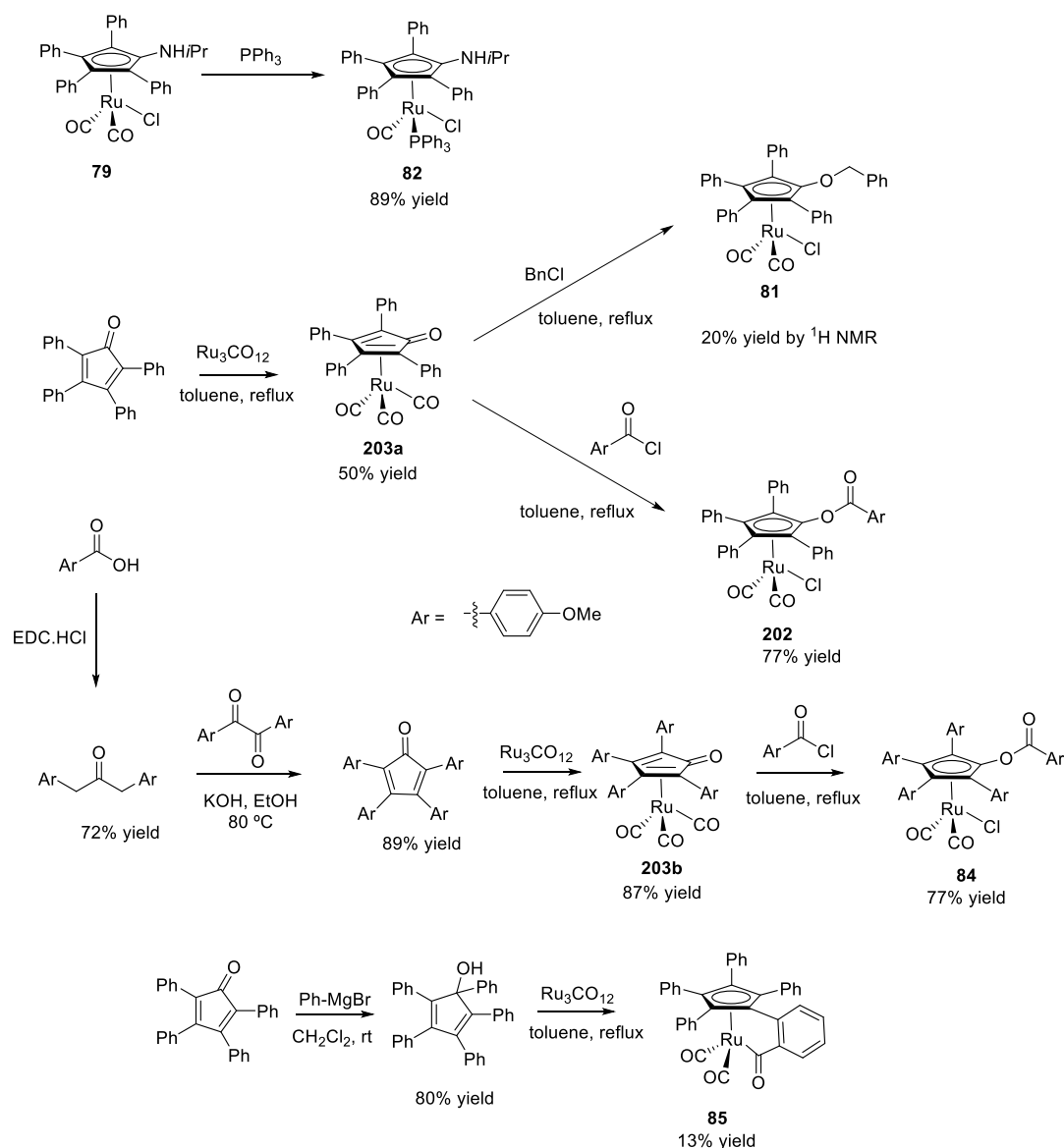


Figure 39. Relative rates of racemisation for ruthenium catalysts **79–82**, **84–85** and **202** as simulated using literature data, rate constants or half-lives.^[231–233,235,236,244]

It can be seen from the data above that catalysts **80** and **85** are expected to be the fastest, with **79** also giving a fast rate of racemisation for a less reactive substrate. Of the remaining catalysts, **82** and **84** were expected to also provide faster rates of racemisation. Notwithstanding this data, we decided to evaluate the performance of these catalysts ourselves. Catalysts **81**, **82**, **84**, **202** and **85** were therefore synthesised in order to test their activity, using the literature routes shown below (Scheme 111):



Scheme 111. Syntheses of catalysts **82**, **81**, **84**, **202** and **85**.

Catalyst **82** was prepared in 89% yield from commercial catalyst **79**. While the initial step for making catalyst **81** proceeded smoothly to Ru-cyclopentadienone complex **203a**, the subsequent *O*-benzylation step proceeded to <20% conversion by ^1H NMR analysis, and so the reaction was re-attempted. Again, <20% conversion could be attained and so the crude reaction mixtures of both reactions were combined and purified to yield the desired catalyst **81**. Catalyst **202** was synthesised readily in good yields from Ru-cyclopentadienone complex **203a**, while catalyst **84** required synthesis of the 4-methoxy cyclopentadienone to give the catalyst in four steps. The synthesis of catalyst **85**, unfortunately, also gave a low yield for the second step, although 42% is reported in the literature.^[235,236]

The next step was to repeat the literature racemisation procedures, while modifying the catalyst loadings to give directly comparable results (**79** and **80** were previously used at 0.5 mol% loading). The results are

shown below for the racemisation of (*S*)-1-phenylethanol using 5 mol% of catalyst, at a 0.5 M concentration (consistent with a KR) and the literature specified quantity of additive (Figure 40). **81** was not examined due to the difficulties experienced preparing sufficient quantities to test.

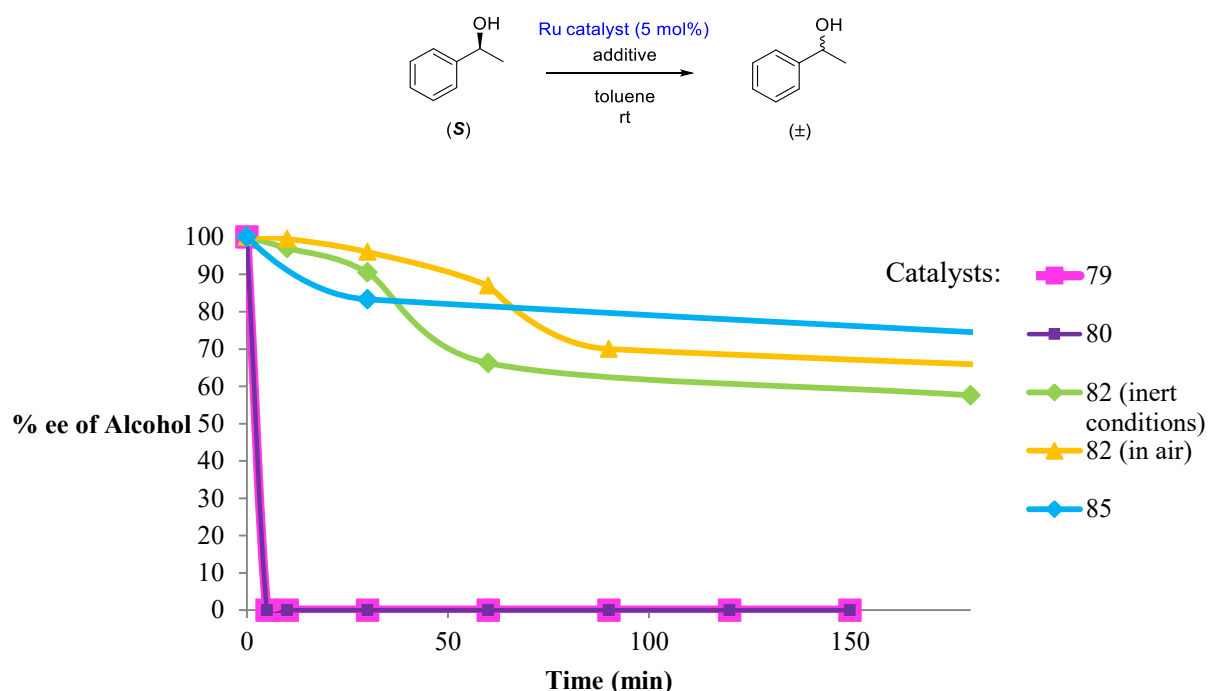
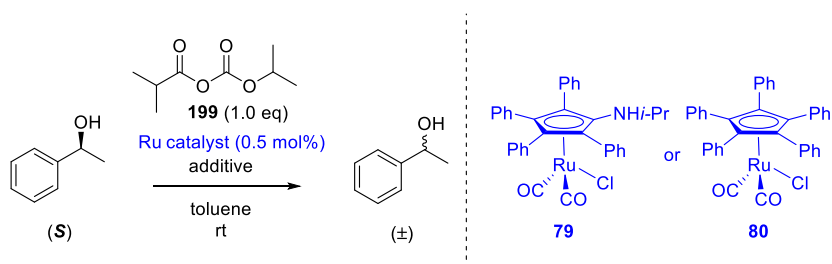


Figure 40. Racemisation of (*S*)-1-phenylethanol with literature racemisation catalysts.

Commercial catalysts **79** and **80** both completely racemised the substrate in 5 minutes with a 5 mol% catalyst loading. Unfortunately, both synthesised catalysts **82** and **85** gave lower rates of racemisation than reported in the literature, with catalyst **82** providing an *ee* of 9% after 24 hours. Racemisation with air-stable catalyst **82** was attempted under moisture and air-free conditions, and although the rate of racemisation increased slightly, the rate was still much slower than reported in the literature, even though the ^{31}P , ^1H and ^{13}C NMR spectra and mass spectrum of the catalyst were all consistent with the literature. In general it was difficult to reproduce the literature values, with the exception of commercial catalysts **79** and **80**. **82** and **85** were therefore found to be too slow and were not used again.

Racemisation with catalysts **79** and **80** were also attempted with *isobutyryl isopropyl carbonate* at a lower catalyst loading to effectively differentiate between the catalysts (Figure 41).



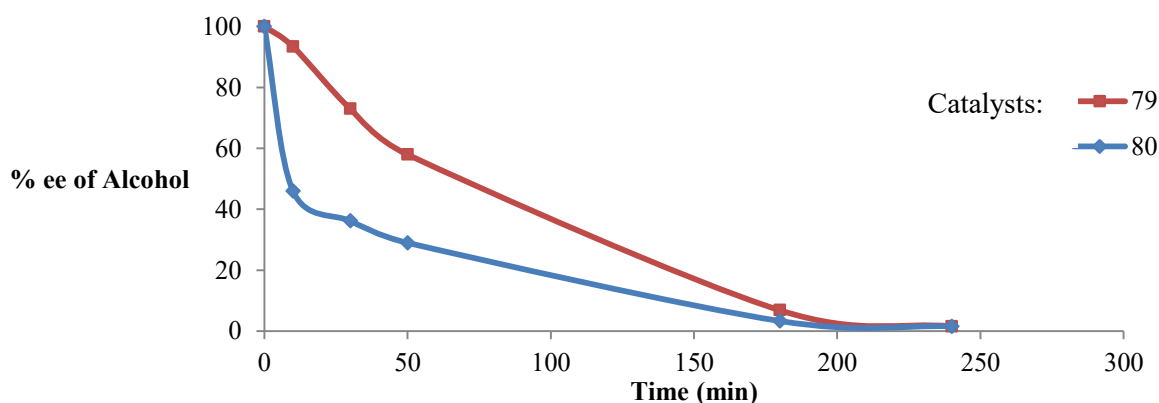


Figure 41. Racemisation of (*S*)-1-phenylethanol in the presence of isobutyryl isopropyl carbonate.

Although the racemisation still took place, it was at a much reduced rate with 0.5 mol% catalyst loading, with complete racemisation within 4 hours. **80** was again found to be the faster catalyst.

Of the remaining catalysts, **84**, although more difficult to synthesise, was reported to be much faster than **202** and the activity of this catalyst was examined using (*S*)-1-phenylethanol (Figure 42):

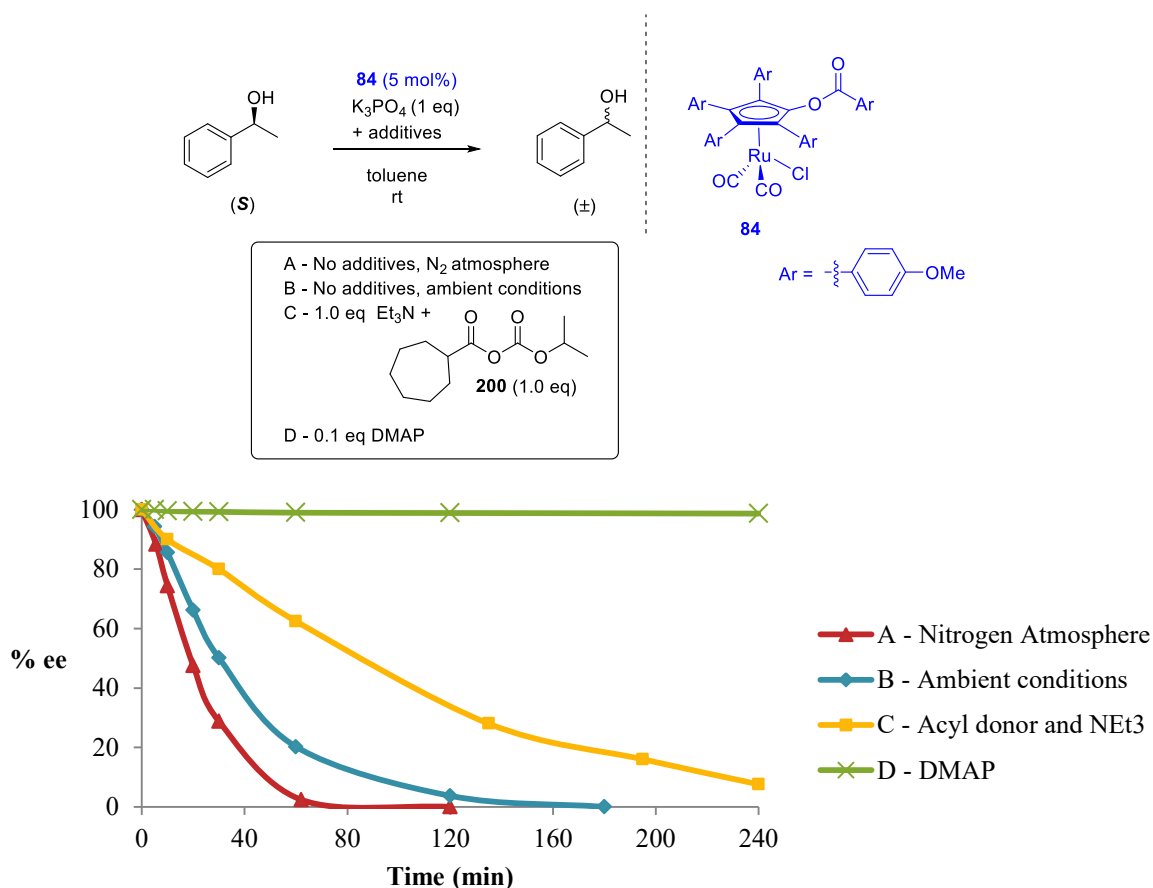


Figure 42. Racemisation of (*S*)-1-phenylethanol using **84** with different additives and conditions.

Although still significantly slower than Bäckvall's catalyst **80** (0% ee within 30 minutes with acyl donor and Et_3N), **84** was stable in air and is recoverable from the reaction mixture. However, the presence of 4-DMAP

in the reaction completely deactivated this racemisation catalyst. In fact, a ^1H NMR of catalyst **84** and 4-DMAP in d_8 -toluene showed changes in the spectrum for **84**, indicating that the 4-DMAP reacts with **84**. We hypothesise that **84** is potentially acting as an acylating agent for 4-DMAP at the ester site.

The effect of 4-DMAP on racemisation catalyst **80** was therefore also evaluated (Figure 43).

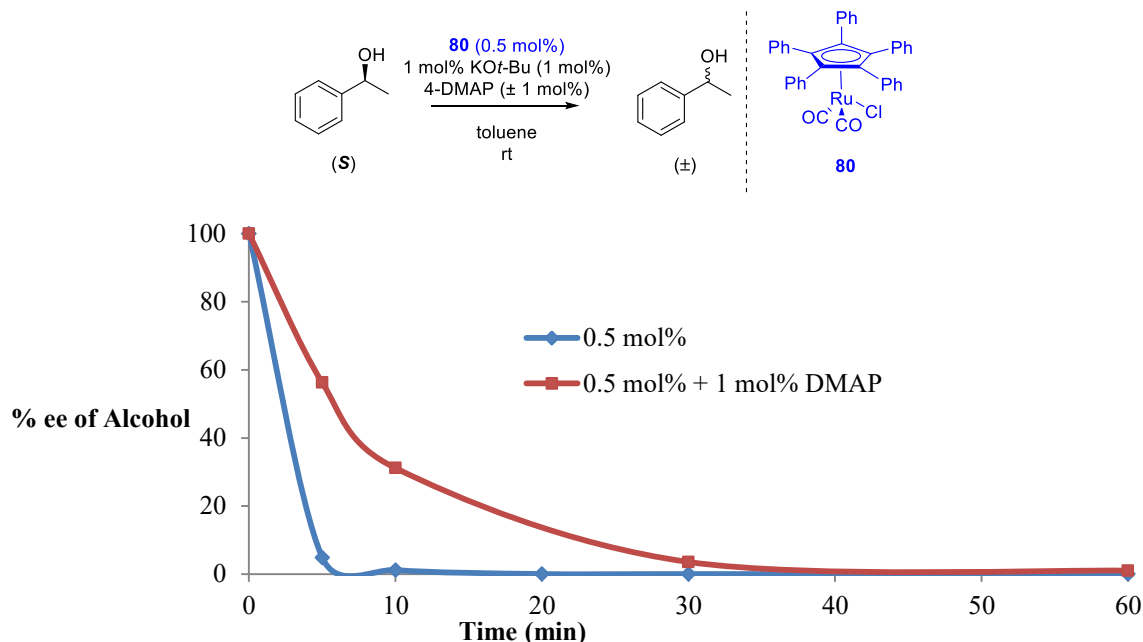
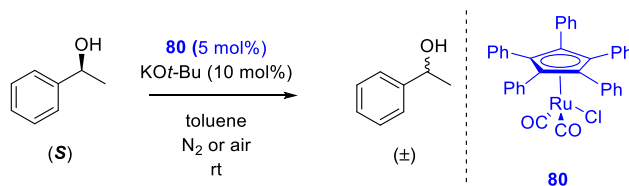


Figure 43. Effect of 4-DMAP on rate of racemisation with **80**.

Surprisingly, 4-DMAP did have an effect on the racemisation even with this catalyst. However, as in this case 2 equivalents of 4-DMAP were used relative to catalyst **80**, and only a maximum of 0.2 equivalents of DBAP* **66** were to be used in the DKR, this rate decrease was not expected to be significant in the DKR.

The air-stability of catalyst **80** was also examined. The presumption that this was air sensitive came from two points, the vigorous glove-box conditions in the published procedure by Bäckvall,^[244] and claims by the Park group that **80** was air-sensitive.^[232] To verify this, the racemisation was first attempted under anhydrous nitrogen conditions for formation of the active catalytic species before putting a needle through the septum to allow air in, and only then adding the alcohol. Surprisingly, the reaction went to completion (*ee* of alcohol = 0%) within five minutes, at the same rate as under a N_2 atmosphere (Figure 44).



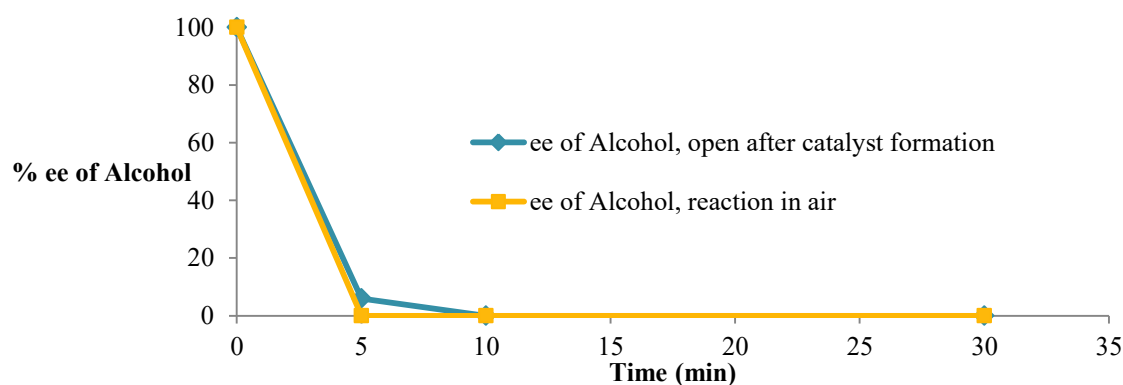


Figure 44. Racemisation of (*S*)-1-phenylethanol with **80** in air.

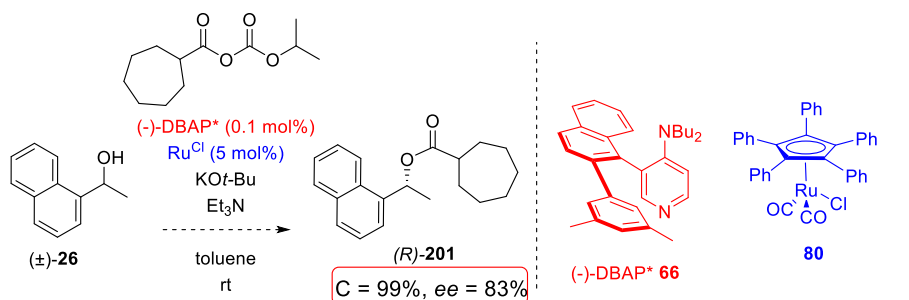
Attempting the reaction in an open flask for the whole process including the formation of the active catalyst also resulted in complete racemisation within five minutes. Evidently, the catalyst was not as air-sensitive as we had believed, although a much higher loading (5 mol%, same as in DKR) was used in these experiments, compared to the 0.5 mol% used by Bäckvall. Even so, this was an interesting result as it meant that this catalyst could also potentially be used in the membrane-enhanced systems, which cannot easily be kept under a rigorous nitrogen atmosphere.

With these results in hand and confirmation that Bäckvall's Ru catalyst **80** was the best racemisation catalyst available for the system, it was decided to combine work on room temperature alcohol KR with the studies on the racemisation catalyst, choosing to keep catalyst **80** as the optimal catalyst for the DKR.

4.3.3 Combination into One-pot DKR

4.3.3.1 Initial Results

The KR and the racemisation component reactions described above were combined into one-pot for our first DKR attempt, using 0.1 mol% loading of the DBAP* catalyst **66** as it was envisaged that this would allow for a slow enough KR to be compatible with the racemisation (Figure 45). If the reaction proceeded under ideal conditions, the following graph would be expected:



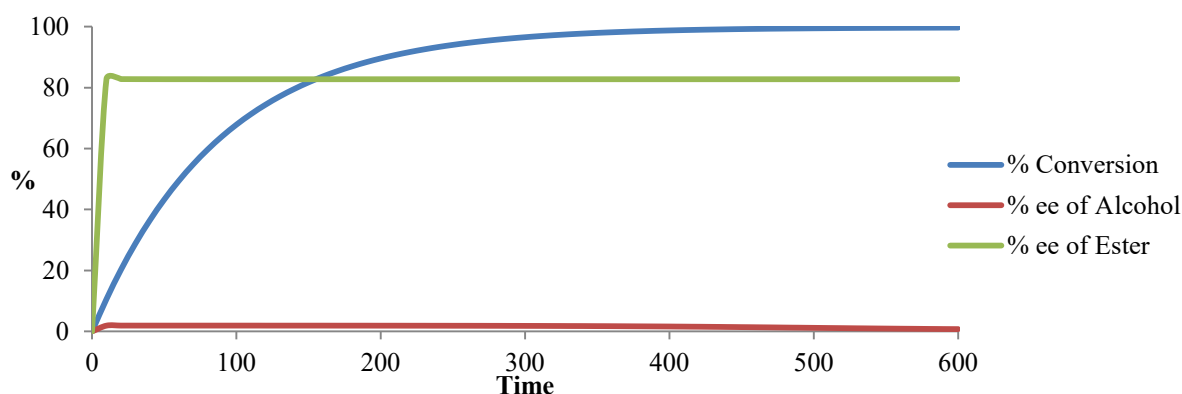
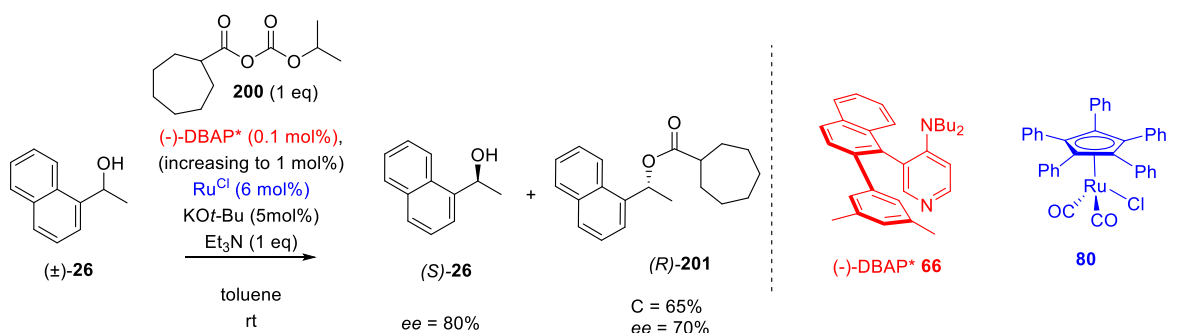


Figure 45. Ideal DKR, with maximum *ee* of product predicted to be 83% for an acylation process with a selectivity factor, $s = 11$.

Ideally, the racemisation catalyst would be efficient enough to allow the *ee* of the alcohol to remain at or near 0%, which would allow the maximum *ee* of for the product (83%) to be achieved throughout the reaction. However, during the initial attempt at a DKR a problem was encountered with the HPLC analysis, as the peaks for one of the product enantiomers and for the racemisation catalyst eluted at almost identical times and conditions could not be found to separate them. The racemisation catalyst also proved difficult to remove by filtration either through silica or a 0.2 μm PTFE syringe filter.

Nevertheless, it soon became clear that the conversion was not proceeding as expected, and that for some reason the KR catalyst was deactivated. After leaving the reaction overnight, a further amount of KR catalyst was added, increasing the catalyst loading to $\sim 1\text{mol}\%$. The reaction was left to stir for a further 6 hours, after which it was diluted with *isopropanol* to quench the reaction, the solvent removed and the residue columned to separate the product and starting material.



Scheme 112. First attempt at DKR of 1-(1-naphthyl)ethanol using DBAP* catalyst **66** and Ru catalyst **80**.

The *ee* of the product was 70%, while the *ee* of the recovered starting material was 80%. Recombining all fractions that contained the product and the starting material gave a conversion of 65% by ^1H NMR analysis. This data reveals that 56% of the '(*R*)' enantiomer is present within the combined ester and alcohol mixtures, thereby providing evidence for our first DKR (*i.e.* formation of $>50\%$ of a single enantiomer).

It is clear that while the (-)-DBAP* catalyst **66** is fast under KR conditions, a 0.1 mol% loading gave only very slow conversion under the DKR conditions, presumably because of deactivation by the racemisation catalyst, which along with KO*t*-Bu is the only additional component in the reaction mixture.

To investigate the decreased rate of acylation shown in the initial DKR, KR reactions were run with both KO*t*-Bu and the Ru^{Cl} pre-catalyst present in order to determine the effects these additives had on the KR (Figure 46).

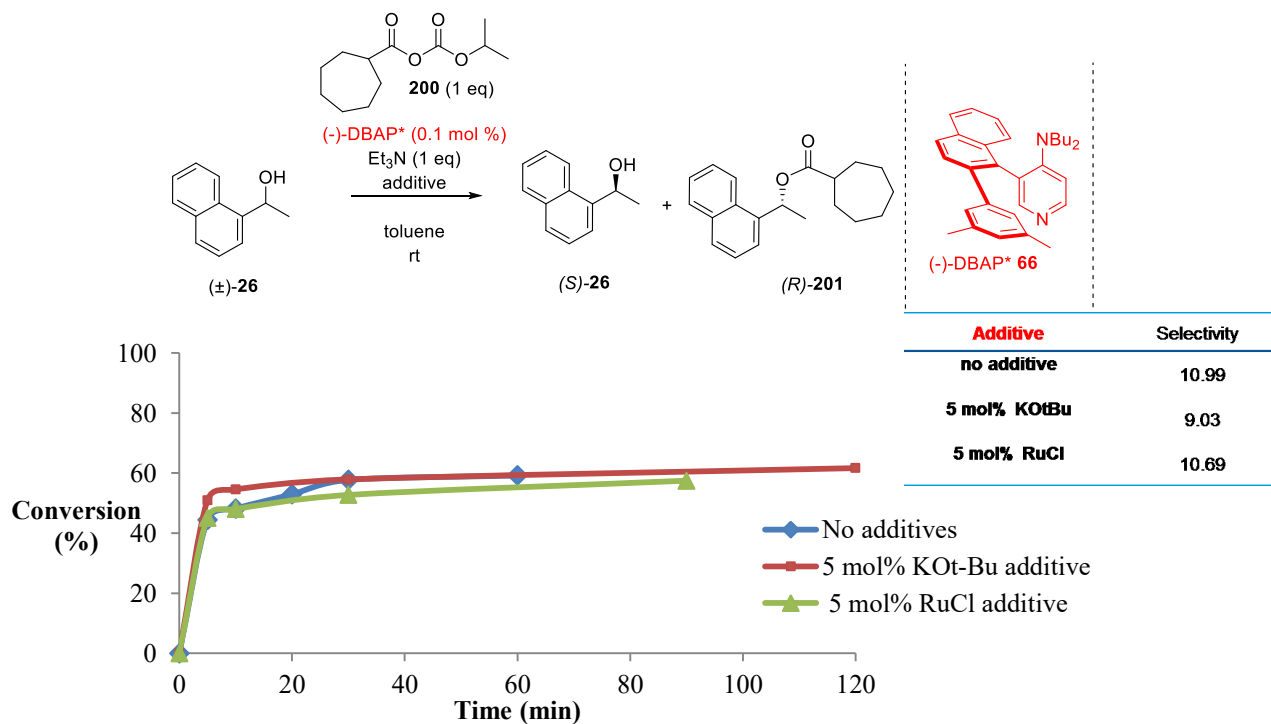


Figure 46. Effect of KO*t*-Bu and Ru^{Cl} pre-catalyst on KR.

Neither the KO*t*-Bu nor the Ru^{Cl} pre-catalyst had any negative impact on the rate of acylation, in fact the addition of KO*t*-Bu gave slightly faster rates of acylation, while the selectivity was slightly lower presumably as the KO*t*-Bu could also catalyse the reaction. Therefore, the only component of the reaction that could be interfering with the acylation is the activated Ru^{Or-Bu} catalyst.

¹H NMR studies were carried out to determine if any interactions between 4-DMAP and the racemisation catalyst occurred. As expected from the KR results, no change in ¹H NMR signals was observed for 4-DMAP when mixed with the Ru^{Cl} pre-catalyst (Figure 47, a). Upon mixing of 4-DMAP and the activated Ru^{Or-Bu} catalyst however, small changes in the ¹H NMR spectrum of 4-DMAP were observed (Figure 47, b).

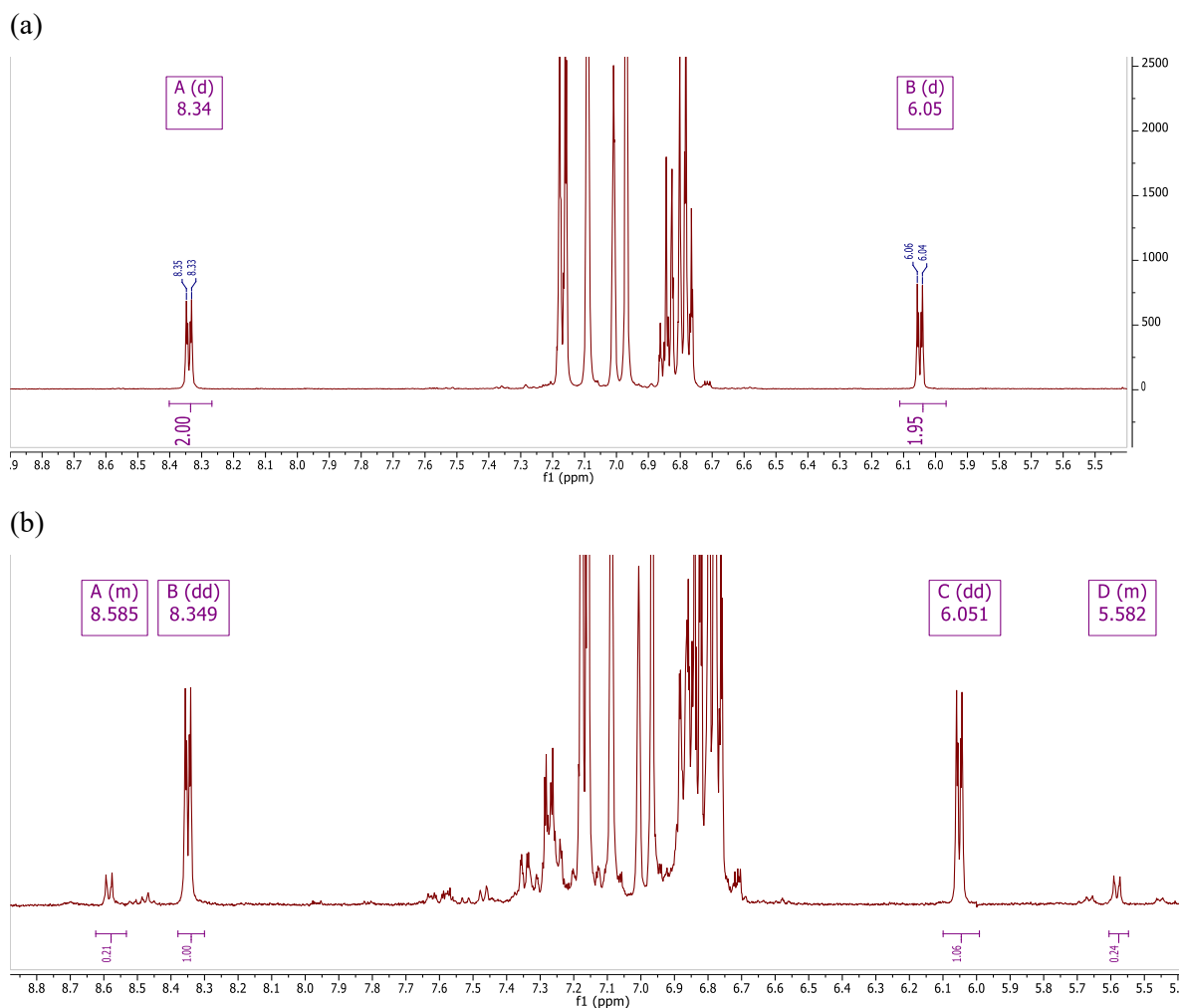
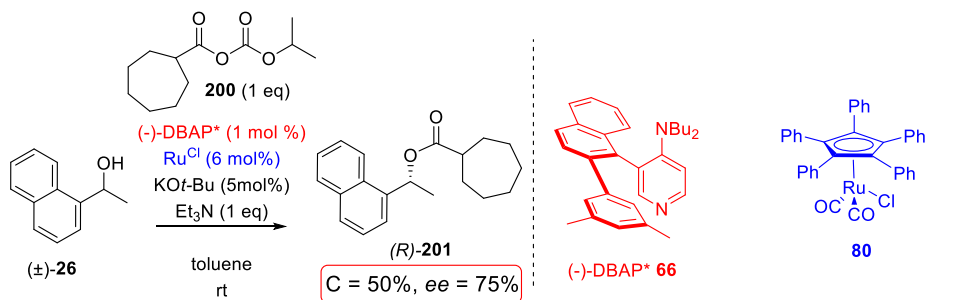


Figure 47. ^1H NMR of (a) unactivated Ru^{Cl} and 4-DMAP and (b) activated catalyst $\text{Ru}^{\text{Ot-Bu}}$ and 4-DMAP overnight in d_8 -toluene.

To combat the interaction between the Ru catalyst and the KR catalyst, a higher KR catalyst loading (1 mol% vs 0.1 mol%) was used in the next attempt at a DKR. To analyse the reaction effectively, the samples taken were quenched into MeOD. This allowed for the *ee* of the alcohol to be analysed by HPLC, while the conversion could be calculated from the ^1H NMR spectrum (Figure 48). The *ee* of the product was only obtained accurately when larger aliquots were collected, as the product could then be purified by column chromatography.



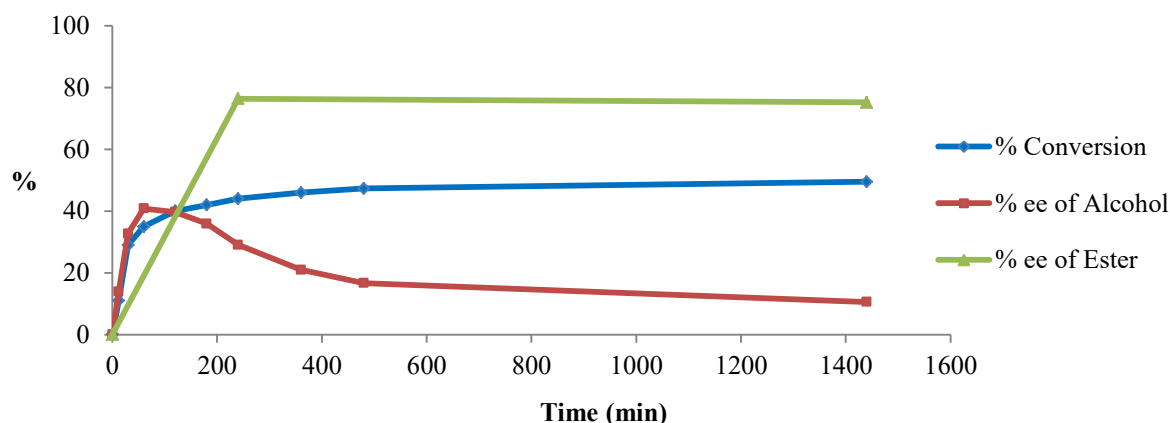


Figure 48. DKR using 1 mol% KR catalyst, 1.0 equiv. acylating agent.

As can be seen from the graph, the initial rate of conversion was too fast for the racemisation catalyst to keep the *ee* of the alcohol low, and this peaked at ~40% before decreasing to 10% over a 24 hour period. Presumably due to the increase in the *ee* of the alcohol, the final *ee* of the product was 75%, below our maximum expected value of 83%. While this was a slightly better result than with the initial conditions (*ee* of alcohol = 80%, *ee* of ester = 70%), the *ee* of the product was still too low, and the conversion of 50% was also too low.

In order to increase the conversion in the DKR, 1.5 equiv. of the acyl donor was added in the next attempt (Figure 49).

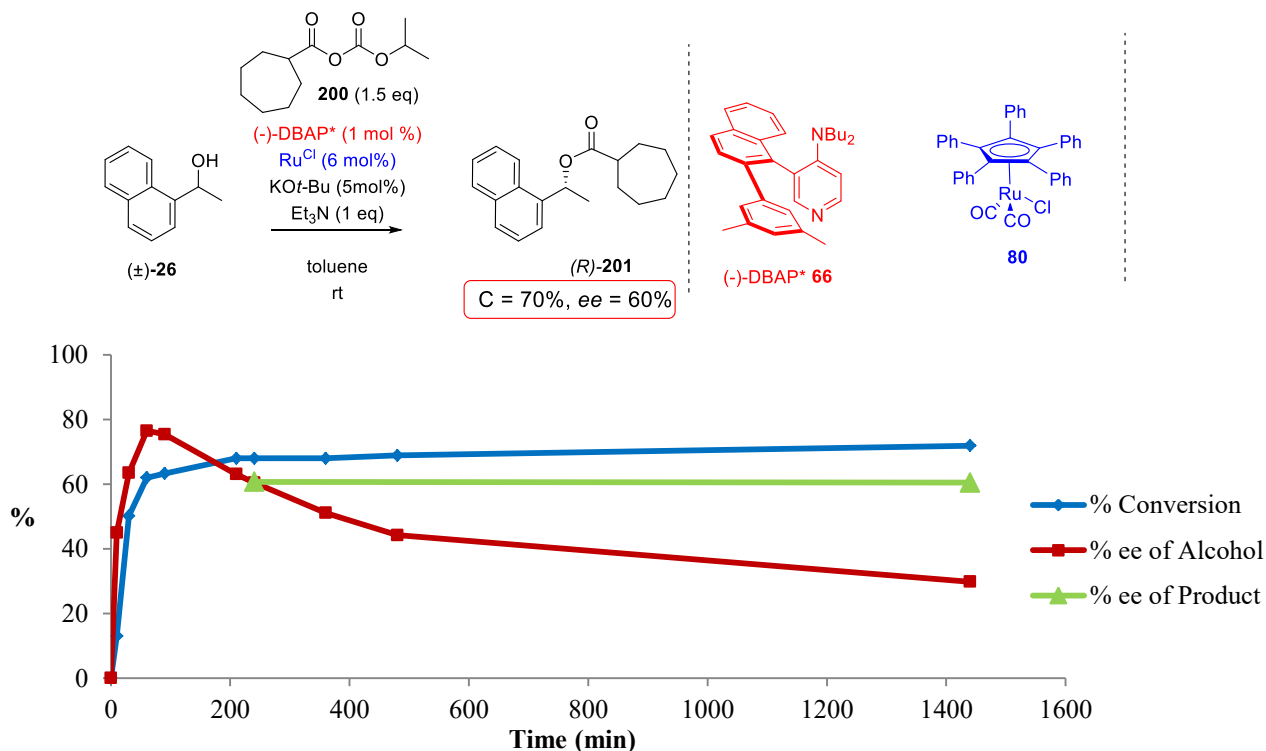


Figure 49. DKR using 1 mol% DBAP* 66 and 1.5 equiv. acylating agent 200.

Unfortunately, although the conversion did increase to 71% by ^1H NMR analysis, the *ee* of the product was also lower, again presumably due to the high *ee* of the alcohol (76%) at one point during the reaction due to the very fast initial rate of acylation.

In order to control the initial rate of acylation, a further reaction was attempted using 0.5 mol% of the KR catalyst and 1.5 equiv. of acyl donor (Figure 50).

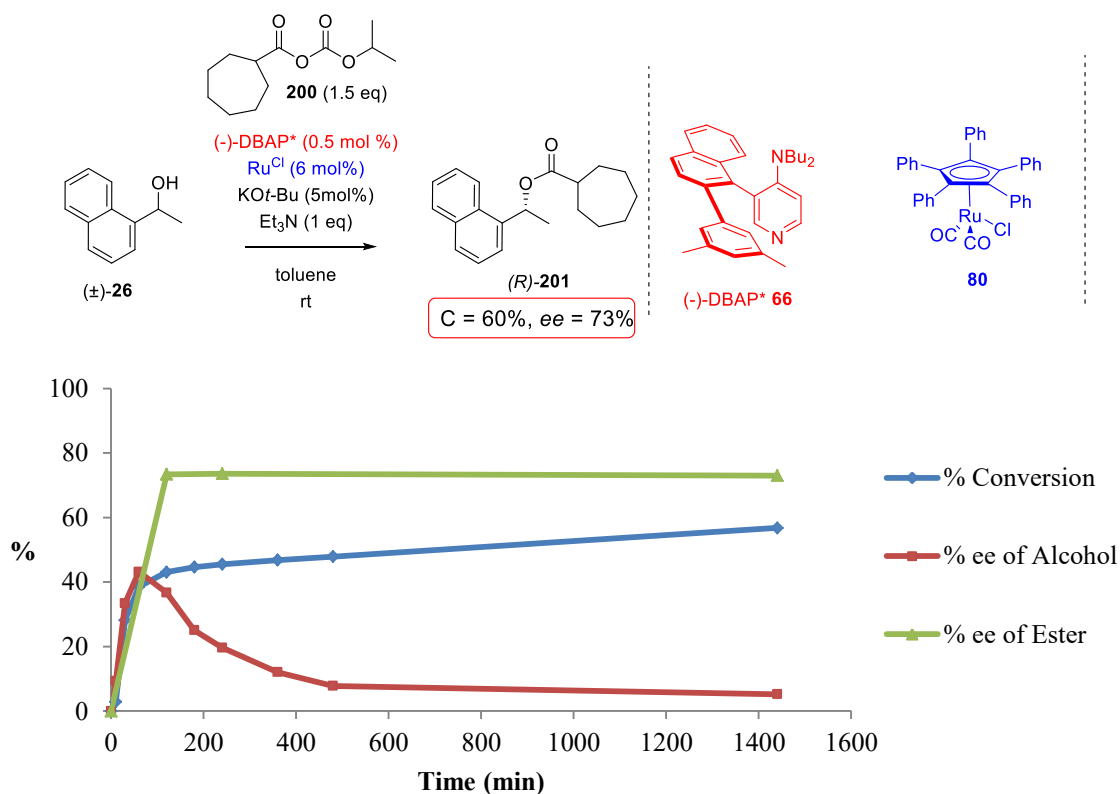
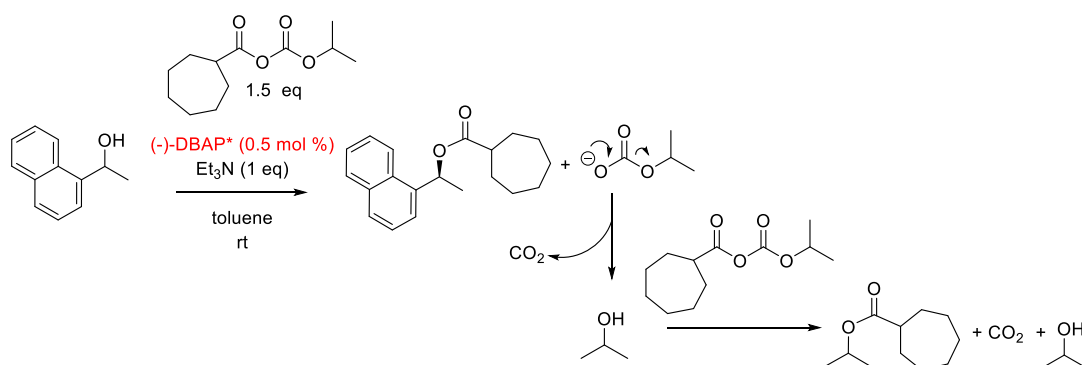


Figure 50. DKR using 0.5 mol% DBAP* **66** and 1.5 equiv. acylating agent **200**.

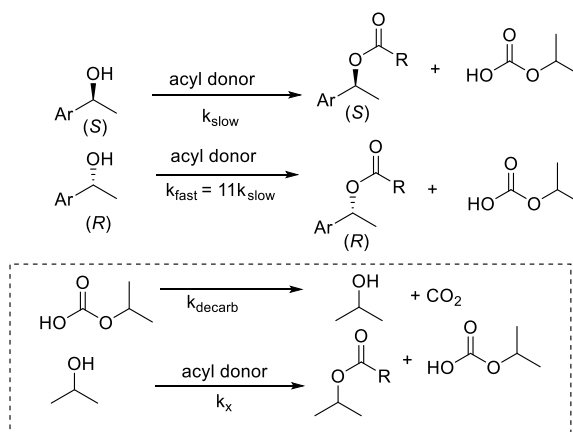
Although the recovered product had a higher *ee* (*ee* = 73%), the *ee* of the alcohol still reached a high of 44% during the reaction. Evidently, the rate of acylation cannot be sufficiently controlled by the KR catalyst loading.

A further challenge posed by all the above DKR reactions is that the reactions stop before complete conversion has been achieved; conversions of 50-70% were obtained and further conversion could not be achieved by adding an excess of the acyl donor. As this was also the case in the KR reactions, this could not be due to the KR catalyst deactivation by **80**, and therefore must be due to the acyl donor being consumed by a side reaction. We hypothesised that the following reaction could be taking place (Scheme 113):



Scheme 113. Postulated side reaction resulting in formation of *i*-PrOH and its potential further reaction with the acyl donor

Decarboxylation of the counter-ion from the acyl donor could be forming *isopropanol* (*i*-PrOH), which is a more reactive nucleophile than 1-(1-naphthyl)ethanol, and could therefore react with the acyl donor to form an ester and a further equivalent of *i*-PrOH, thus effectively consuming the acyl donor in a non-productive fashion. This hypothesis is supported by modelling the reaction with Copasi^[43] and entering estimated relative rates of reaction for each expected process (Scheme 114).



Scheme 114. Model reactions input into Copasi modelling program.

Including an equation for the fast formation of *i*-PrOH and the following acylation, it was possible to model the reaction, and indeed similar results were found to those observed experimentally (Figure 51):

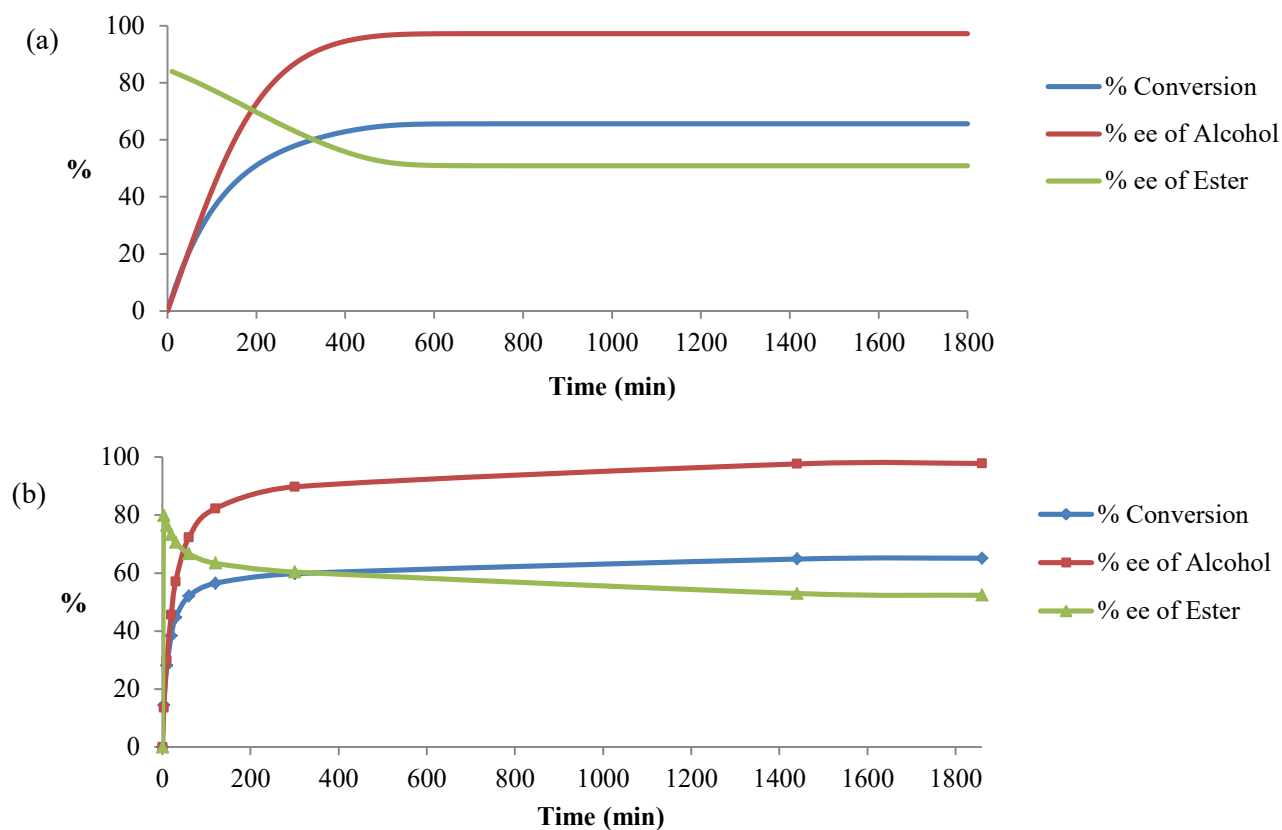


Figure 51. (a) Model of KR reaction with Copasi including decarboxylation of counter-ion and formation of *i*-PrOH. (b) Data from KR using acyl donor **200** (Figure 36).

4.3.3.2 Change to Acyl Donor

In order to avoid the problem associated with the formation of *i*-PrOH in the reaction we required an acyl donor that would not form a *sec*-alcohol upon decarboxylation. It was hypothesised that if a *tert*-alcohol was formed in the decarboxylation, this would be unreactive towards esterification and therefore not interfere in the KR, as *tert*-alcohols are very difficult to acylate. This theory has substantiation from the fact that *tert*-amyl alcohol (a *tert*-alcohol) can be used as a solvent in KR and DKR reactions.^[105,150,291] Therefore efforts were undertaken to synthesise the following reagents (Figure 52):

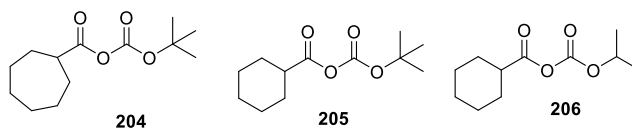
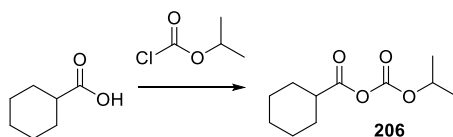


Figure 52. Alternative acyl donors **204-206**.

Acyl donor **204** contained a *tert*-butyl group instead of an *isopropyl* group, while the cyclohexyl analogues of both the *tert*-butyl acyl carbonate and *isopropyl* acyl carbonates were also targets (**205** and **206**), as cyclohexane carboxylic acid is more than 50× cheaper than cycloheptane carboxylic acid, and it was expected that large quantities of acyl donor would eventually be needed for membrane studies.

The cyclohexyl isopropyl carbonate **206** was synthesised using the previous method adapted from Fu^[291] (Scheme 115):

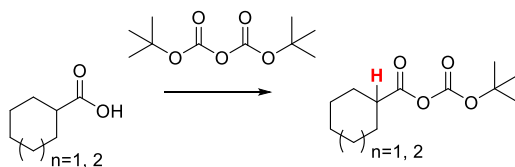


Scheme 115. Synthesis of cyclohexyl isopropyl carbonate **206**.^[291]

Reagents and Conditions: (i) Et_3N , Et_2O , rt, 4 h (67%).

Fortunately, the selectivity using this acyl donor was very similar to the cycloheptyl analogue under the standard conditions, with a selectivity factor $\sim s = 10$ -11 (*cf.* $s = 11.5$ for the cycloheptyl congener, see Table 27, entry 13)

The two *tert*-butyl acyl carbonates proved to be difficult to prepare. *tert*-Butyl chloroformate is not commercially available, and the use of Boc anhydride in place of the chloroformate proved unsuccessful for preparation of acyl carbonate **204**. An alternative procedure was found in the literature using pyridine as the base and so this method was investigated (Scheme 116).^[332]



Scheme 116. Synthesis of *tert*-butyl acyl carbonates **204** and **205**.

Reagents and Conditions: (i) pyridine, Et_2O , rt, 40 h (**204** = 33%, **205** = 47%).

Although evidence of product formation was evident by analysis of the ^1H NMR spectra following reactions designed to form both the cyclohexyl and cycloheptyl compounds **204** and **205**, it was very difficult to determine their purity as two *tert*-butyl peaks were present both for **204** and **205** in CDCl_3 . In d_8 -toluene on the other hand, two peaks were also observed for the proton α to the acyl carbonyl (marked in red in Scheme 116, above) for both compounds **204** and **205** (Figure 53). At the time, this was attributed to rotamers or conformers of the product.

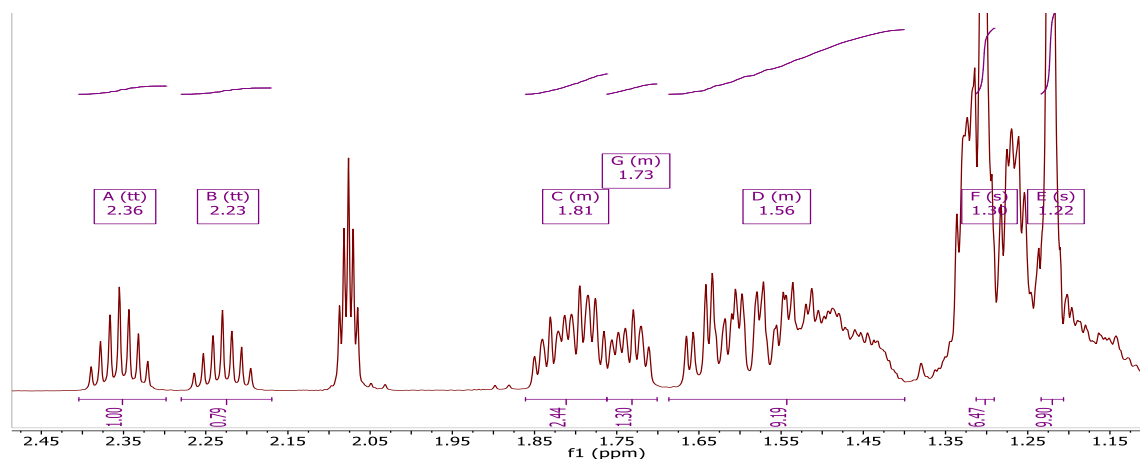


Figure 53. ^1H NMR of **204** in d_8 -toluene showing two C-H acid peaks for **204**.

As mass spectrometry confirmed the presence of the acyl carbonate, the cycloheptyl *tert*-butyl acyl carbonate was then tested in a KR to determine its selectivity (Figure 54).

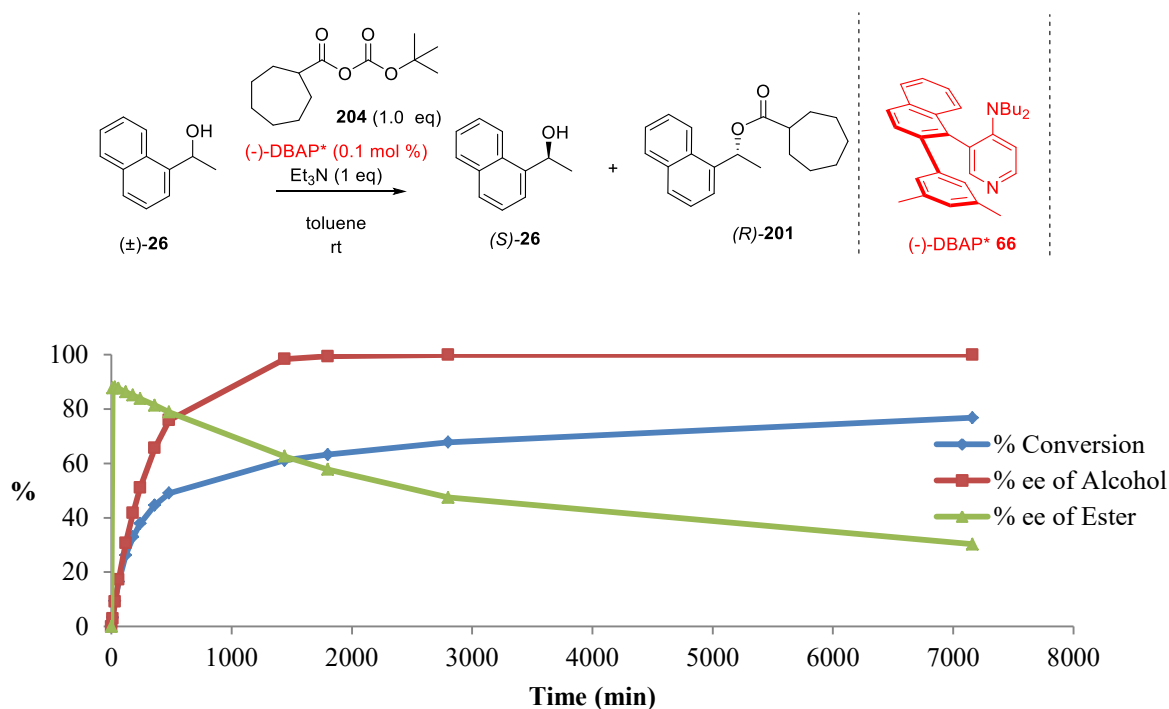


Figure 54. KR using cyclohexyl *tert*-butyl acyl carbonate **204**.

Encouragingly, the selectivity factor of the reaction was $s = 19$ (cf. $s = 11.5$ for the corresponding *isopropyl* congener, see Table 27) and moreover the reaction also went to 80% conversion. An increase in the selectivity factor equates to an increase in the maximum theoretical *ee* of the product that can be achieved in a DKR process (*i.e.* 90% vs. 83%). The cyclohexyl acyl carbonate **205** showed a similar level of selectivity ($s = 18$).

It was decided to evaluate the two new acyl donors under our conditions for racemisation at room temperature (Figure 55).

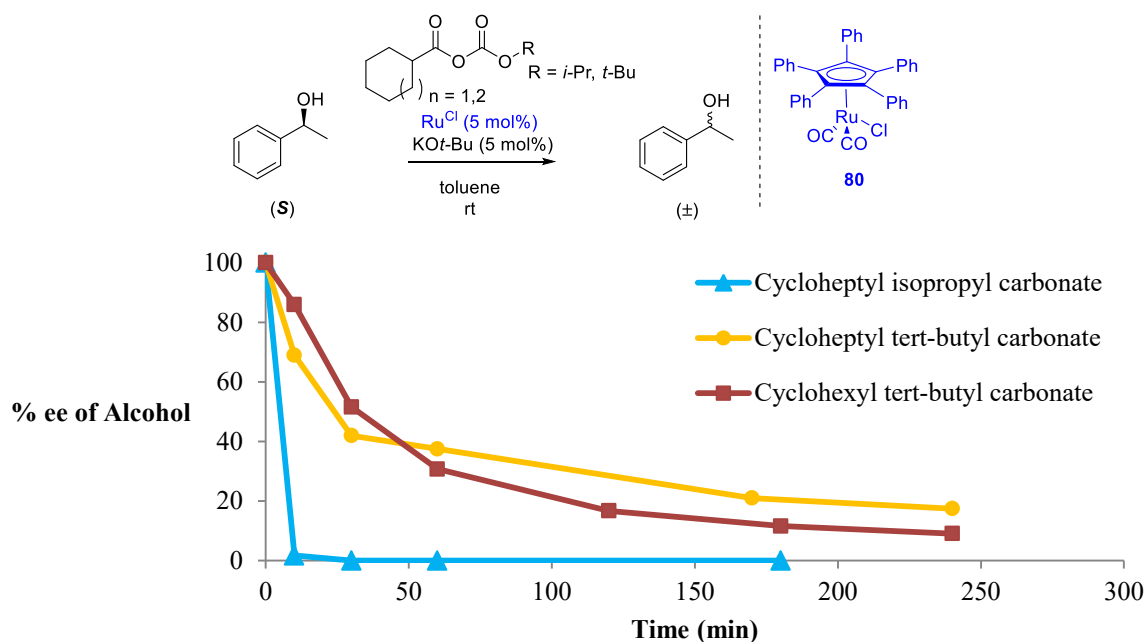
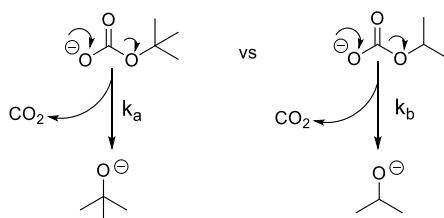


Figure 55. Relative rates of racemisation with acyl donors **201**, **204** and **205** with racemisation catalyst **80**.

As can be seen from Figure 55, both the cycloheptyl *tert*-butyl carbonate **204** and the cyclohexyl *tert*-butyl carbonate **205** appeared to interfere significantly with the racemisation process resulting in significantly slower rates of racemisation than when the cycloheptyl *isopropyl* carbonate **200** was present. As we knew that *tert*-butyl alcohol does not have a negative impact on the racemisation, the difference in the carbonate anion was presumed to be causing the decrease in reactivity of the racemisation catalyst (Scheme 117).



Scheme 117. Decarboxylation of carbanions to form *tert*-butanol or isopropanol.

It was initially hypothesised that this may have been because the rate of decarboxylation for the *tert*-butyl carbonate is slower than for the *isopropyl* carbonate, and that the carbonate anion deactivates the ruthenium catalyst by coordination to the Ru centre. A DKR with cycloheptyl *tert*-butyl carbonate **204** was nevertheless attempted (Figure 56).

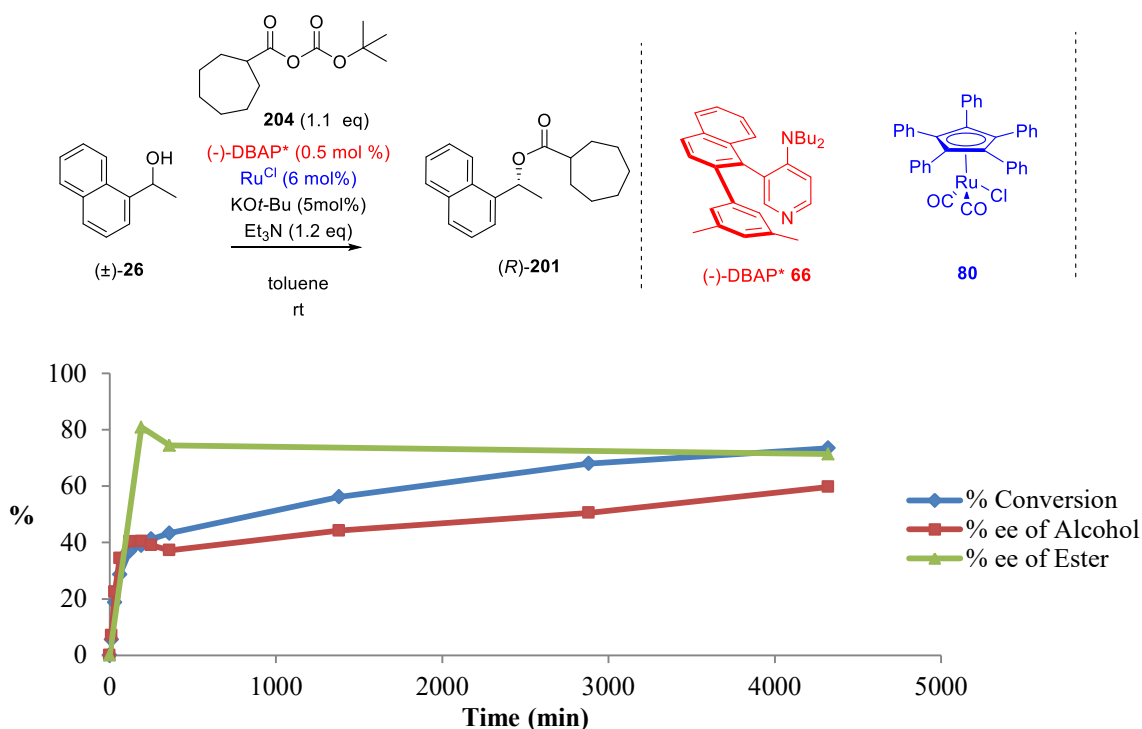


Figure 56. DKR with cyclohexyl *tert*-butyl carbonate **204**.

Unfortunately, although the conversion proceeded to over 70%, the racemisation was not successful, and after an initial drop in the *ee* of the starting alcohol, the *ee* continued to rise, indicating that the racemisation catalyst had been deactivated. A second attempt also showed a similar deactivation of the racemisation catalyst.

From these results it became clear that the *tert*-butyl carbonates could not be used in a one-pot DKR using the current racemisation catalyst. Indeed, further analysis of the different batches of *tert*-butyl carbonates synthesised revealed that the ratio of peaks corresponding to the protons α to the acyl carbonyl in the d_6 -benzene ¹H NMR of the *tert*-butyl carbonate varied from batch to batch (Figure 57).

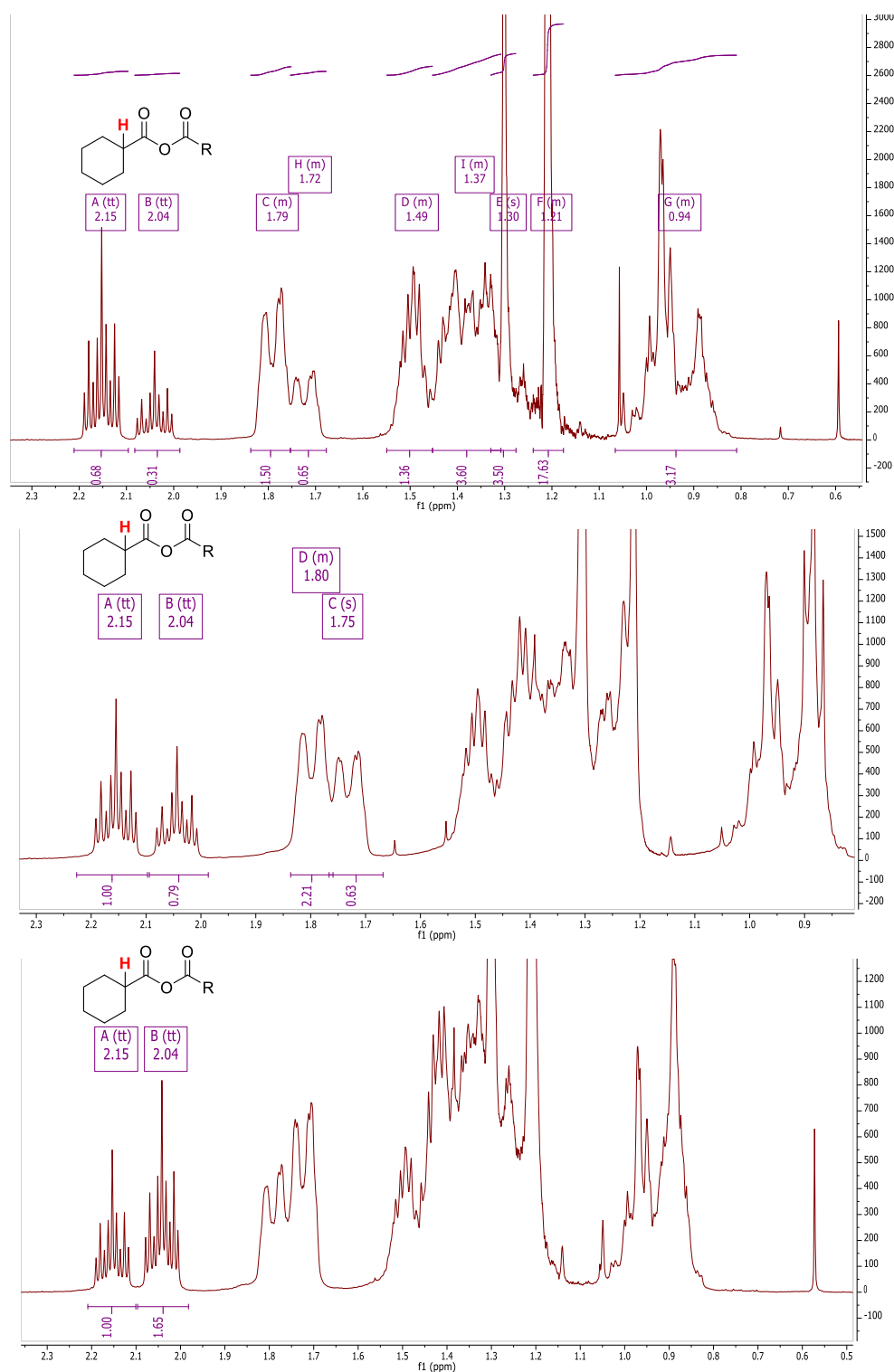
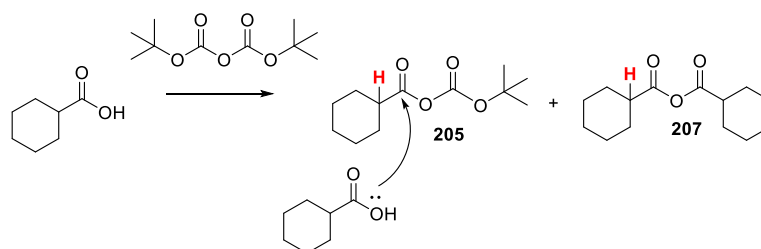


Figure 57. ^1H NMR in d^6 -benzene of products from three attempted carbonate syntheses of **205**.

The two key peaks are at $\delta = 2.15$ and 2.04 ppm, both clearly showing a triplet of triplets. While these peaks were originally associated with possible isomerism/rotamers in the molecule (*vide supra*), the batches with different ratios of these peaks also gave significantly different selectivity values ($s = 18$ for 70:30, $s = 15$ for 55:45 and $s = 11$ for 40:60). Further ^1H NMR and mass spectrometric analysis of these batches of product led to the conclusion that one of the peaks was indeed attributable to the *tert*-butyl acyl carbonate **205**, but

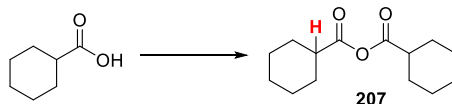
that the other was from dicyclohexane carboxylic anhydride, which was presumably also formed during the reaction *via* attack on the carbonate by the remaining carboxylic acid (Scheme 118).



Scheme 118. Possible mechanism of formation of cyclohexane *tert*-butyl carbonate **205** and dicyclohexane carboxylic anhydride **207**.

It was hoped that by making the pure carbonate compound (assumed to be peak at $\delta = 2.15$ ppm) it would be possible to keep the high selectivity, whilst also allowing the racemisation to occur, as presumably the inhibition of this vital process was attributable to the anhydride impurity. While various attempts to prepare the carbonate cleanly were unsuccessful, an attempt at distillation was partially successful, and led to the realisation that the peak previously associated with the carbonate **205** was actually that of the anhydride **207**, and that high selectivity reactions correlated with high proportions of the anhydride being present in the acyl donor mixture as opposed to the acyl carbonate.

To confirm this and allow the unambiguous determination of the correct selectivity for the anhydride alone, the authentic anhydride was prepared *via* the conventional method using DCC as a coupling reagent (Scheme 119).^[208]

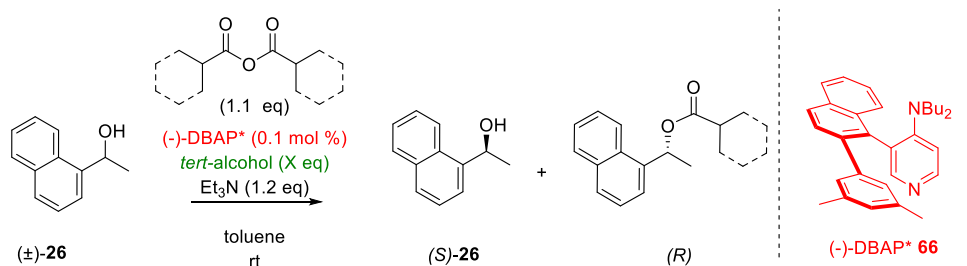


Scheme 119. Formation of dicyclohexane carboxylic anhydride **207** through DCC mediated coupling.^[208]

Reagents and Conditions: (i) DCC, CH_2Cl_2 , rt, 24 h (72%).

However, the selectivity of this compound was found to be reproducibly in the range $s = 13.5 \pm 0.5$. This value was significantly lower than the previously observed selectivity obtained when running the identical KR but with the mixed sample of anhydride **207** and carbonate **205** (**207:205** ~70:30; $s = 18$). Clearly another factor must be responsible for the higher selectivities obtained when employing an acyl carbonate mixture with an anhydride relative to using the anhydride alone. Given that higher proportions of carbonate deliver lower selectivity still (**207:205** ~40:60, $s = 11$), we hypothesised that maybe the by-products from the carbonate acylation process, *i.e.* the carbonic acid or the *tert*-butanol from the decarboxylation, were having a positive influence on the selectivity. To test this hypothesis, one equivalent of *tert*-butanol was added to a KR reaction using *isobutyric* anhydride and a KR reaction using dicyclohexane carboxylic anhydride under otherwise standard conditions (*i.e.* in toluene) and then also with increasing numbers of equivalents of *tert*-butanol in the case of the dicyclohexane carboxylic anhydride system (Table 28).

Table 28. KR of 1-(1-naphthyl)ethanol with isobutyric or dicyclohexane carboxylic anhydride with *tert*-alcohols as additives.



Entry	Anhydride	<i>Tert</i> -alcohol (eq)	Conversion (2 h)	Selectivity
1	isobutyric	-	30.2	9.9
2	isobutyric	<i>t</i> -BuOH (1.1)	29.9	11.7
3	cyclohexane	-	29.1	13.8
4	cyclohexane	<i>t</i> -BuOH (1.1)	26.3	15.4
5	cyclohexane	<i>t</i> -BuOH (2)	28.3 (2.5 h)	17.2
6	cyclohexane	<i>t</i> -BuOH (5)	18.6	18.7
7	cyclohexane	<i>t</i> -BuOH (10)	14.4	19.3
8	cyclohexane	<i>t</i> -AmOH (5)	19.5	18.9
9	cyclohexane	<i>t</i> -AmOH (solvent)	33.0	22.5
10	cyclohexane	HOCPhMe ₂ (5)	19.4	19.6
11	cyclohexane	HOC(Ph) ₃ ^a (5)	9.9 (1 h)	15.5
12	cyclohexane	Adamantanol ^a (5)	14.2 (1 h)	15.9

^a The *tert*-alcohol did not dissolve in reaction, suspension of *tert*-alcohol.

Interestingly, the addition of 1.1 equivalents of *t*-BuOH in the reaction with isobutyric anhydride did indeed increase the selectivity relative to the reaction in just toluene (entry 2 vs entry 1), while the effect was also present with the more selective dicyclohexane carboxylic anhydride **207** (entry 4 vs entry 3). Increasing equivalents of *t*-BuOH further increased the selectivity (entry 5), while with 5 equivalents of *t*-BuOH the selectivity increased to ~18 (entry 6), the value we had observed with the 70:30 ratio of the anhydride **207**/carbonate **205** mix (*i.e.* 1:0.85 equivalents anhydride to carbonate). Increasing the number of *tert*-alcohol equivalents to 10 marginally increased the selectivity (entry 7), whilst giving a lower conversion. It was hypothesised that the drop in conversion as the number of equivalents of alcohol is increased is due merely to dilution of the reaction mixture. Changing the alcohol to *t*-AmOH (5 equiv.) gave similar results to *t*-BuOH (entry 8), while changing to *t*-AmOH as the solvent further increased the selectivity to 22.5 (entry 9). Although *t*-AmOH had been reported previously to facilitate high levels of selectivity relative to other solvents,^[333] even within our research group,^[118] this was the first time it has been observed that a *tert*-alcohol can also facilitate high levels of selectivity when used just as an additive rather than as the bulk solvent. Further screening of sterically hindered and/or aromatic *tert*-alcohols did not uncover any alcohols that displayed increased levels of selectivity, although several of the alcohols evaluated displayed poor solubility (entries 11 and 12).

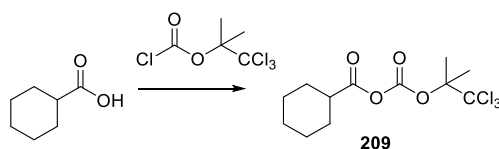
It was then decided to explore whether the positive effect of *tert*-alcohol additives on the selectivity in this reaction was mirrored using cyclohexyl isopropyl carbonate **206** (Table 29).

Table 29. KR of 1-(1-naphthyl)ethanol with cyclohexyl isopropyl carbonate **206** and *tert*-alcohol additives.

Entry	<i>Tert</i> -alcohol (eq)	Conversion (2 h)	Selectivity
1	-	57.7	10.7
2	<i>t</i> -BuOH (5)	33.6	12.7
3	<i>t</i> -AmOH (solvent)	53.2	11.5

In this case however, while the addition of 5 equivalents of *t*-BuOH increased the selectivity from $s = 10.7$ to 12.7 (entries 1 and 2), using *t*-AmOH as the solvent only increased the selectivity to $s = 11.5$ (entry 3). Thus toluene was retained as the solvent of choice for future DKR experiments, with the addition of 5 equivalents of *t*-BuOH as an additive to increase the selectivity, increasing the maximum theoretical *ee* of the product from 83% to 85%.

In order to try to throw light on whether the *tert*-butyl acyl carbonate would have displayed improved conversion relative to its *isobutyl* congener (had we been able to obtain it pure), 2,2,2-trichloro-1,1-dimethylethyl cyclohexane acyl carbonate **209** was prepared in the hope that this compound would similarly furnish a *tert*-alcohol by-product (2,2,2-trichloro-1,1-dimethylethanol) which would both be unreactive towards acylation and engender high levels of selectivity *via* the aforementioned ‘additive effect’. Importantly, the starting material for the synthesis of acyl carbonate **209**, 2,2,2-trichloro-1,1-dimethylethyl chloroformate is commercially available (Scheme 120).^[291]



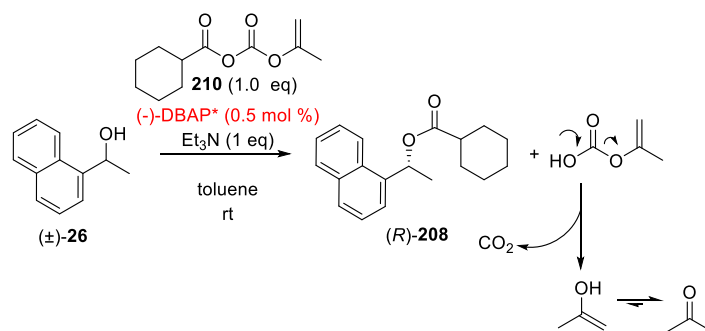
Scheme 120. Synthesis of 2,2,2-trichloro-1,1-dimethylethyl cyclohexane acyl carbonate **209**.

Reagents and Conditions: (i) Et_3N , Et_2O , 0 °C, 2 h (80%).

Synthesis of acyl carbonate **208** proceeded as expected, with <10% of the anhydride observed by ^1H NMR analysis. Testing of this acyl carbonate in the KR using the previous conditions yielded a selectivity of $s \sim 8.0$, which could be increased to $s \sim 9$ upon addition of *t*-BuOH. Although disappointing, this was partially expected from previous results where it had been found that acyl carbonate/anhydride mixtures having a high

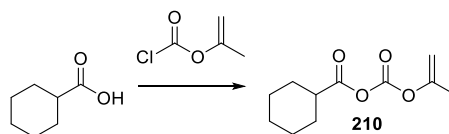
proportion of the *tert*-butyl acyl carbonate yielded lower levels of selectivity ($s \sim 11$) relative to those with low proportions ($s \sim 18$). As this level of selectivity would only have provided a maximum product *ee* of 79% in a DKR, no further efforts were made to deploy this carbonate

An alternative solution for overcoming the problem of by-product formation from the acyl donor therefore had to be found. We were attracted to the possibility of using an *isopropenyl* group as the leaving group. *iso*Propenyl acetates have been used widely as acyl donors in enzymatic (D)KRs,^[244] because for these vinyl esters the enol formed upon transesterification rapidly tautomerises to the keto-form (acetone in the case of an *isopropenyl* acetate) rendering the process irreversible. It was envisaged that replacing the *isopropyl* carbonate with an *isopropenyl* carbonate should also prevent the released alcohol becoming esterified thereby solving the low conversion issue. However, the compatibility of the process with acetone was unknown (Scheme 121).



Scheme 121. Expected reaction of 1-(1-naphthyl)ethanol with an *isopropenyl* carbonate, forming acetone (cf. *i*-PrOH when using an *isopropyl* carbonate).

The *isopropenyl* carbonate **210** was synthesised using the same method as for *isopropyl* carbonates, although it could not be purified by distillation due to decomposition and was therefore used crude (~10% anhydride impurity)(Scheme 122).^[291]



Scheme 122. Synthesis of cyclohexyl *isopropenyl* carbonate **210**.^[291]

Reagents and Conditions: (i) Et_3N , Et_2O , 0 °C, 90 min (88%).

However, initial KR results were disappointing. The conversion proceeded to ~10 % after 30 minutes with a selectivity of $s = 9$, but remained at 10% for the duration of the reaction (24 hours), even after a further equivalent of the acyl donor had been added. In order to determine whether the formation of acetone was inhibiting the KR, three parallel reactions were carried out: reaction (a) using the *isopropyl* carbonate **206**, reaction (b) using the *isopropyl* carbonate **206** and 1 equiv. of acetone, and (c) using the *isopropenyl* carbonate **210** (Figure 58).

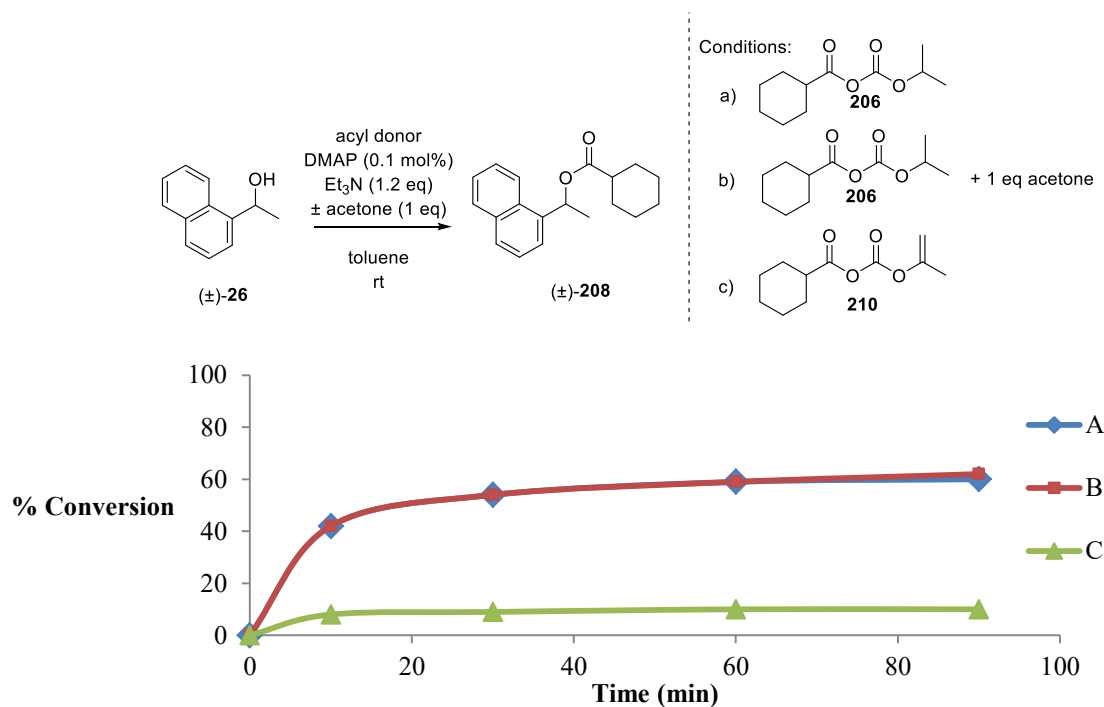
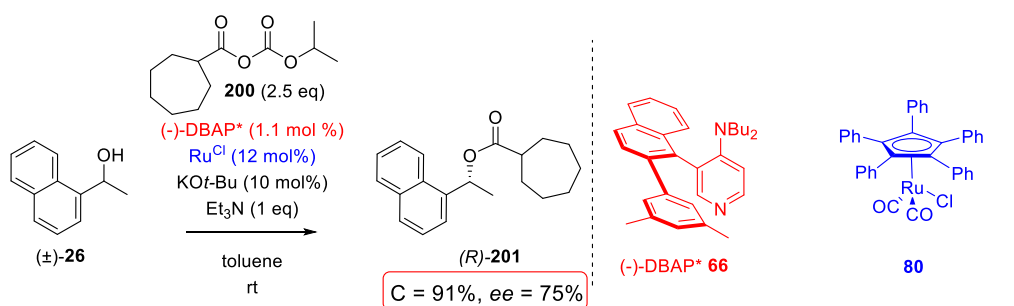


Figure 58. Investigation into the effect of acetone on the rate of acylation in KR reaction.

The presence of acetone had no effect on the rate of acylation with the *isopropyl* acyl carbonate **206**, while the *isopropenyl* acyl carbonate **210** again exhibited the same deactivation as in the KR. Although we had no explanation for the poor performance of the *isopropenyl* carbonate, no further experiments were carried out with this acyl donor.

4.3.3.3 Back to Isopropyl Carbonate

As the attempts to identify a better acyl donor than the *isopropyl* carbonate had not proved fruitful, we turned our attention to trying to adapt our procedures to minimise the impact of the limitations of this reagent. Specifically, the possibility of adding both the catalyst and the acyl donor in batches over the course of the reaction was explored, and increasing the racemisation catalyst loading to 10 mol% (Figure 59).



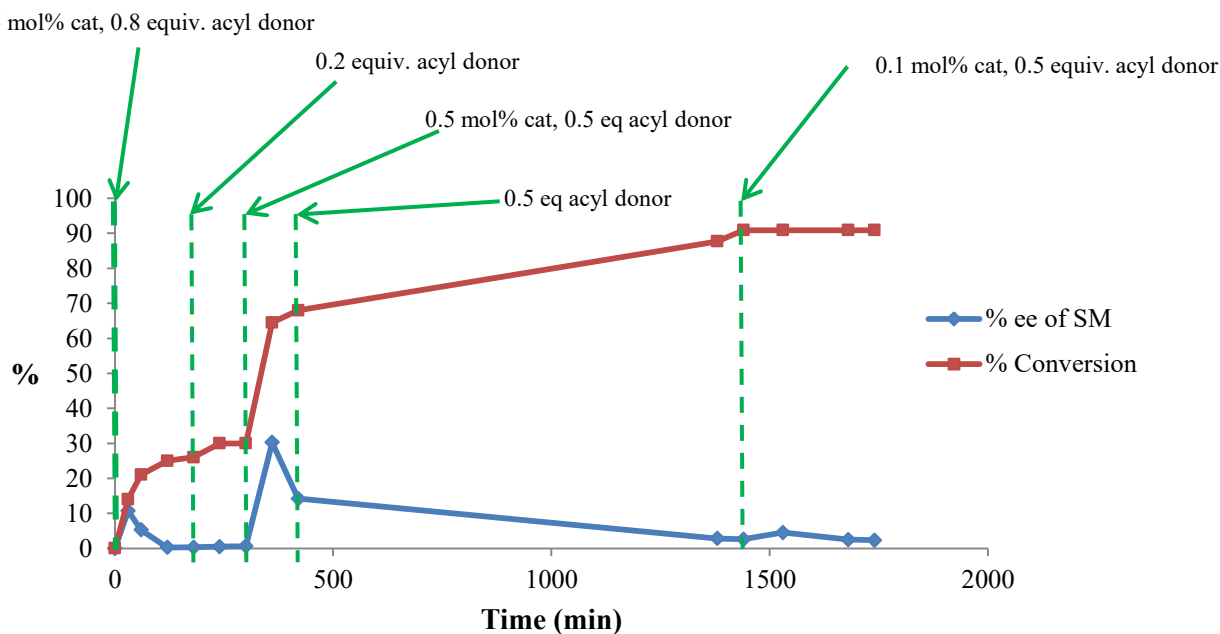
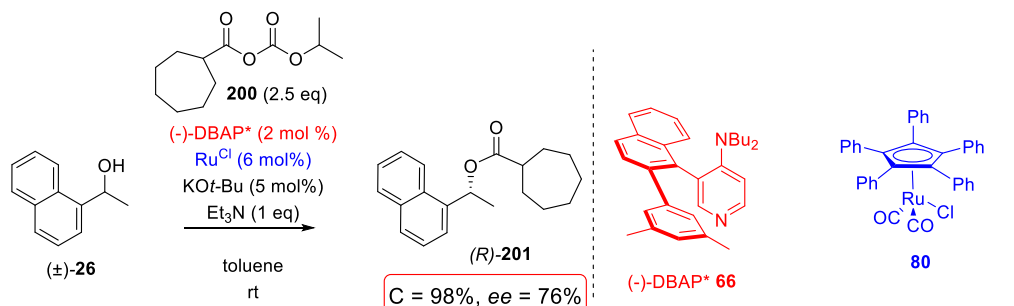


Figure 59. DKR with batch-wise addition of catalyst and acyl donor.

In total, 1.1 mol% of catalyst and 2.5 equiv. of acyl donor was added and the reaction proceeded to **91% conversion**, with the **final ee of the product at 75%**. This was the most successful attempt at a DKR we had achieved up to this point. The decreased *ee* of the product from a theoretical 83% was undoubtedly due to the rise in the *ee* of the alcohol to ~30%, which would have compromised the *ee* of the product. From these results, it appeared that the acylation catalyst was deactivated quickly, with the addition of 0.2 equiv. of acyl donor after 3 hours not increasing the conversion significantly, while the second addition of 0.5 equiv. of acyl donor with 0.5 mol% of catalyst initially gave a very sharp increase in conversion initially, followed again by a much slower increase. These results showed that the conversion could be increased with addition of further portions of the acyl donor, as long as enough active acylation catalyst remained in the reaction.

Further slowing down the addition of the KR catalyst, even with a reduction of the racemisation catalyst loading (10 → 5 mol%) led to improved results (Figure 60).



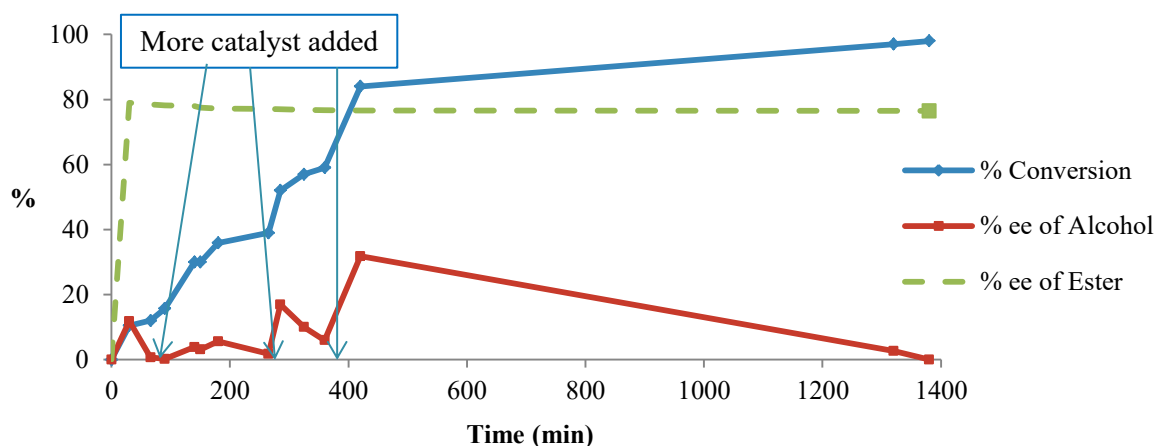
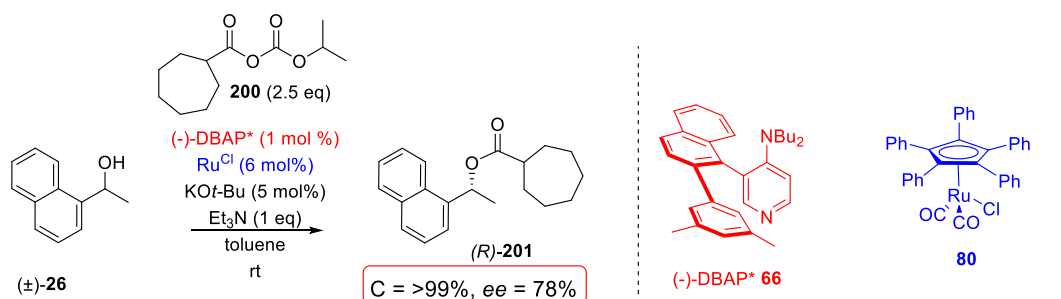


Figure 60. DKR with batch-wise addition of catalyst and acyl donor^a

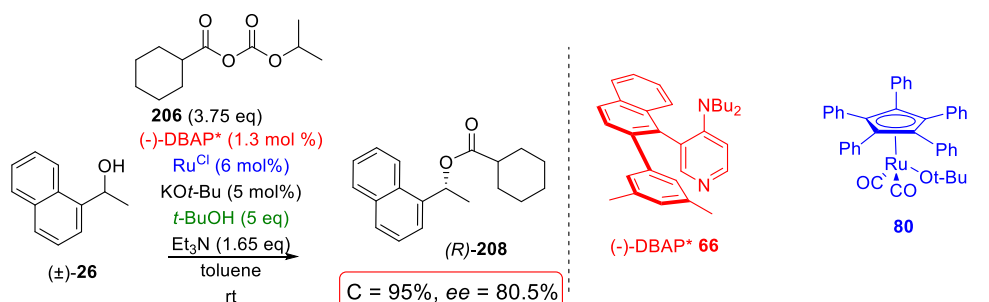
^aOnly the final data point for the product *ee* was collected, therefore the dashed line for product *ee* is hypothesised.

The final *ee* of the ester was 76%. Again, this was lower than the theoretical maximum of 83%, presumably due to the increases in the *ee* of the alcohol above the desired 0% *ee* at various time points during the reaction. Attempts were made to use two syringe pumps for slow addition of both the acyl donor and catalyst over 5 hours instead of batchwise addition. Although this resulted in a higher conversion and *ee* (Scheme 123), further portions of catalyst still had to be added after the addition had finished in order for the reaction to go to completion. It appeared that the KR catalyst deactivation was not linear, and the conversion at the start of the reaction was slower, while adding small amounts of catalyst later in the reaction had a large effect on the conversion.



Scheme 123. One-pot DKR using slow addition of both KR catalyst and acyl donor.

A DKR was then attempted using 5 equivalents of *t*-BuOH as a selectivity-increasing additive (Scheme 124).



Scheme 124. One-pot DKR using *t*-BuOH as an additive to increase selectivity.

We originally envisaged adding 1 mol% of the catalyst over 5 hours, and 1.5 equiv. of the acyl donor over the same period of time. However, after 5 hours <10% conversion was observed by HPLC. Therefore, after 5 hours, a further 0.5 equiv. of acyl donor and 0.1 mol% of catalyst was added to the reaction. After 24 hours, a further 0.2 mol% catalyst, and 0.75 equiv. acyl donor was added, and the reaction was stopped after 48 hours. Pleasingly, the reaction had gone to 95 % conversion, and the *ee* of the product was 80.5%, especially as the acyl donor in this reaction was the slightly less selective cyclohexyl acyl carbonate **206**, not the cycloheptyl acyl carbonate **200**.

It was evident that slow addition of both the catalyst and the acyl donor was not a solution to the challenge faced with the reactivity/deactivation of the catalyst, as the catalyst was still deactivated too quickly. Slow addition of just the acyl donor, or just the catalyst was also unsuccessful, and therefore batch addition of both the catalyst and the acyl donor together proved to be the only method of increasing the conversion in these reactions. It was hypothesised that this is because deactivation of the KR catalyst occurs predominantly when it is in its non-acylated form, consequently, provided there is sufficient acyl donor present it only undergoes slow deactivation by the racemisation catalyst because its 'resting state' is the acyl pyridinium salt. However, when there is insufficient acyl donor present, the resting state of the KR catalyst is the free pyridine and this suffers apparently irreversible deactivation. Interestingly, the amount of KR catalyst deactivated is not in proportion to the amount of catalyst added – at the beginning of the reaction, even large quantities are deactivated quickly, whereas later in the reaction a small quantity of KR catalyst (0.1 mol%) can catalyse a significant increase in the conversion before becoming deactivated. This could possibly be due either to the decreased quantities of active racemisation catalyst, or from build-up of the by-product from the KR, namely the initial counter-ion or carbonate.

Further attempts were made to develop a robust procedure for the DKR, and a slightly better result (*ee* of ester = 81.5% out of possible 85%) was obtained with batch-wise addition of the catalyst and acyl donor, again in the presence of 5 equiv. of *tert*-butanol (Figure 61 – addition of acyl donor and KR catalyst represented by hashed red lines).

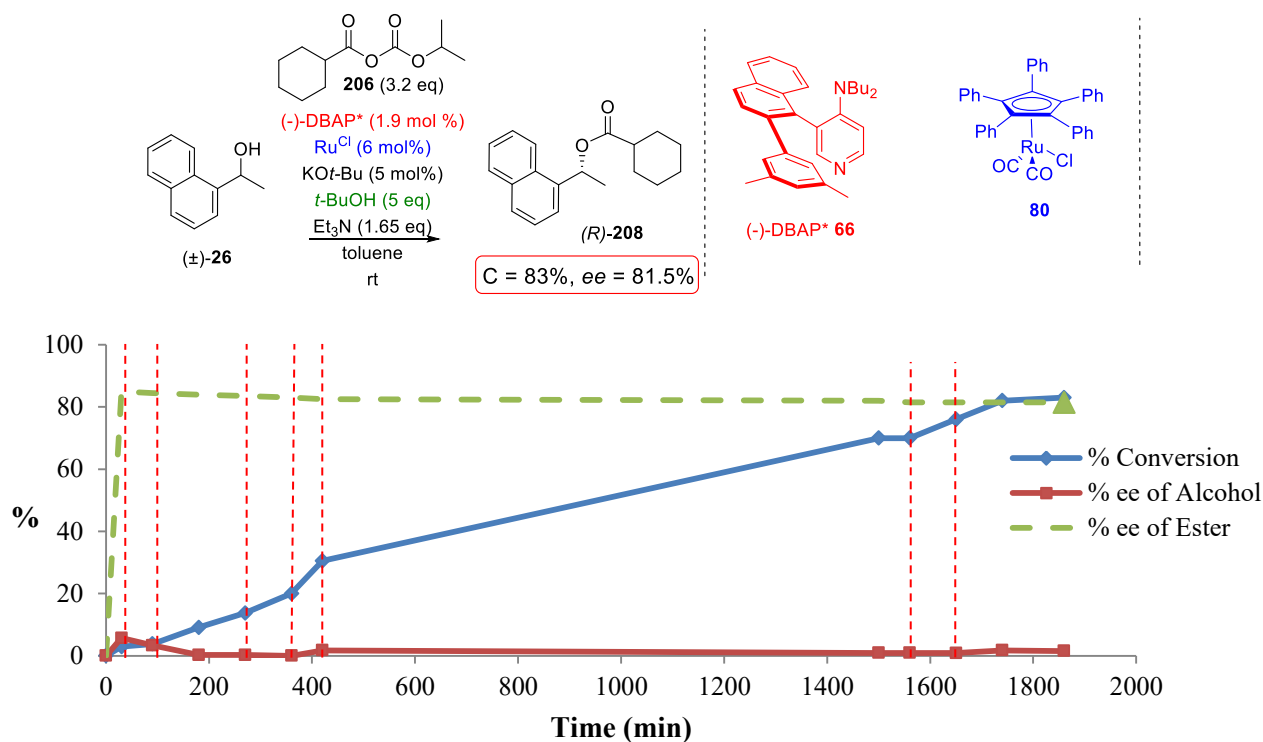


Figure 61. KR with batchwise addition of acyl donor and KR catalyst (additions represented by hashed red lines) providing 83% C and 81.5% ee product.

^aOnly the final data point for the product ee was collected, therefore the dashed line for product ee is hypothesised.

The procedure however was still not very elegant. In a further DKR, batchwise addition of the acyl donor and catalyst every 30 minutes was attempted (0.1 mol% catalyst, 0.3 equiv. acyl donor each time). Although the reaction did go to completion within 8 hours compared to the previous 30-48 hours, the ee of the product was much lower (65%), as the rate of acylation was too fast near the end of the reaction, consistent with the observation that any catalyst added later in the reaction is deactivated slower (Figure 62).

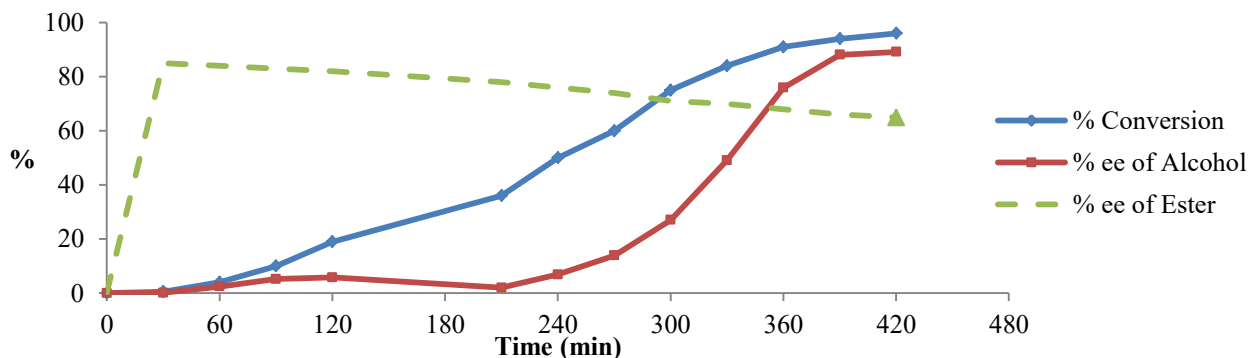


Figure 62. KR with addition of acyl donor and KR catalyst every 30 minutes providing 99% C and 65% ee product.

Although the *ee* of the product from this reaction was disappointing (due to the very large increase in the *ee* of the alcohol), we were pleased to see that the reaction could go to completion relatively quickly. It was also interesting to note that the racemisation was efficient up to ~4 h/40% conversion, and that it was only after this time that the rate of acylation overwhelmed the racemisation. It was therefore decided to study the rate of coordination of 4-DMAP to the activated ruthenium catalyst.

In order to determine the rate of coordination of 4-DMAP to the activated ruthenium racemisation catalyst, a reaction was set up in an NMR tube with dry *d*₈-toluene to form the activated ruthenium catalyst, and then a slight excess of 4-DMAP was added and the rate of coordination measured. This was determined by the change in chemical shift of the peaks for 4-DMAP and the peaks of the *tert*-butoxide ligand of the ruthenium catalyst, using the same concentrations as employed in a typical DKR experiment (Figure 63).

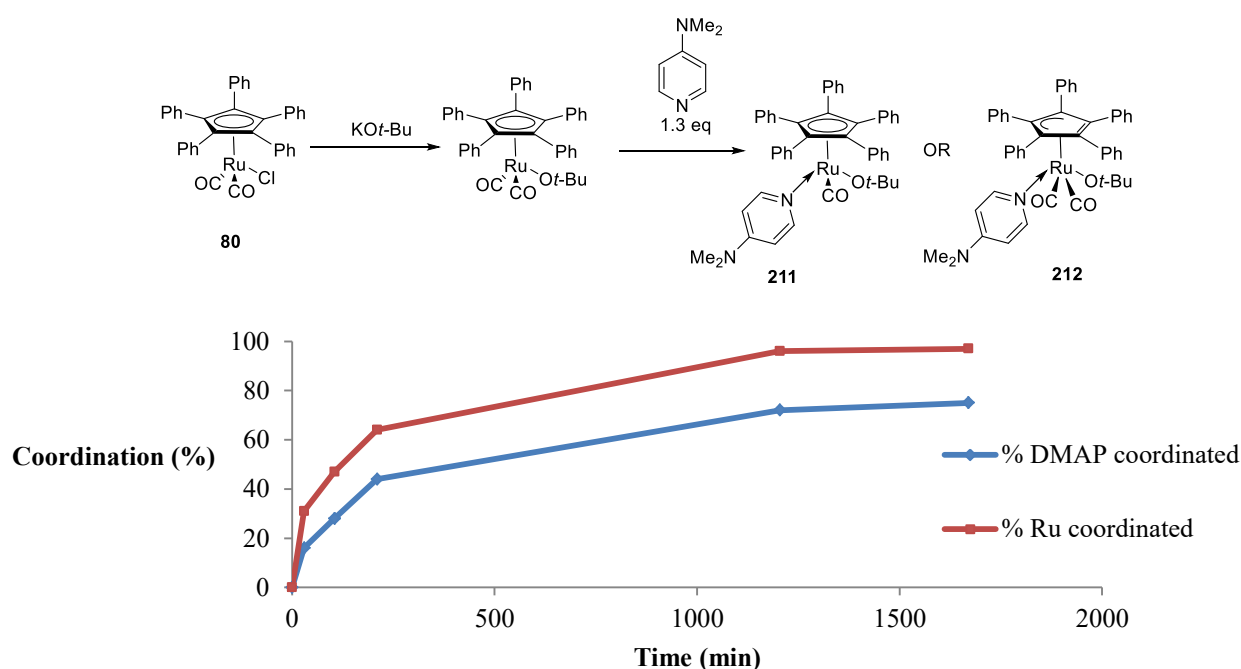


Figure 63. Rate of coordination of DMAP to activated ruthenium catalyst.

After 28 hours, 75% of the 4-DMAP was coordinated to the ruthenium, and 97% of the ruthenium was coordinated to the DMAP. Interestingly, the peaks for the cyclopentadiene ligand also changed during the coordination process. Two possible mechanisms have been proposed by Bäckvall for the racemisation of alcohols: CO dissociation (**211**) and η^5 to η^3 ring slippage (**212**). Recent work has provided support for the CO dissociation mechanism, as evidenced by computational methods, the observation of ¹³C incorporation into the catalyst and also inhibition of racemisation by CO (*vide supra*).^[228] We therefore hypothesise that 4-DMAP is coordinating to the ruthenium centre following loss of CO (**211**), rather than by ring slippage of the cyclopentadiene ring.

In order to investigate whether the 4-DMAP-Ru complex **211** was a viable catalytic system, *i.e.* whether the 4-DMAP and/or a remaining CO can dissociate from the Ru centre, the 4-DMAP-Ru complex was re-formed as above, and after 24 hours (*S*)-1-phenylethanol was added to the flask (Figure 64).

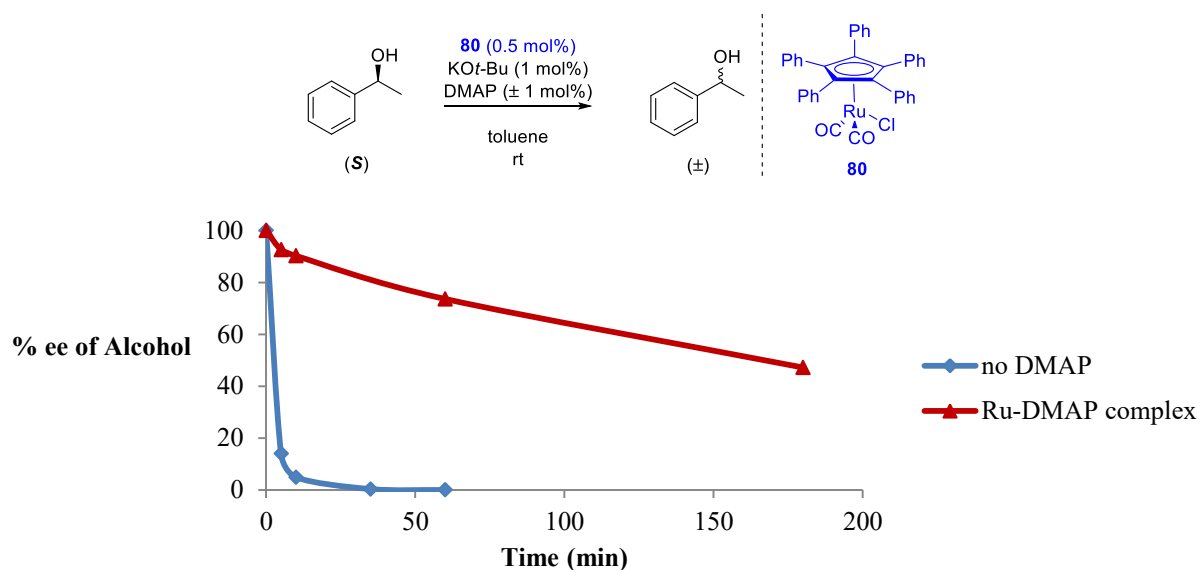


Figure 64. Rate of racemisation with 4-DMAP-Ru complex compared to the activated Ru catalyst.

Although a similar experiment had been carried out before and the presence of 4-DMAP was found to have slightly decreased the rate of racemisation, the previous experiment was without the 24 hours ‘pre-mix’ period designed to allow the 4-DMAP to fully coordinate to the ruthenium. While the 4-DMAP-Ru complex retained a strong red/orange colour for 24 hours, addition of the alcohol at this point caused a black solid to precipitate and the solution to turn from orange to black/green. Although the racemisation still occurred, it was much slower than without any 4-DMAP present. As ten equivalents of 4-DMAP had been added to the Ru catalyst in this experiment, essentially all of the ruthenium was expected to be coordinated to the 4-DMAP; the observed racemisation could therefore be attributed to dissociation of either the 4-DMAP or CO from the ruthenium centre. However, given that the 4-DMAP-free ruthenium catalyst **80** is very active, it is also possible that very low concentrations of this catalyst could potentially be responsible for the observed residual racemisation activity.

Assuming that 4-DMAP and DBAP* catalyst **66** behave similarly, the above experiments suggest that not only does the ruthenium racemisation catalyst deactivate the DBAP*’s KR activity in our DKR reactions, but also that DBAP* catalyst **66** deactivates the ruthenium racemisation catalyst – *i.e.* the interaction is one of mutual deactivation. The reason that the ruthenium deactivation is less apparent in the DKR experiments is that a large excess of the ruthenium catalyst is employed in comparison to the KR catalyst due to its overall lower level of activity even in its most active state.

4.3.4 Conclusions and Future Work

To conclude, our attempts to develop a one-pot *sec*-alcohol acylative DKR procedure with the Spivey DBAP* catalyst **66** effecting KR and the Bäckvall ruthenium catalyst **80** effecting racemisation, proved to be

challenging. The following features of the process in particular have been noted: firstly, the selectivity of KR reactions catalysed by the DBAP* catalyst **66** are significantly lower when employing acyl carbonates rather than anhydrides, but only the former acyl donors are compatible with the racemisation catalyst. Moreover, the levels of selectivity obtained are strongly influenced by the reaction temperature and at room temperature, as required for racemisation, they are significantly lower than at -78 °C. This reduced selectivity compared to results at -78 °C with anhydrides limited the maximum *ee* achievable for the product ester to 85% in the optimised conditions. Secondly, the counter-ion from the acyl donor can decarboxylate to form *i*-PrOH, which as a relatively unhindered *sec*-alcohol itself can out-compete our substrate for reaction with the acyl donor, thus slowing the desired reaction down and necessitating the use of excess acyl donor. Thirdly, we found that DBAP* **66** can coordinate to Bäckvall's Ru catalyst **80**, deactivating both the DBAP* **66** and the Ru catalyst **80** in the process.

Nevertheless, we developed a procedure for this reaction whereby good yields and *ee* could be achieved by batch-wise addition of both the acyl donor and the DBAP* catalyst **66** during the reaction, with a maximum *ee* of 81.5% achieved in the process, close to the maximum theoretical *ee* obtainable (given the intrinsic selectivity of the KR with *tert*-butanol) of 85%. The realisation that stoichiometric quantities of *tert*-alcohols can improve the selectivity in our KR reactions thus allowed for a facile improvement of the selectivity by the simple addition of 5 equivalents of *tert*-butanol.

Further work is required to optimise the rate of addition of the acyl donor and catalyst, by studying the rate of deactivation of the DBAP* catalyst **66**, and to then apply this procedure to other alcohol substrates.

4.4 Development of Membrane-Enhanced DKR

This chapter focuses on the development of a MEDKR process. The basis for developing a non-enzymatic MEDKR came from previous work from the Livingston group, where they had successfully developed a semi-continuous flow process for the MEDKR of amines.^[286] Due to the base-lability of organic-solvent nanofiltration (OSN) membranes, a base-stable microfiltration membrane was used in this work to retain the enzyme, while the ruthenium racemisation catalyst was not retained. Since then the group has developed a more base-stable membrane (PEEK), and it was this development that re-initiated efforts to achieve a separated MEDKR.

4.4.1 Types of Membrane Available

4.4.1.1 Selection of Membranes

While there are many OSN membranes commercially available, none of these are base-stable. A polyether-ether-ketone membrane (PEEK) was recently developed in the Livingston group by Joao da Silva Bursal *et al.* (Figure 65).^[334]

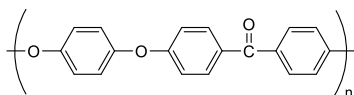
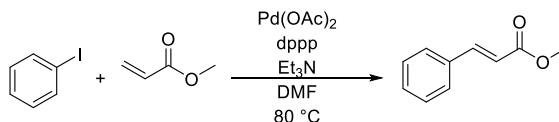


Figure 65. Structure of PEEK membrane.^[334]

PEEK is a highly resistant semi-crystalline thermoplastic that is only soluble in sulfuric acid and methanesulfonic acid. It is prepared from commercially available PEEK powder that is dissolved in a mixture of methanesulfonic acid and sulfuric acid (3:1) and then cast into a 250 μm membrane on a polypropylene support using a bench top laboratory casting machine.^[334]

The membrane is then immersed in deionised water to remove all traces of acid, with the water bath changed until the pH reaches 6-7, and then finally dried in air.

The PEEK membrane has been successfully used by the Livingston group for the retention of a palladium catalyst in a continuous-flow Heck reaction (Scheme 125).^[335]



Scheme 125. Continuous flow Heck reaction using PEEK membrane for catalyst retention.^[335]

This work demonstrated the high base-stability of this membrane at high temperatures (80 °C) and for long reaction times (>10 days). This membrane was therefore chosen for testing, as well as a commercially available Puramem 280 polyimide membrane for comparison (Figure 66).

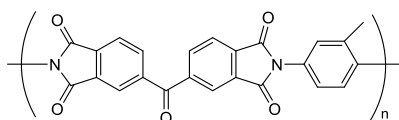


Figure 66. Commercially available Puramem 280 polyimide membrane.

4.4.2 Testing of Membrane for MEDKR

The first step in the development of the MEDKR was testing whether the membranes could in fact retain the chosen catalysts and if they were permeable to the substrate and product. Due to the large quantities of catalyst required for the testing, 5-Azy* catalyst **131** was used to test the rejection characteristics of the membranes, in the expectation that its behaviour would be indistinguishable from the catalyst actually planned to be used, *i.e.* DBAP* catalyst **66**. Similarly, Park's ruthenium racemisation catalyst **202**^[234] was used instead of Bäckvall's racemisation catalyst **80** (Figure 67).

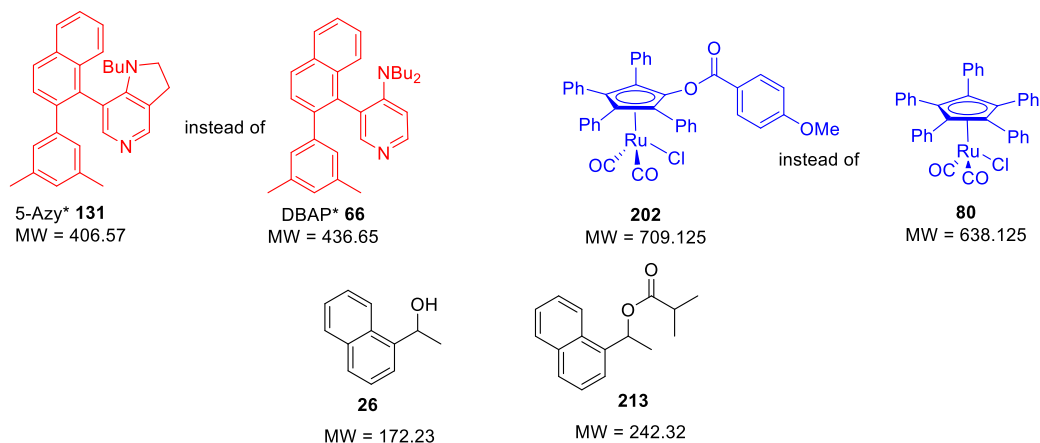


Figure 67. Catalysts and substrates used for membrane testing.

The testing of the rejection was carried out using a 'dead-end filtration' cell, shown below (Figure 68).

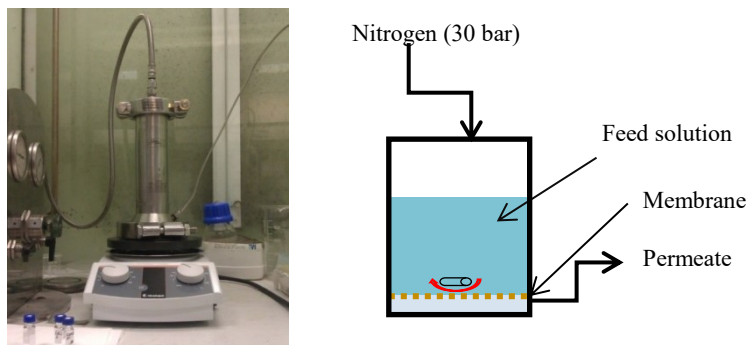


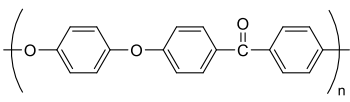
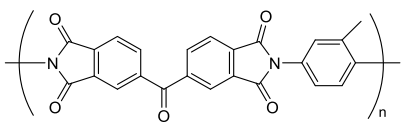
Figure 68. 'Dead-end' filtration cell and schematic.

The rejection of the substrate **26**, product **213** and 5-Azy* KR catalyst **131** were tested with both Puramem and the base-stable PEEK membrane by passing a solution of the alcohol, ester and 5-Azy* through the cell using a 30 bar pressure from a nitrogen cylinder. Once ~10 mL had been filtered, the pressure was released and samples were taken from the permeate and the retentate and compared. The rejection can be calculated using the following formula:^[335]

$$R = 1 - \frac{C_p}{C_r} \quad (6)$$

where the area for each peak (C_p = area of permeate, C_r = area of retentate) is measured by HPLC analysis. The results for each membrane are shown below (Table 30).

Table 30. Rejections of KR catalyst, alcohol and ester with PEEK and Puramem.

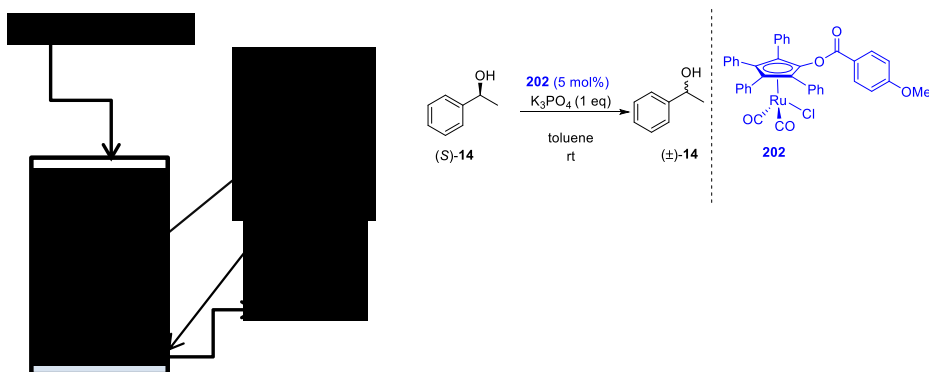
Substrate	PEEK (% Rejection)	Puramem (% Rejection)
		
5-Azy* 131	95	97
Alcohol 26	41	47
Ester 213	60	85

The KR catalyst **131** was well rejected by both membranes, while both the alcohol **26** and the ester **213** passed freely through the membrane. The molecular weight cut off (MWCO), the lowest molecular weight when 90% of the substrate is retained, is therefore ~350-400 for both membranes.

The one significant difference with the two membranes was found to be the flow rate: it took 30 minutes to filter 10 mL of toluene for Puramem, while 9 hours were required for 10 mL with PEEK.

4.4.3 Testing of Membrane in Racemisation

In order to test the rejection of the racemisation catalyst **202** and the feasibility of carrying out the racemisation in a cell, the two experiments were combined into a flow-racemisation using PEEK. The dead-end cell was filled with a suspension of Park's ruthenium catalyst **202** and potassium phosphate in toluene, and the (*S*)-1-phenylethanol ((*S*)-**14**) was added to initiate the reaction. Samples were then taken periodically to compare the rate of racemisation to the one-pot process (Figure 69).



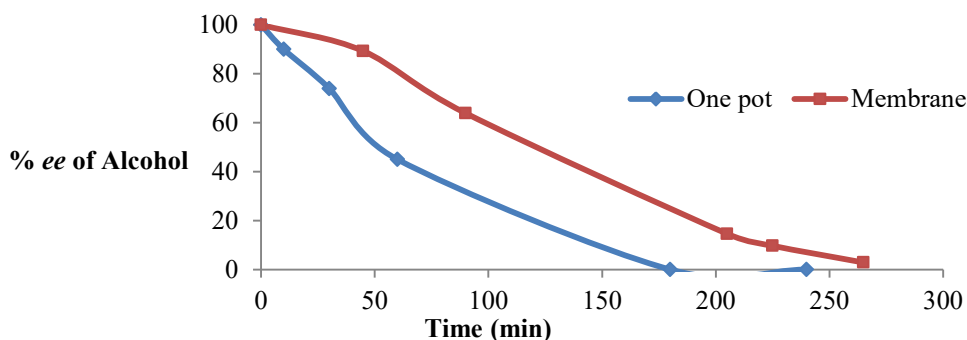


Figure 69. Set-up and racemisation of (*S*)-1-phenylethanol in a flow cell.

Pleasingly, although the rate of racemisation was slightly slower in the cell, the catalyst was still active despite being in solution for 2 hours while the reactor was set-up prior to addition of the alcohol substrate. The rejection of the catalyst was also good at $R = 95\%$. These positive results and the good rejection of both catalysts meant that the next step was to set up the MEDKR reactor.

4.4.4 Combination into MEDKR

The MEDKR was set-up as shown below, using the PEEK membrane (Figure 70).

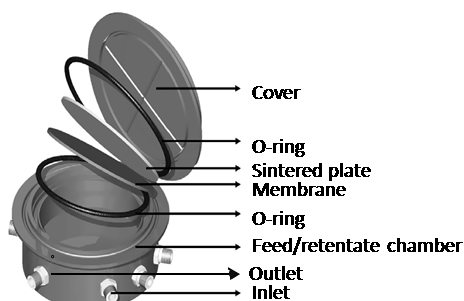
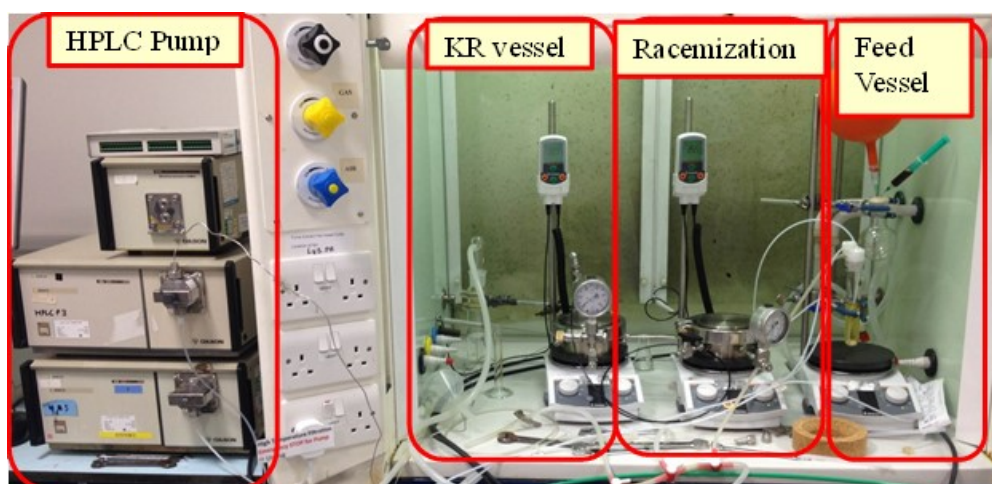


Figure 70. MEDKR rig including HPLC pump, two stainless steel reaction vessels and a feed flask.^[335]

Upside-down cells, as shown above, were used instead of the dead-end cells, as these can be heated and allow two cells to be combined one after the other. The reaction scheme is shown below, as well as initial

amounts of each material in each flask and the results obtained after running for 24 hours and separately analysing the contents of each vessel (Figure 71).

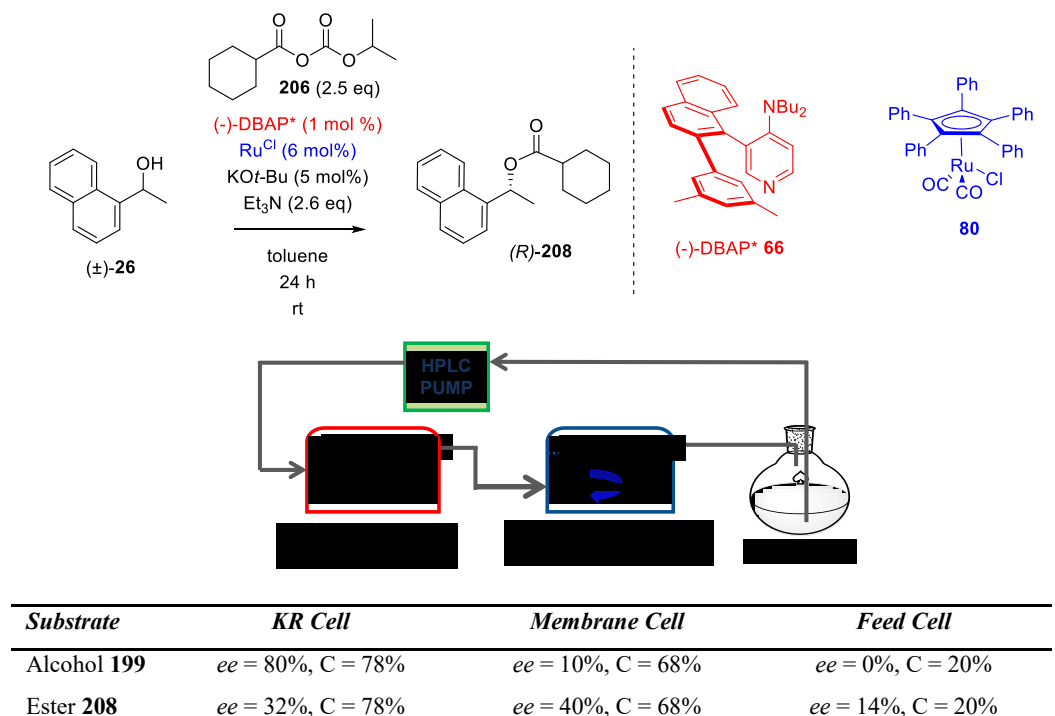
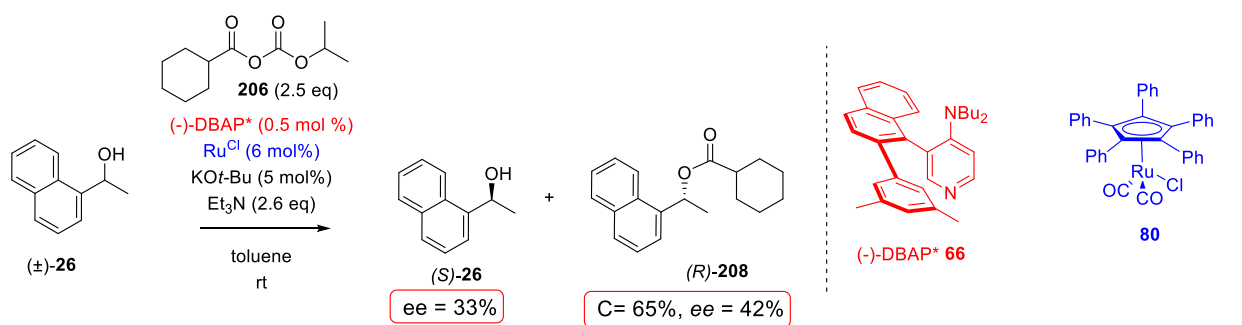


Figure 71. Scheme and schematic for a MEDKR showing results after 24 hours.

Conditions: Flow rate 0.05 ml/min; KR vessel (25 ml, 25 °C): 1 equiv. (±)-1-(1-naphthyl)ethanol, 1 mol% (-)-DBAP* **66**; Racemisation vessel (25 ml, 25 °C): 6 mol% Ru catalyst **80**, 5 mol% KOt-Bu, 2.6 equiv. Et₃N; Feed Vessel (25 ml, 25 °C): 2.5 equiv. cyclohexyl acyl carbonate **206**.

The initial results were promising: the acylation and the racemisation appeared to be working as expected as was the racemisation, as evidenced by the low *ee* of the alcohol in both the racemisation vessel and the following feed flask relative to that in the KR vessel. The low *ee* of the ester in the KR vessel is presumably due to inconsistencies with the quenching, as the reaction was only quenched 6 hours after the flow had been stopped. The low conversion in the feed flask is undoubtedly because the product is retained more than the alcohol by the membranes, which would cause a build-up of the product **208** relative to the alcohol **26** in both the KR and racemisation vessels. The overall conversion was >70%, while the majority of the ester **208** recovered had a 40% *ee*.

In a second attempt, the reaction was run for longer (48 hours *cf.* 24 hours), there was a lower KR catalyst loading (0.5 mol% *cf.* 1 mol%) and the reaction was quenched by the addition of methanol to the feed flask, which then continued pumping for a further 48 hours (Scheme 126).



Scheme 126. The outcome of a MEDKR run for 48 hours.

The set-up and initial conditions for this reaction were very similar to previously (Figure 71) with an overall reactor volume of 75 mL and a flow rate of ~0.065 mL/min for 48 hours. Problems with adjusting the flow rate were observed as the pressure was found to fluctuate, and therefore the flow rate had to occasionally be decreased or increased to keep the pressure in the first vessel ~30 bar. In order to recover as much of the product as possible and to purify the catalysts, after quenching the system was flushed with EtOAc for 24 hours to flush the product and alcohol into a collection vessel. This was successful in that >90% of the material was recovered from the collection vessel, while some small product remained in the KR and racemisation vessels. Combining the different materials gave an overall yield of 65%, while the *ee* of the product throughout each vessel was ~42% *ee*, and that of the alcohol was 33% *ee*. While this was an improved overall *ee* of the product compared to the previous attempt, it was still very low.

We hypothesised that the low *ee* may have been due to the residence times in the KR vessel. With a flow rate of 0.065 mL/min and a KR vessel volume of 25 mL, the residence time for the alcohol (assuming no rejection, when this is in fact 41%), is around 6 ½ hours. A normal one-pot KR run under these conditions (0.03 M concentration, 1.5 mol% effective catalyst loading, 2.5 equiv. of acyl donor) gives a product *ee* of 40% after this length of time (6 h) (Figure 72).

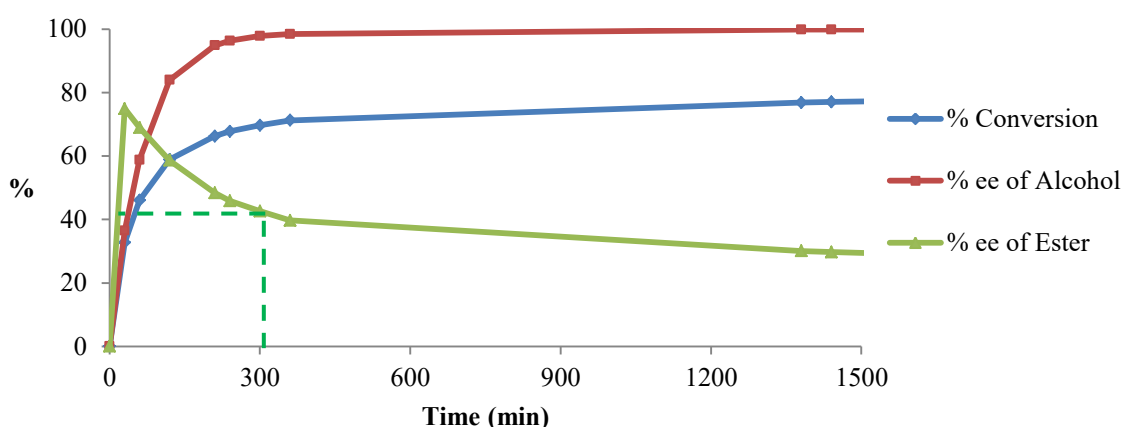


Figure 72. KR run under conditions experienced in MEDKR (0.03 M, 1.5 mol% effective catalyst concentration).

The KR reaction therefore had too much time to progress, reducing the *ee* of the recovered ester product, before the alcohol had a chance to be racemised in the next vessel. To overcome this, a number of parameter

changes were available. First, to reduce the catalyst loading to slow down the acylation reaction. Second, to reduce the volume of the KR vessel, decreasing the residence time, and third, to use a faster membrane that would allow the flow rate to be increased and therefore the residence time to be reduced. All three options were examined.

An additional challenge with the MEDKR was the relatively low conversion of 65%. It is possible to calculate how many times the alcohol would have to circulate the system in order to reach full conversion, and the number of cycles needed to achieve full conversion (ensuring >80% *ee* of the ester) is dependent on the selectivity.

For example, with a selectivity of ~11.5 (*i.e.* corresponding to a selectivity using cycloheptyl *isopropyl* acyl carbonate **201**, see Table 27), in order to keep the ester *ee* >80%, the reaction can only run to ~20-25% conversion each cycle (Figure 73).

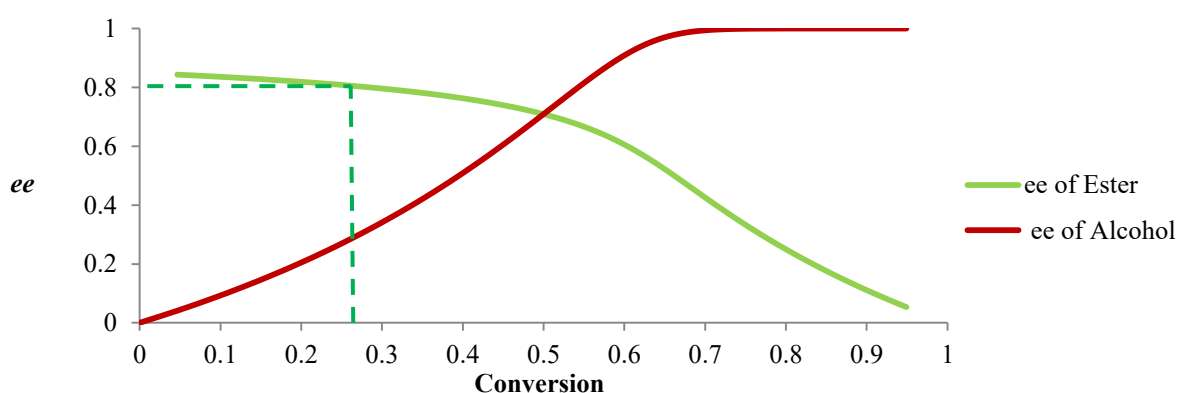


Figure 73. Copasi simulation of how the *ee* of the alcohol and ester should vary with conversion at a selectivity of 11.5.

If the reaction is only allowed to run to 25% conversion during each cycle, 17 cycles would be needed to reach 99% conversion. When the selectivity is higher, the reaction can go to higher conversions keeping the same (>80%) *ee* of the ester, and therefore fewer cycles are needed (Figure 74).

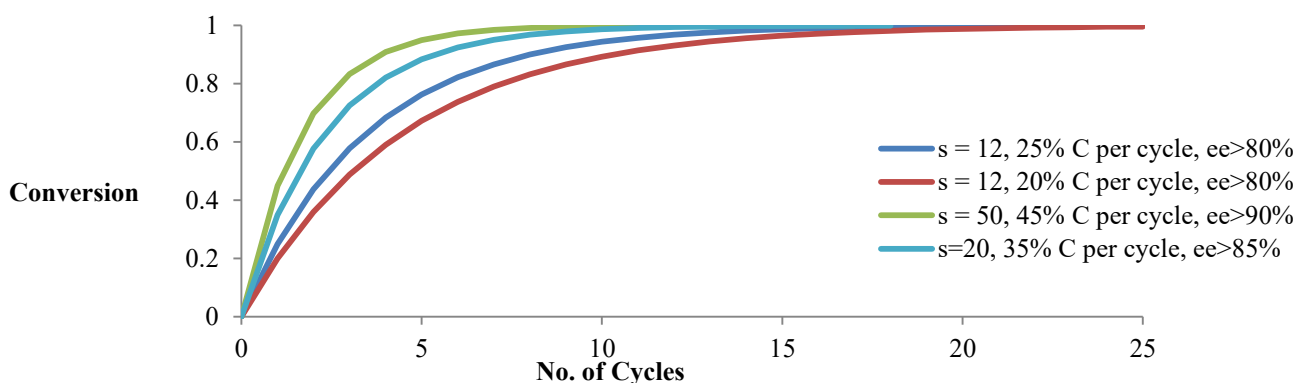
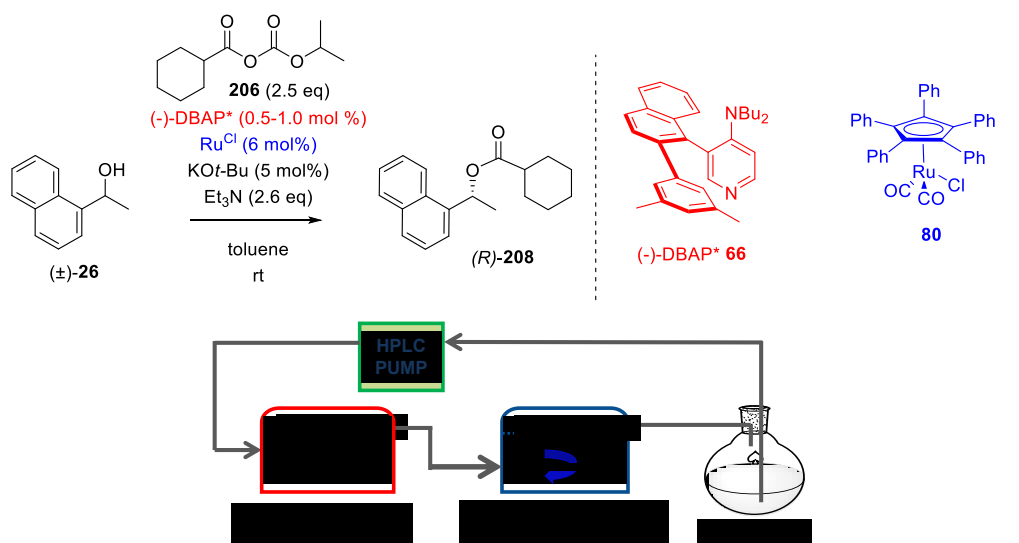


Figure 74. Copasi simulation of the number of cycles required for a MEDKR depending on the selectivity, the desired *ee* of the ester and the conversion per cycle.

When the selectivity is 50, less than 10 cycles are needed to achieve full conversion, even keeping the *ee* of the ester above 90%, while for the lower selectivity present in this system, more cycles are required. As the

MEDKR was run for 48 hours, at 0.065 mL/min this corresponds to 187.2 mL being filtered, only 2.5 cycles, and therefore would explain why the overall conversion was so low.

Two further MEDKR reactions were carried out, aiming to increase the *ee* of the ester product from 42%. In order to do this, two changes were made. First, the volume of the KR cell was reduced, in order to reduce the retention time in the KR cell and therefore reduce the extent of acylation and increase the *ee* of the ester (Run 2). Secondly the KR catalyst loading was also dropped, again to reduce the extent of acylation in the KR cell (Run 3). The results for these two experiments are shown below, compared to the previous result (Figure 75).



Run #	Conditions	% <i>ee</i> of alcohol	% <i>ee</i> of ester	% Conversion
1	25 mL KR vessel, 1.0 mol% KR cat.	33	42	65
2	5 mL KR vessel, 1.0 mol% KR cat.	8	50	44
3	5 mL KR vessel, 0.5 mol% KR cat.	3	57	20

Figure 75. Scheme, schematic and results for MEDKR runs with a duration of 7 days.

Conditions: Flow rate : 0.065 ml/min; KR vessel (25 ml, 25 °C): 1 equiv. (±)-1-(1-naphthyl)ethanol, 0.5-1 mol% (-)-DBAP* **66**; Racemisation vessel (25 ml, 25 °C): 6 mol% Ru catalyst **80**, 5 mol% KOt-Bu, 2.6 equiv. Et₃N; Feed Vessel (20 ml, 25 °C): 2.5 equiv. cyclohexyl acyl carbonate **206**.

Reducing the KR vessel size had the desired effect of increasing the *ee* of the ester (Run 2, 50% *ee* compared to 43% *ee*). The extent of conversion in the reaction was however also reduced from 65% to 44%. Reducing the catalyst loading to 0.5 mol% in the KR vessel (Run 3) also increased the *ee* of the ester to 57%, while decreasing the conversion to only 20%. The *ee* of the recovered starting material also decreased in these two runs. The lower conversion observed for both of these experiments is presumably due to the lower conversion in the KR cell per cycle, and therefore more cycles would be needed to increase the conversion (longer reaction time). Interestingly, the recovered material from Run 3 shows <15% of the cyclohexyl *i*-Pr ester by-product, which means that there was enough acyl donor in solution for the reaction to go to

completion and that self-reaction of the acyl donor did not occur as rapidly as we had been expecting. The acyl donor was instead quenched by the methanol added at the end of the reaction. Therefore, we presume that leaving the reaction for longer would have led to a higher conversion even with no added acyl donor.

One MEDKR reaction was attempted with a Puramem 280 membrane for comparison. Puramem 280 is a much faster membrane when compared with PEEK, and in the initial dead-end cell experiments the flux with Puramem was 0.33 mL/min, while with PEEK it was 0.02 mL/min. In order to determine the compatibility of Puramem with both the catalysts, a KR and a racemisation were carried out in the presence of small pieces of the membrane to determine interaction between the membrane and the catalysts. No change in reaction or activity for either catalyst was detected (Figure 76).

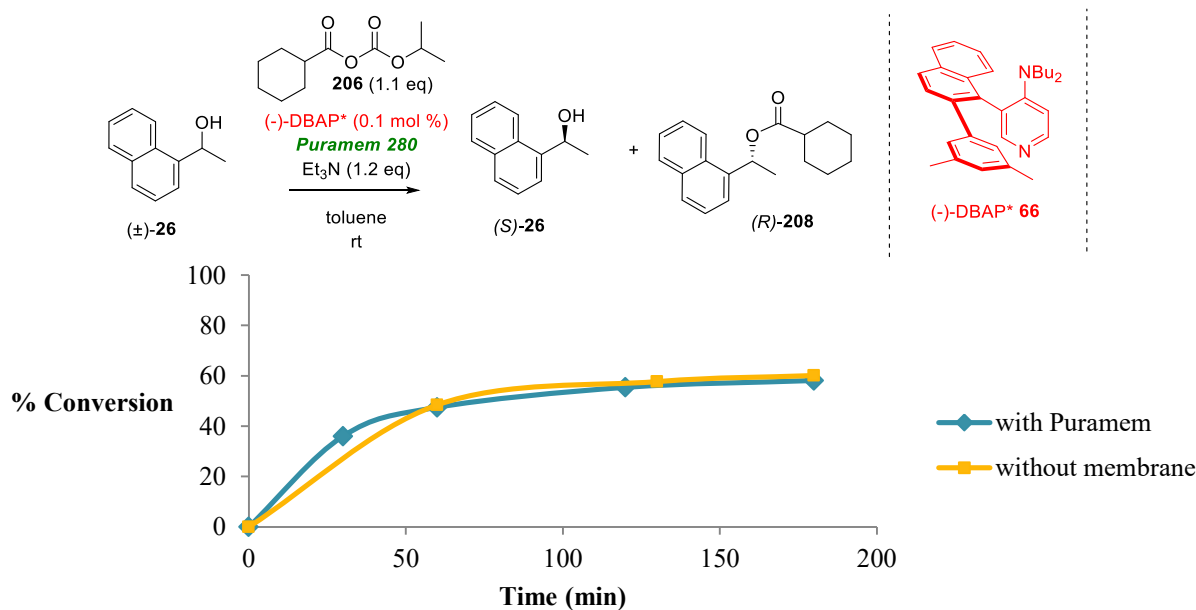


Figure 76. Comparison of % conversion in a KR with and without contact with a Puramem membrane.

A MEDKR reaction using the Puramem membrane was therefore set-up and it was found that the flow rate could be increased to 1.5 mL/minute, which is almost 23 $\times$ faster than with PEEK. Due to the base-sensitivity of Puramem, triethylamine was not used in this reaction, while the KR vessel volume was increased to 25 mL to allow direct comparison with initial PEEK experiments (Figure 77).

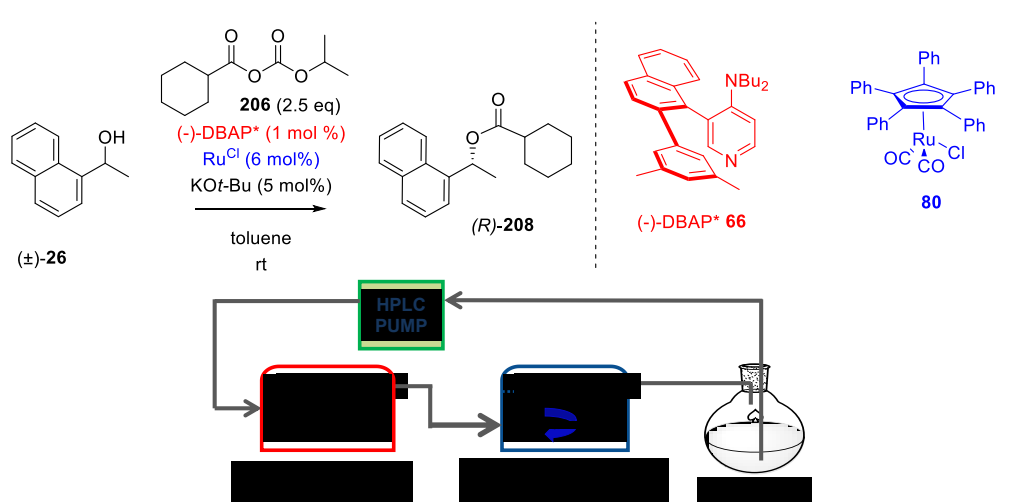


Figure 77. Set-up and reaction with Puramem 280 membrane.

Conditions: Flow rate : 1.2-1.5 ml/min; KR vessel (25 ml, 25 °C): 1 equiv. (±)-1-(1-naphthyl)ethanol, 1 mol% (-)-DBAP* **66**; Racemisation vessel (25 ml, 25 °C): 6 mol% Ru catalyst **80**, 5 mol% KOt-Bu; Feed Vessel (20 ml, 25 °C): 2.5 equiv. cyclohexyl acyl carbonate **206**.

The acyl donor was added in batches throughout the reaction (72 h), and we were pleased to see an increase in the *ee* of the product to ~72% in the initial samples from the reaction, and an apparent conversion of 9.5% after 48 hours from the racemisation cell, which when taking into account the differing rejections of the alcohol and ester is >50% C (Figure 78).

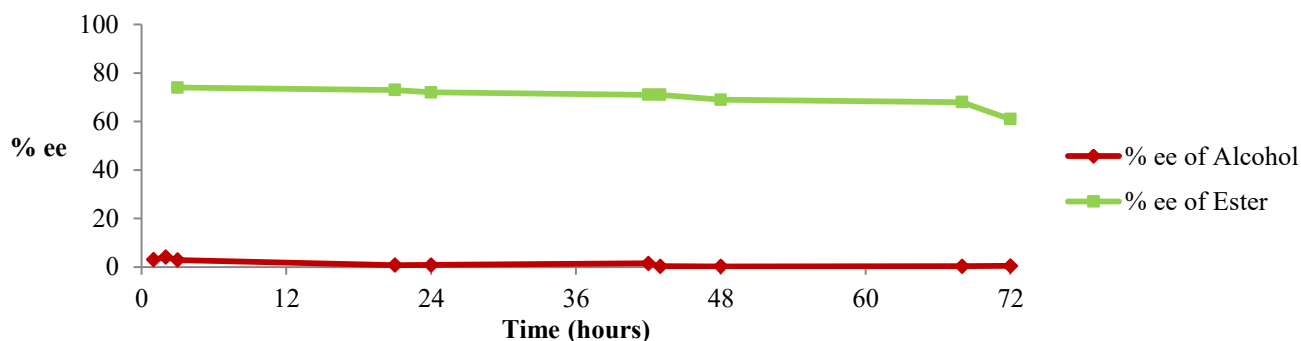


Figure 78. % ee of alcohol and ester during MEDKR reaction.

After 72 hours the cells were flushed for two hours with pure toluene and then with MeOH and toluene to quench the reaction and recover the product and alcohol. ¹H NMR analysis showed a conversion of 62% after 72 hours, with an *ee* of 56%. While the conversion was much higher (62% vs 20%), the overall *ee* was similar to previously (56% *cf.* 57%) at the end of the reaction. As all samples up to 68 hours had shown *ees* in excess of 65%, the low *ee* might be due to a late stage addition of the acyl donor, which caused a higher conversion than expected in the last 4 hours of the reaction. Due to the relatively high rejection of the alcohol, the concentration in the cell was also increased, increasing the rate of reaction. The *ee* of the recovered alcohol was also 56%, which would explain the lowered *ee* of the product. This value also shows

that, even with the increased flow rate, the high rejection of the alcohol still gives extended retention times in the KR vessel, allowing the alcohol *ee* to increase.

Upon an attempted repeat of this reaction however, problems with the membrane were experienced, with degradation of the membrane – possibly due to any residual KO*t*-Bu in the system. For this reason the ruthenium catalyst was not very well retained on the membrane (high MW catalyst should be completely retained), causing problems with purification and potentially interfering with the DBAP* catalyst **66**. The *ee* of the ester recovered from this reaction was also low (<40%). Due to these stability problems, we decided to revisit the PEEK membranes for the MEDKR and attempt further optimisation of this system.

4.4.5 DKR in THF

As we were hoping to keep on using the PEEK membranes due to their increased stability, we needed to increase the flow rate with this membrane. THF is the fastest solvent for this membrane, ~2x faster than toluene. Testing the flux of the membrane with a 1:1 mixture of THF/toluene found that the flux was in fact the same in this mixture as with pure toluene, while an 8:2 mixture gave a similar flux to THF. These solvent systems were also used in the KR to test the effect on the selectivity (Table 31).

Table 31. Comparative flux and selectivity with THF/toluene solvent mixtures in KR of 1-(1-naphthyl)ethanol.

Entry	Solvent	Selectivity	Maximum <i>ee</i> of Ester	Flux ($L M^{-2} h^{-1} bar^{-1}$)
1	Toluene	11	83	0.07
2	THF	7.1	75	0.20±0.02
3	THF:toluene 1:1	7.5	77	0.07
4	THF:toluene 8:2	7.1	75	0.18

With THF, the selectivity was $s = 7.1$, while in an 8:2 THF/toluene mixture the selectivity was also $s = 7.1$, with a maximum product *ee* of 75%. As the maximum *ee* reached in a toluene MEDKR was only 57% with the PEEK membrane, even this decrease in the theoretical maximum would be an improvement assuming we could approach this figure.

The rate of racemisation of (*S*)-1-phenylethanol in these solvents was also evaluated, and although toluene was much faster, the THF/toluene mixture of 8:2 gave better results than pure THF (Figure 79).

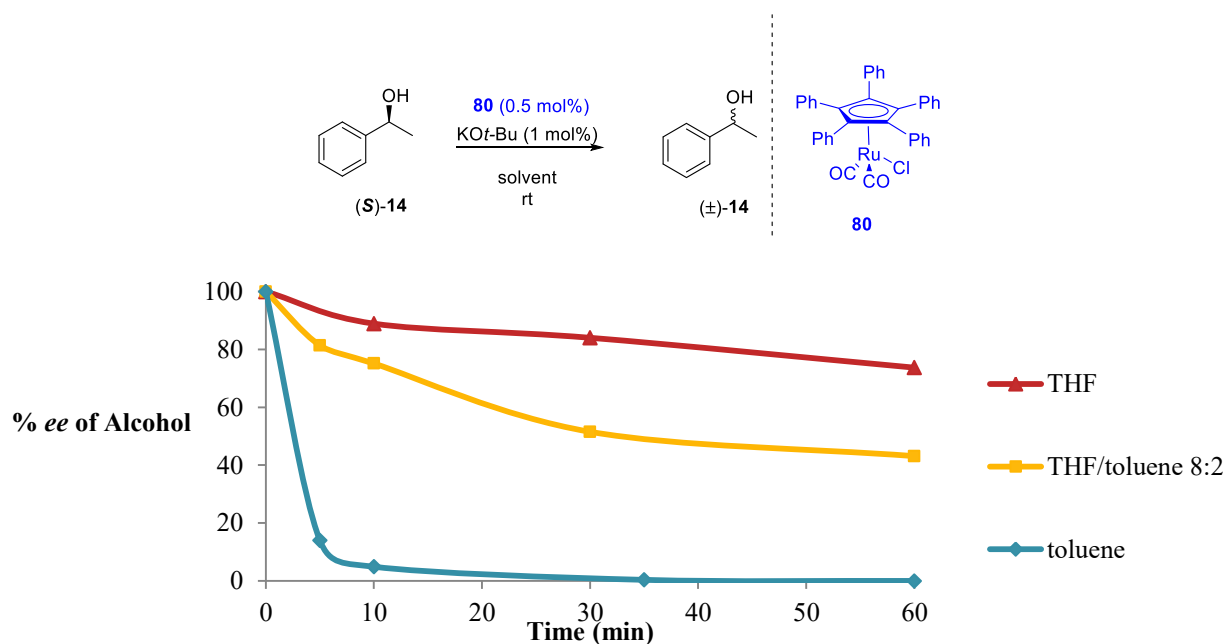


Figure 79. Comparison of racemisation of (S)-1-phenylethanol with Ru catalyst **80** in different solvents.

The MEDKR was therefore attempted with the PEEK membrane and a THF/toluene 8:2 solvent system, using the original 25 mL vessel size for both reaction vessels (Figure 80).

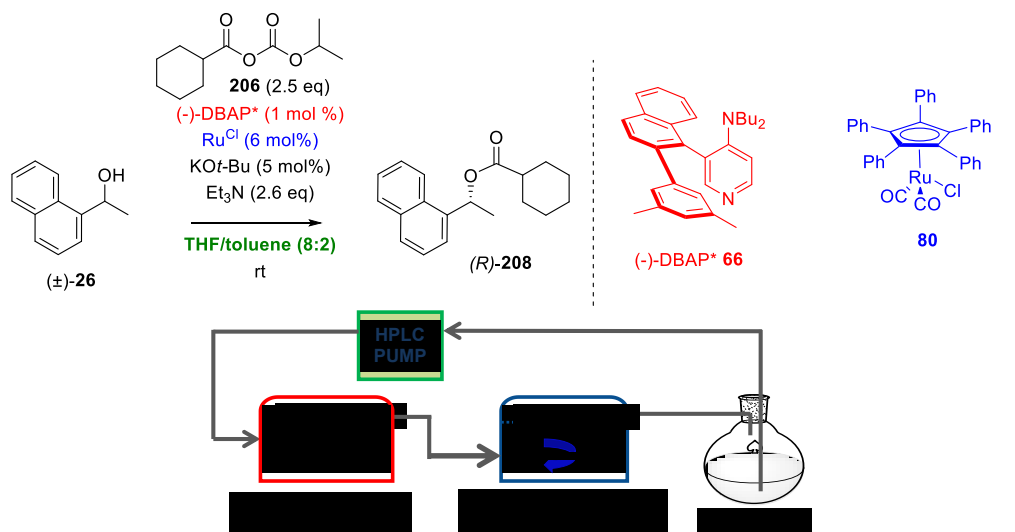


Figure 80. MEDKR with THF/toluene solvent mixture

Conditions: Flow rate: 0.07 ml/min¹; KR vessel (25 ml, 25 °C): 1 equiv. (±)-1-(1-naphthyl)ethanol, 1 mol% (-)-DBAP* **66**; Racemisation vessel (25 ml, 25 °C): 6 mol% Ru catalyst **80**, 5 mol% KOt-Bu; Feed Vessel (20 ml, 25 °C): 2.5 equiv. cyclohexyl acyl carbonate **206**.

We were delighted to see an initial product *ee* of ~71%, and also a higher conversion than previously observed. The acyl donor was added in batches to reduce decarboxylation and side reactions. While the

¹ Different HPLC pump to original process, possible problem with flow rate calibration means similar value was seen for flow rate with both solvent systems.

conversion increased as expected, the racemisation catalyst appeared to be decomposing, as the *ee* of the starting material was gradually increasing and the *ee* of the product was therefore decreasing (Figure 81).

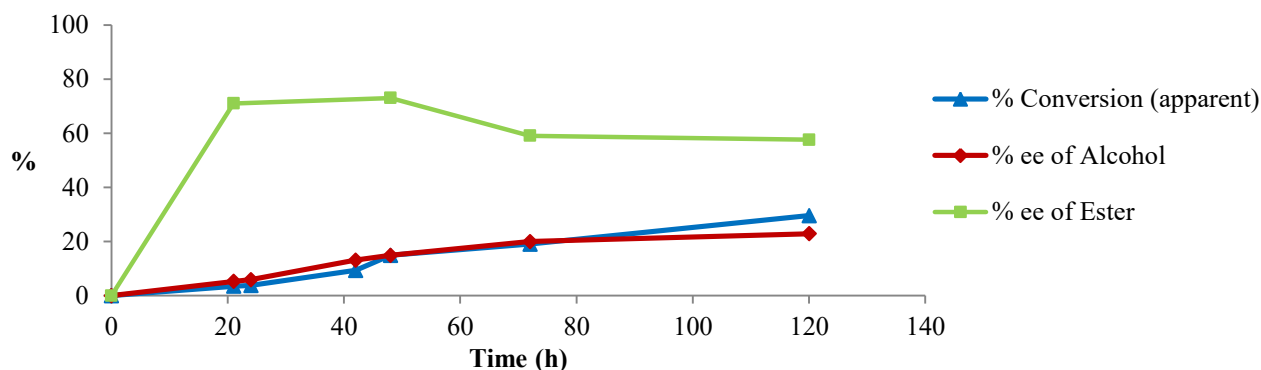


Figure 81. Change in *ee* of alcohol and ester as MEDKR progresses.

It was therefore decided to stop the reaction after 5 days, compromising on the yield in order to obtain higher *ee* material. The final values obtained were 61% conversion with a 58% *ee*. Flushing the system with THF to recover the product led to 39% product recovery of the maximum 61%, with a further 4% recovered from the racemisation cell, bringing total product recovery to 43%. These results confirmed the prediction that increasing the flow rate could also increase the *ee* of the ester, even with the reduced selectivities observed in the THF/toluene solvent mixture.

A final attempt at the MEDKR aimed to change the relative reaction temperatures for both vessels; to lower the temperature in the KR vessel and therefore increase the maximum theoretical *ee*, and to increase the temperature and the rate of racemisation in the racemisation vessel. To this end, the KR vessel was cooled using a cryostat to $\sim 7^{\circ}\text{C}$, while the racemisation vessel was heated to 35°C . An initial sample after 20 hours showed a $\sim 76\%$ *ee* of the product, the best value yet. However, it soon became clear that the change in temperature was also adversely affecting the membranes: the permeate from the racemisation cell took on a very pale yellow colour and the racemisation catalyst could be seen by HPLC in the permeate. Increased temperature is known to increase the permeability of PEEK, and therefore at 35°C more of the racemisation catalyst was allowed through. This in turn could then poison the KR catalyst, and after 7 days only traces of the product were found in the reaction. The increased temperature could also have been promoting a racemic background reaction, as the initially high *ee* of the product quickly dropped to $<50\%$ *ee*, although this was hard to determine due to the racemisation catalyst impurity in the HPLC spectrum. Nevertheless, even though the increased temperature had a negative effect on the reaction, the lower temperature in the KR cell proved to be beneficial, with the highest initial *ee* in the MEDKR observed in this run.

4.4.6 Conclusions and Future Work

During this work we have successfully shown that membrane-enhanced catalyst separation can be developed for the synthesis of enantioenriched *sec*-alcohols *via* an acylative DKR process.

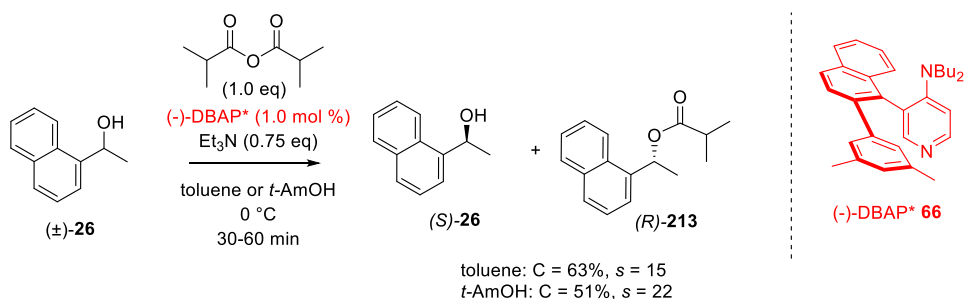
We found that both the KR and the racemisation reactions are compatible with the membranes and membrane reactors, and that the rejection of the catalysts (**66** and **80**) by the membranes is efficient at room temperature. During our studies we realised that although the two-cell system can overcome catalyst incompatibility, the relative rates of reaction are still important. Although the relative catalyst loadings and cell residence times could be changed, the low flux of the membranes was the limiting factor, as this meant the system could not be efficiently tuned to the requirements. The low flux also increased the residence time in the KR cell, and even with low catalyst loadings, the *ee* of the product was lower than the maximum expected. It was found that by changing the solvent mixture from toluene to THF/toluene, the flux could be increased. While this helped to improve the *ee* of the ester by reducing the residence time in the KR cell, the racemisation catalyst was less efficient in this solvent system and therefore the *ee* of the alcohol increased over time, reducing the *ee* of the ester product.

Attempting to vary the temperatures of the two cells was unsuccessful, as although the initial *ee* of the ester formed was higher due to the low KR cell temperature, the higher temperature in the racemisation cell reduced the rejection of the membrane, and the racemisation catalyst could pass through to poison the KR catalyst.

In further studies, work should focus on keeping the temperature in the KR cell low (<0 °C), thus ensuring a high *ee* of the product (near the theoretical maximum), while the properties of PEEK at this temperature could also be evaluated. In order to ensure efficient racemisation of the alcohol, a number of options are available, including increasing the loading of the racemisation catalyst from 5 mol%, using a tighter membrane (MWCO<300) with a higher temperature tolerance (good MWCO at 35 °C or higher), or finally using a larger cell (>25 ml) for the racemisation to ensure efficient racemisation of the alcohol. Further in the future, alternate KR catalysts should be explored to increase the *ee* of the recovered product. After testing of these catalysts for rejection and membrane compatibility, the potential advantages of using more selective catalysts are evident, as the maximum theoretical *ee* of the recovered product would be higher than currently, and the KR reaction more tolerant of slow racemisation processes than the current system.

4.5 Alcohol KR Improvements

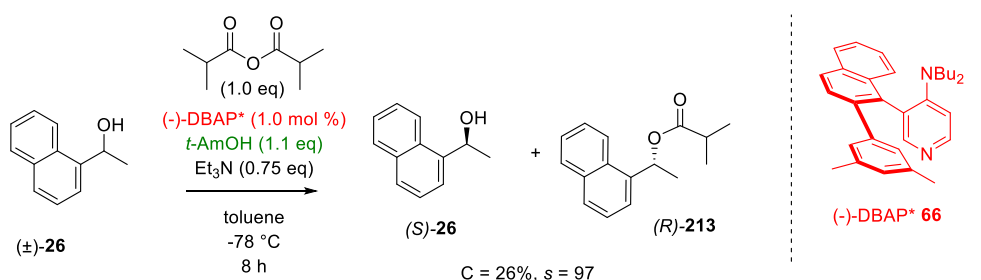
In parallel with the aforementioned studies on one-pot and membrane enhanced DKR reactions, we became interested in optimising *sec*-alcohol KR reactions using the DBAP* catalyst **66**. Our discovery that the addition of 1-10 equivalents of a *tert*-alcohol into a KR increased the selectivity at room temperature, encouraged us to explore whether this result was mirrored at low temperature. As indicated previously, although *tert*-amyl alcohol has been used to increase selectivity both as the main solvent and as a co-solvent in alcohol KRs previously, it has never been used as an ‘additive’.^[150,333] We previously noted the strong temperature dependence of the selectivity with DBAP* catalyst **66** in toluene ($s = 64$ vs $s = 9$ at -78 °C and rt respectively, see Table 27), and now planned to determine if that situation was mirrored in *t*-AmOH (Scheme 127).



Scheme 127. Selectivity in KR of 1-(1-naphthyl)ethanol at 0 °C in toluene and *t*-AmOH.

Although the selectivity of the KR at 0 °C in *t*-AmOH was improved relative to both the room temperature and 0 °C procedure in toluene ($s = 22$ vs. $s = 9$ and 15 respectively), it was still not as selective as in toluene at -78 °C ($s = 64$, see Table 27). It should be noted however that the KR is relatively fast at this temperature in *t*-AmOH, as after 1 hour a maximum of 35% of the alcohol (70% of maximum recovery) could be recovered at 99% *ee*.

Nevertheless, as *t*-AmOH freezes at -9 °C, the temperature cannot be lowered much more to increase the selectivity when *t*-AmOH is used as the solvent, and even as a co-solvent the temperature range is limited. In fact, even five equivalents of *t*-AmOH (the optimal number of additive equivalents at room temperature) proved to freeze an alcohol/toluene solution at -78 °C. A reduction to 1.1 equivalents of *t*-AmOH in toluene however stayed liquid at -78 °C, and therefore a KR was attempted using these conditions (Scheme 128).

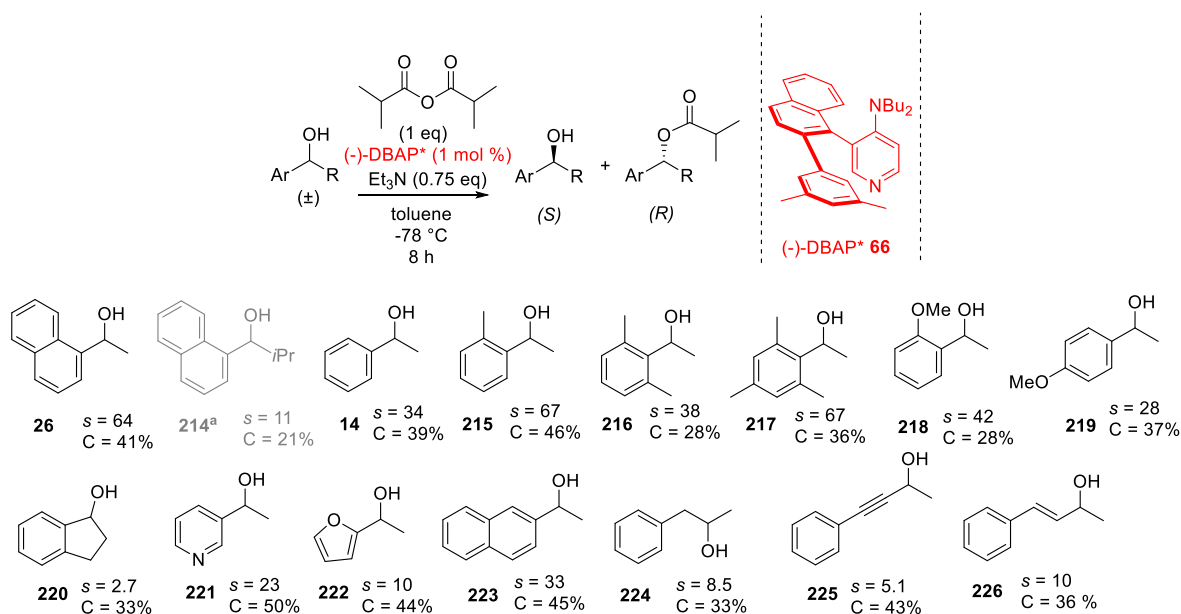


Scheme 128. KR of 1-(1-naphthyl)ethanol at -78 °C with 1.1 equiv. of *t*-AmOH as an additive.

We were delighted to see an increase in selectivity from $s = 64$ ($C = 42\%$) without the *t*-AmOH to $s = 97$ ($C = 26\%$) with the additive. Further testing to determine the optimal acyl donor found that both dicyclohexane carboxylic anhydride **207** and dicycloheptane carboxylic anhydride gave lower selectivity factors at -78 °C (56 and 51 respectively) and much lower conversions (<10% after 8 h). *iso*Butyric anhydride was therefore kept as the acyl donor of choice, and 1.1 equivalents of *t*-AmOH as the preferred additive (2 equivalents reduced the conversion to <10%), in order to see whether this effect could be mirrored for both for previously run and new substrates.

4.5.1 Further Substrates

First, a number of new substrates were tested in the original KR conditions in toluene to further determine the scope of this catalyst for the KR of alcohols (Figure 82).



^aAs carried out by Kerti Ausmees^[297]

Figure 82. Substrate scope for KR using DBAP* catalyst **66**.

Five 1-aryl-1-ethanols were examined: *ortho* substituents were found to increase selectivity, with 2-methylphenylethanol **215** providing a selectivity of $s = 67$ (Fu^[333] and Vedejs^[91] also found this to be a good

substrate for KR with their catalysts), and 2-methoxyphenylethanol **218** providing a higher selectivity than its 4-methoxy analogue ($s = 42$ vs. $s = 28$). 3-Pyridyl and 2-furyl congeners **221** and **222** were well tolerated giving $s = 23$ and $s = 10$ respectively, and acceptable selectivities were achieved both for non-aryl-containing substrate **224** and cinnamyl alcohol **226**, while propargylic alcohol **225** gave a selectivity of only 5.1, showing the limitations of this catalyst for different substrate classes.

4.5.2 KR with *tert*-Amyl Alcohol

The selectivity for a number of these substrates was then determined using 1.1 equivalents of *tert*-amyl alcohol as an additive (Table 32).

Table 32. KR of alcohols by isobutyrylation catalysed by DBAP* **66** with *t*-AmOH additive.

Entry	Substrate	C (C original) (%)	s (s original)
1	199	26(41)	97 (64)
2	214	20(21)	13 (11)
3	215	46(46)	112(67)
4	216	42(28)	87 (38)
5	217	36(36)	123(67)
6	218	33(28)	55 (42)
7	219	30(37)	47 (28)
8	221	47 (50)	27(23)
9	226	42(36)	15(10)

We were delighted to see that the increase in selectivity was mirrored for other substrates, although the % increase was not always consistent. The greatest increase was for compound **216** (entry 4) with a 130% increase in the selectivity observed upon the addition of the *tert*-amyl alcohol additive. We hypothesise that this increase in selectivity is due to the solvent effect of the *tert*-amyl alcohol: it is anticipated that the charged acyl pyridinium salt will attract the alcohol to form a solvent cage around it and that despite the low amount of the additive it is still in large excess compared to the catalyst loading. This might also explain why the increase in selectivity is lower with compound **218** than **215** (30% vs 74%), as the solvent cage and hydrogen bonding would be disrupted by the methoxy group in **218**. The change in conversion with the

additive in these reactions was not consistent, with decreases in conversion observed for **26** and **219**, increases in conversion for **216** and **218**, and no change observed for **214** and **215**.

4.5.3 Conclusions

To summarise, optimised conditions have been delineated for the acylative KR of *sec*-alcohols using DBAP* catalyst **66** and under these conditions this catalyst conveys some of the best selectivity factors found for 4-DMAP-based chiral catalysts. While the process is efficient at -78 °C in toluene, *t*-AmOH provides greater selectivity at room temperature than toluene. However, as *t*-AmOH freezes at -9 °C, this precludes its use as a solvent at low temperature. Using *t*-AmOH as an additive instead at -78 °C still conveys the same advantages as when used as a solvent, and increases the levels of selectivity in our KR reactions sometimes more than two-fold. Furthermore, the development of the synthesis, in particular the classical resolution, increase the practicality of this catalyst.

5 Conclusions and Future Work

The four main primary objectives of this work were to firstly develop an amine KR, secondly to develop a room temperature alcohol KR, and thirdly to combine this with a racemisation catalyst for both a one-pot and a membrane-enhanced DKR.

The two lead catalysts essential for the objectives above (DBAP* **66** and 5-Azy* catalyst **131**) were both successfully synthesised during these studies and the many of the steps optimised on a large scale. In addition, our collaborators at Eli Lilly developed a method for the classical resolution of DBAP* **66**, thus removing the requirement for tedious HPLC separation into enantiomers. Further work is required to optimise the last two steps of the DBAP* **66** synthesis, while a classical resolution method for 5-Azy* catalyst **131** would be desirable.

Results obtained as part of this work towards amine KR highlight the difficulties and challenges associated with developing this process. Future work to develop this area with the Spivey catalysts should focus on secondary amine substrates, which display reduced reactivity compared to primary amines.

Our aim to develop a one-pot *sec*-alcohol acylative DKR procedure with DBAP* **66** and Ru catalyst **80** proved to be challenging. While a room temperature KR procedure was successfully developed with a racemisation-compatible acyl donor, the selectivity values were modest (*s*~11). Combination of this procedure into a DKR highlighted a further number of challenges, such as the formation of *i*-PrOH from the counter-ion from the acyl donor *via* decarboxylation, and coordination of DBAP* **66** to Ru catalyst **80**, deactivating both the DBAP* **66** and the Ru catalyst **80** in the process. Nevertheless, a batchwise addition procedure was developed providing a maximum *ee* of 81.5% of the ester with 83% conversion. Further work to optimise the rate of addition of the acyl donor and catalyst should result in a procedure which can then be applied to other alcohol substrates.

A membrane-enhanced DKR was successfully developed during this work for the synthesis of enantioenriched *sec*-alcohols *via* an acylative DKR process. Unmodified non-enzymatic acylation catalyst DBAP* **66** and commercial Ru catalyst **80** were well retained by the membrane ($\geq 95\%$ rejection), and a two-cell flow system was designed to separate the two catalytic systems. While the low flux of the PEEK membranes used was our limiting factor, by optimising the solvent system a faster flux could be achieved and initially good (near to maximum theoretical) *ee* of the product obtained. Further studies should continue to focus on temperature changes in the two cells within the MEDKR, to optimise selectivity in the KR and

rate of racemisation, while still working within the membrane property parameters. Alternate KR catalysts could also be evaluated for this process to increase the selectivity.

Finally as part of this work, the use of stoichiometric quantities of *tert*-alcohols as KR additives has been developed, increasing the selectivity in *sec*-benzylic alcohol KR at -78 °C, by up to 130% on occasion. Further work should determine whether this effect can be applied to other KR catalysts other than DBAP* catalyst **66**.

6 Experimental Procedures

General Directions: All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in oven-dried glassware unless otherwise stated. Solvents were dried using a Grubbs Pure-Solv 400 solvent purification system. The moisture content of the solvents was monitored by Karl Fischer coulometric titration (Mettler-Toledo DL39). “*Degassing*” was carried out by either repeated freeze-thawing until evolution of dissolved gasses ceased, or *via* bubbling of nitrogen or argon through the solvent for 30 minutes prior to reaction. Reagents were used as obtained from commercial sources or purified according to known procedures. Yields refer to chromatographically homogenous materials, unless otherwise indicated.

Chromatography: Flash chromatography (FC) was always performed on silica gel (Merck Kieselgel 60 F₂₅₄ 230-400 mesh) according to the method of W.C. Still.^[336] Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄) which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 and 366 nm), by charring with 10% KMnO₄ in 1M H₂SO₄ or by charring in phosphomolybdic acid in ethanol.

Melting points: These were determined on a Kofler hot stage.

Infra-red spectra: These were recorded as thin films on a Perkin-Elmer Paragon 1000 Fourier transform spectrometer. Only selected absorbances (ν_{max}) are reported.

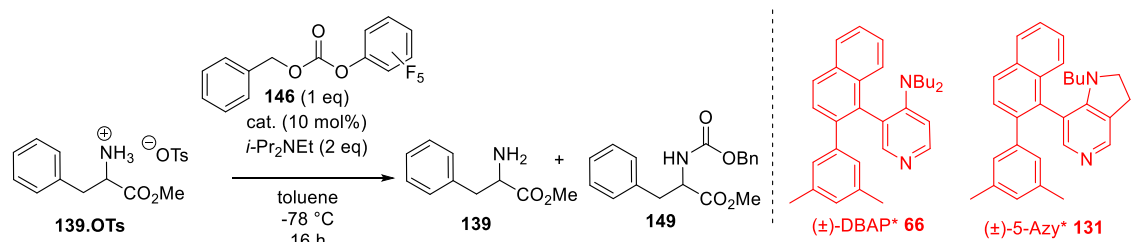
¹H NMR spectra: These were recorded at 400 MHz on Bruker AMX-400 instruments respectively. Chemical shifts (δ_{H}) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak.

¹³C NMR spectra: These were recorded at 100 or 125 MHz on Bruker AMX-500 MHz instrument. Chemical shifts (δ_{C}) are quoted in ppm, referenced to the appropriate residual solvent peak. Degenerate peaks are suffixed by the number of carbons.

Mass spectra: Low resolution mass spectra (m/z) were recorded on either a VG platform II or VG AutoSpec spectrometers, or on Agilent LCMS spectrometers, with only molecular ions (M^+ , $M+H^+$, $M+NH_4^+$) and major peaks being reported with intensities quoted as percentages of the base peak. High Resolution Mass Spectrometry (HRMS) measurements are valid to ± 5 ppm.

Absolute configurations: Absolute configurations of both DBAP* **66** and 5-Azy* **131** catalysts have yet to be established.

Representative procedure for test reactions with (±)-phenylalanine methyl ester tosylate salt **139.OTs (Table 15)**

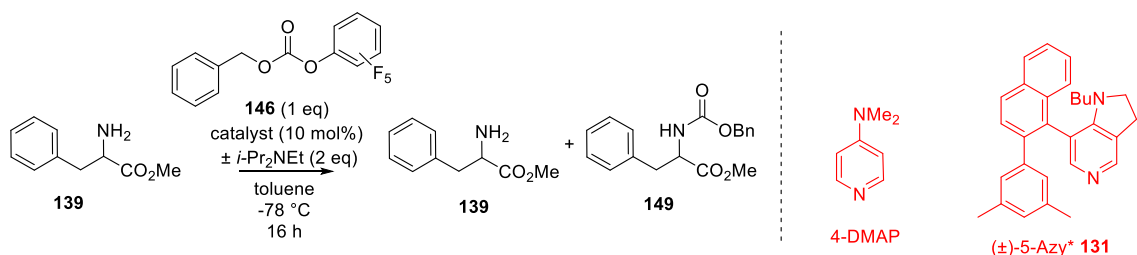


A suspension of (±)-phenylalanine methyl ester tosylate salt (24.5 mg, 0.07 mmol) and carbonate **146** (22.2 mg, 0.07 mmol) in toluene (110 µL) was cooled to -78 °C. Hünig's base (24 µL, 0.14 mmol) and a catalyst solution (0.007 mmol in 30 µL of toluene) were added dropwise. The reaction was stirred for 16 h, before quenching with propylamine (80 µL, 0.9 mmol) and stirring for a further 1 h. The reaction was allowed to warm to rt, diluted with CH₂Cl₂, washed with water, dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude mixture of products was analysed by ¹H NMR spectroscopy (400 MHz, CDCl₃):

- Phenylalanine methyl ester: δ_H = 7.37 – 7.15 (5H), 3.76 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.74 (s, 3H), 3.12 (dd, *J* = 13.5, 5.2 Hz, 1H), **2.89 (dd, *J* = 13.5, 7.9 Hz, 1H)**
- N-Cbz-phenylalanine methyl ester: δ_H 7.40 – 7.22 (8H), **7.11 (dd, *J* = 7.8, 1.7 Hz, 2H)**, 5.11 (s, 2H), 4.68 (m, 1H), 3.73 (s, 3H), 3.13 (qd, *J* = 13.9, 5.9 Hz, 2H).
- 4-DMAP: δ_H 8.23 (d, *J* = 6.0 Hz, 2H), 6.54 (d, *J* = 6.0 Hz, 2H), 3.05 (s, 6H).
- Quench product (propyl carbamic acid benzyl ester): δ_H 7.44 – 7.24 (5H), 5.11 (s, 2H), 3.17 (dt, *J* = 12.6, 6.1 Hz, 2H), 1.53 (h, *J* = 7.4 Hz, 2H), **0.93 (t, *J* = 7.4 Hz, 3H)**.

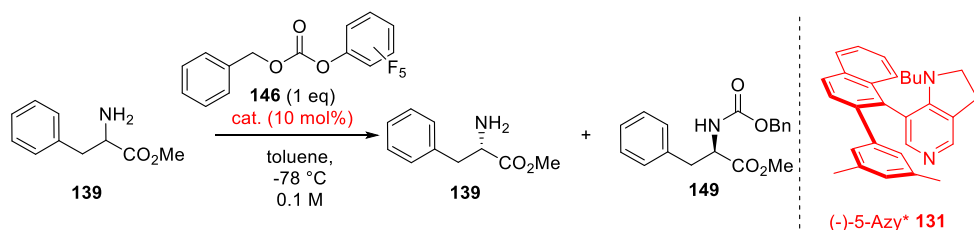
Characteristic Peaks are marked in red and were used to calculate conversion.

Representative procedure for test reactions with (±)-phenylalanine methyl ester (Tables 16 – 22, 25)



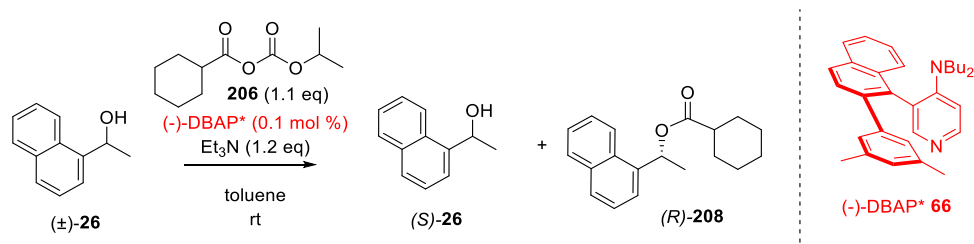
A solution of (±)-phenylalanine methyl ester (45 mg, 0.25 mmol), catalyst (0.025 mmol) and Hünig's base if used (0.09 mL, 0.5 mmol) in toluene (0.3 mL) was cooled to -78 °C. A solution of carbonate **146** (80 mg in 0.2 mL of toluene) was added dropwise. The reaction was stirred for 16 h, before quenching with propylamine (0.22 mL, 2.5 mmol) and stirring for a further 1 h. The reaction was allowed to warm to rt, diluted with CH₂Cl₂, washed with water, dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude mixture of products was analysed by ¹H NMR spectroscopy as above.

Representative Procedure for KR with (±)-phenylalanine methyl ester (Tables 19, 23-26)



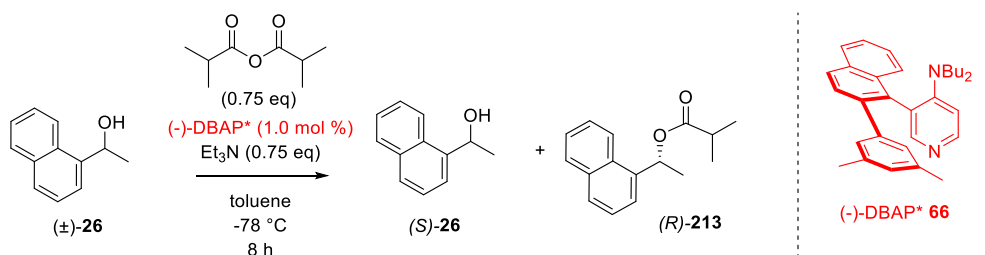
A solution of (±)-phenylalanine methyl ester (16.5 mg, 0.09 mmol) and catalyst **131** (3.7 mg, 0.009 mmol) in toluene (0.52 mL) was cooled to -78 °C and allowed to stir for ten minutes. A solution of carbonate **146** (29.2 mg, 0.09 mmol, in 0.2 mL of toluene) was added dropwise. The reaction was stirred for 1, 4 or 24 h, before quenching with propylamine (60 µL, 0.72 mmol) and stirring for a further 1 h. The reaction was allowed to warm to rt, diluted with CH₂Cl₂, washed with water, dried over Na₂SO₄ and the solvent removed *in vacuo*. The residue was diluted into EtOAc (0.5 ml) and analysed by chiral HPLC to determine conversion and selectivity. **HPLC conditions:** IC column (46 x 250 mm), 20 °C, flow: 1 mL/min, eluent: hexane:*i*-PrOH (90:10), detection: 254 nm. Phenylalanine methyl ester: 16.9 and 20.5 minutes. *N*-Cbz phenylalanine methyl ester: 19.2 and 27.3 minutes.

Representative procedure for room temperature alcohol KR (Tables 27-39; Figures 35-36, 46, 58, 76)



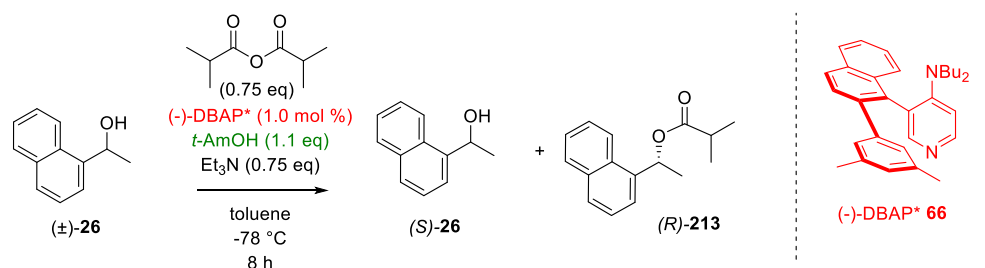
To a solution of (±)-1-(1-naphthyl)ethanol **26** (86 mg, 0.5 mmol) in toluene (0.9 mL) was added (-)-DBAP* (0.22 mg, 0.0005 mmol, 0.1 mol%, 0.1 mL of a 2.2 mg/mL solution) and Et₃N (84 µL, 0.6 mmol, 1.2 eq). The solution was stirred at room temperature and the acyl donor (cyclohexyl isopropyl carbonate **206** (112 µL, 0.55 mmol, 1.1 eq) was added dropwise. Aliquots of 0.05 mL were periodically taken, diluted and quenched with 0.5 mL MeOH and analysed directly by chiral HPLC to determine conversion and selectivity. **HPLC conditions:** OD-H column (46 x 250 mm), 20 °C, flow: 1 mL/min, eluent: graduated method using hexane:*i*-PrOH, detection: 280 nm. 0-8 minutes: 1% *i*-PrOH, 8-11 minutes: 1→10% *i*-PrOH, 11-28 minutes: 10% *i*-PrOH, 28-30 minutes 10-1% *i*-PrOH, 30-35 minute 1% *i*-PrOH. Cyclohexane acetate: 7.5 min (*R*) and 9.8 minutes (*S*), 1-(1-naphthyl)ethanol: 21.0 min (*S*) and 24.9 (*R*).

Representative procedure for low temperature alcohol KR (Table 27, Figure 82)



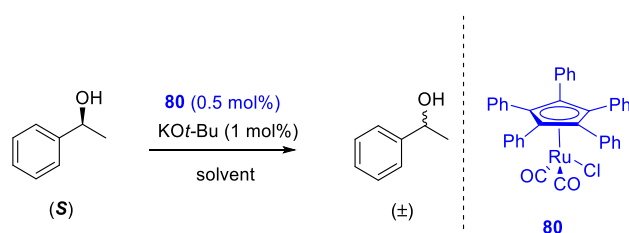
To (±)-1-(1-naphthyl)ethanol **26** (43 mg, 0.25 mmol) was added (-)-DBAP* (1.1 mg, 0.0025 mmol, 1 mol%, 0.5 mL of a 2.2 mg/mL solution) and Et₃N (26 µL, 0.1875 mmol, 0.75 eq). The solution was stirred at -78 °C for 30 minutes before adding dropwise isobutyric anhydride (41.5 µL, 0.25 mmol, 1.0 eq). After 8 hours, the solution was quenched with 1 mL of pre-cooled MeOH (-78 °C for a minimum of 1 h), and left to warm up overnight. The reaction was either analysed directly by HPLC or was subjected to purification by column chromatography (hexane→hexane:EtOAc 6:4). *R_f* of alcohol: 0.3 (hexane:EtOAc 9:1), *R_f* of Ester: 0.7 (9:1 hexane:EtOAc). The purified starting alcohol was analysed by HPLC (see methods below), while the ester was subjected to hydrolysis: Stirring for 5-10 minutes at 80 °C in a 5% solution of NaOH in MeOH. The solution was dried *in vacuo*, diluted with EtOAc and water, the organic layer separated and dried over Mg₂SO₄. The solvent was removed *in vacuo* and the hydrolysed product analysed by HPLC.

Representative procedure for low temperature KR with *t*-AmOH (Table 32)



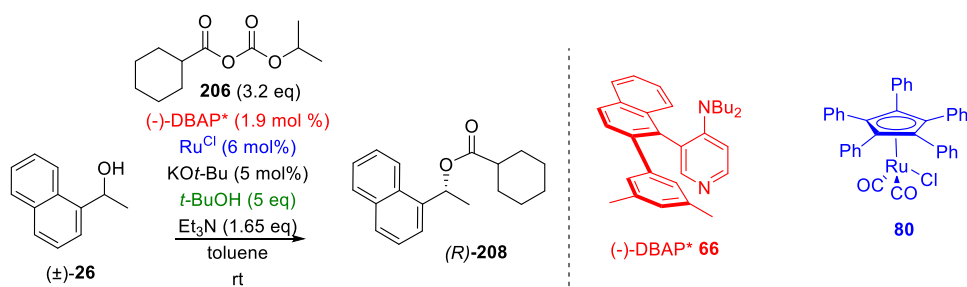
To (±)-1-(1-naphthyl)ethanol **26** (43 mg, 0.25 mmol) was added (-)-DBAP* (1.1 mg, 0.0025 mmol, 1 mol%, 0.5 mL of a 2.2 mg/mL solution), Et₃N (26 µL, 0.1875 mmol, 0.75 eq) and *t*-AmOH (30 µL, 0.275 mmol, 1.1 eq). The solution was stirred at -78 °C for 30 minutes before adding dropwise isobutyric anhydride (41.5 µL, 0.25 mmol, 1.0 eq). After 8 hours, the solution was quenched with 1 mL of pre-cooled MeOH (-78 °C for min. 1 h), and left to warm up overnight. The reaction was either analysed directly by HPLC or was subjected to purification by column chromatography (hexane→hexane:EtOAc (6:4)). *R_f* of alcohol: 0.3 (9:1 hexane:EtOAc), *R_f* of ester: 0.7 (9:1 hexane:EtOAc). The purified starting alcohol was analysed by HPLC (see methods below), while the ester was subjected to hydrolysis: stirring for 5-10 minutes at 80 °C in a 5% solution of NaOH in MeOH. The solution was dried *in vacuo*, diluted with EtOAc and water, the organic layer separated and dried over Mg₂SO₄. The solvent was removed *in vacuo* and the hydrolysed product analysed by HPLC. The HPLC methods are described in the appendix.

Representative procedure for alcohol racemisation (Figure 37, 40 (other additives used), 41-44, 55, 79)



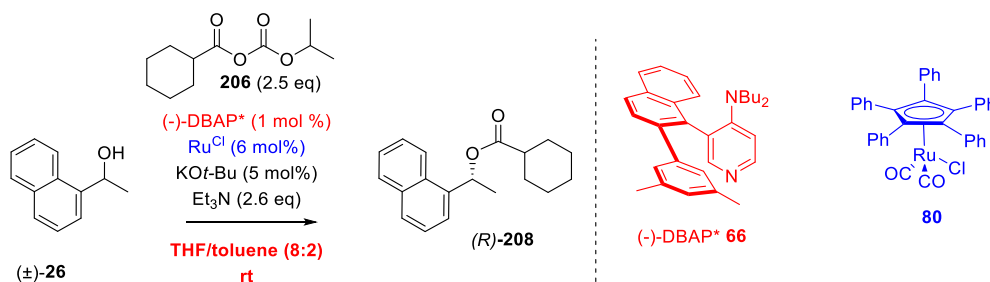
To a solution of Ru^{Cl} pre-catalyst (1.6 mg, 0.0025 mmol, 0.5 mol%) in toluene (1 mL) was added KOt-Bu solution (1.0 M in THF, 5 μ L, 0.005 mmol, 1 mol%). The solution was stirred for 6 minutes, turning quickly from yellow to orange/red. Additives such as Et₃N or the acyl donors were added at this point. (S)-phenylethanol (60 μ L, 0.5 mmol, 1 eq) was then added. Aliquots of 0.05 mL were periodically taken, diluted and quenched with 0.5 mL MeOH and analysed directly by chiral HPLC to determine *ee*. The HPLC methods are described in the appendix.

Optimised procedure for DKR (Figure 61)



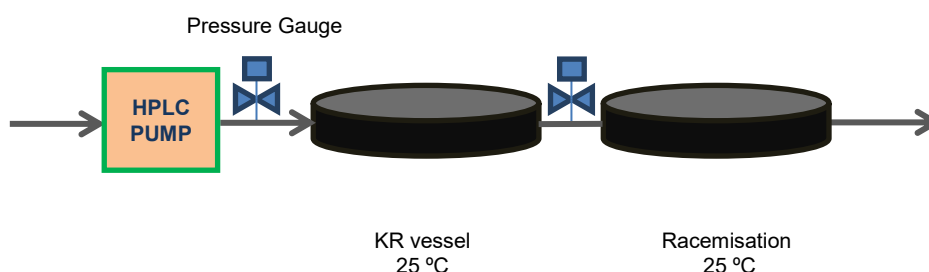
To a solution of Ru^{Cl} pre-catalyst (19.1 mg, 0.03 mmol, 6 mol%) in toluene (0.3 mL) was added KOt-Bu solution (1.0 M in THF, 25 μ L, 0.025 mmol, 5 mol%). The solution was stirred for 6 minutes, turning quickly from yellow to orange/red. To the solution was added Et₃N (110 μ L, 0.825 mmol, 1.65 eq), *t*-BuOH (0.25 mL, 2.5 mmol, 5 eq), and a solution of (±)-1-(1-naphthyl)ethanol (86 mg, 0.5 mmol, 1 eq) and (-)-DBAP* (1.1 mg, 0.0025 mmol, 0.5 mol%, 0.5 mL of a 2.2 mg/mL solution). To this solution was added cyclohexyl isopropyl carbonate (50 μ L, 0.25 mmol, 0.5 eq) dropwise. Aliquots of 0.05 mL were periodically taken from the reaction, diluted and quenched with 0.5 mL MeOH and analysed directly by chiral HPLC to determine *ee* and conversion (see graduated method above). After 90 minutes, a further portion of (-)-DBAP* (0.44 mg, 0.2%, 0.2 mL of catalyst solution) and acyl donor (30 μ L, 0.15 mmol, 0.3 eq) was added. After the next four 90 minute intervals (up to 7.5 h) further portions of (-)-DBAP* (0.44 mg, 0.2%, 0.2 mL of catalyst solution) and acyl donor (40 μ L, 0.2 mmol, 0.4 eq) were again added. The solution was left to stir overnight. After a total of 26 h reaction time, a further portion of catalyst (0.2 mol%) and acyl donor (0.4 eq) were added, and 90 minutes later this was repeated. The reaction was then stopped after a total of 31 h reaction time by adding 2 mL MeOH. The solvent was removed *in vacuo*, and the conversion analysed by ¹H NMR analysis (83% C). The reaction was purified by column chromatography (hexane→hexane:EtOAc (6:4)). *R_f* of Alcohol: 0.3 (9:1 hexane:EtOAc), *R_f* of Ester: 0.7 (9:1 hexane:EtOAc), and the *ee* of the ester determined by chiral HPLC analysis (81.5% *ee* observed).

Optimised procedure for MEDKR (Figures 80 and 81)

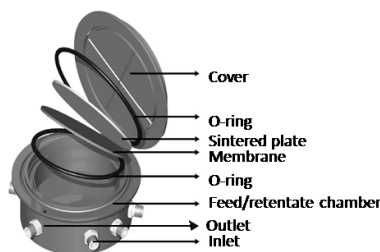


Reactor Set-up

Two reactor cells as shown below were set up in series:



The 100 mL volume of the cells was reduced to 25 mL by placing a Teflon insert inside the cell. The three of the six ports of the cell were used for the inlet (from HPLC or previous cell), outlet (permeate to feed flask or next cell), and the third for loading the cells. Pressure gauges were connected before the first cell and in between the two cells for pressure monitoring. A magnetic stirrer bar was placed inside each cell. A 51 cm² disk of the PEEK membrane, obtained from the Livingston group, was placed inside the cell with the active side facing towards the reaction mixture. This was kept in place by a sintered plate to provide support. The cell was closed by clamping the base to the cover using high pressure clamps. The cells were purged overnight with nitrogen through the loading ports.



The cells were filled with the solvent mixture (THF/toluene 8:2) by pumping with the HPLC pump until full to check for leaks (fill until pressure reaches 30 bar in first cell). The pumping was stopped and the pressure was allowed to reduce to 0, and ~10 mL of solution was taken from each cell through the loading port. Each cell was then filled with the required catalyst.

For the KR cell:

A solution of (-)-DBAP* catalyst (5.5 mg, 0.0125 mmol, 0.5 mol%) and (±)-1-(1-naphthylethanol) (150 mg, 0.87 mmol, 0.35 eq) and Et₃N (0.49 mL, 3.5 mmol, 1.4 eq) in 6.25 mL solvent (1.25 mL toluene, 5 mL THF).

For the Racemisation cell:

A solution of Ru^{Cl} pre-catalyst (80 mg, 0.125 mmol, 5 mol%) and KO^t-Bu (1.0 M in THF, 0.12 mL, 0.12 mmol, 4.8 mol%) was stirred in toluene (1.25 mL) for 6 minutes. After this time Et₃N (0.49 mL, 3.5 mmol, 1.4 eq) and 5 mL THF were added, and the solution loaded into the racemisation cell.

The HPLC pump was then started with the feed consisting of the THF/toluene solvent mixture. This was pumped until the cells were again filled and the permeate was coming out of the second cell (~2 h pumping @ 0.08 mL/min). The feed for the HPLC pump was then placed into the feed vessel, which was filled with:

For the Feed Vessel:

A solution of (±)-1-(1-naphthylethanol) (280 mg, 1.63 mmol, 0.65 eq) (total of 2.5 mmol alcohol) in THF/toluene (8:2) (20 mL).

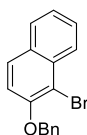
The pump was adjusted to 0.06 mL/min flow rate, and cyclohexyl isopropyl carbonate (0.127 mL, 0.625 mmol, 0.25 eq) was added to the feed vessel. Further portions of acyl donor (0.127 mL, 0.25 eq) were added to the feed vessel at the following time points: 17 h, 24 h, 48 h.

The reaction was monitored by taking samples from the permeate (0.5 mL diluted with 0.5 mL MeOH) and the samples analysed by chiral HPLC (see graduated method above).

After 120 h (5 days), the feed vessel was replaced with the solvent mixture (THF/toluene) and the cells flushed for 24 h into a beaker containing MeOH (100 mL). After 24 h, the flush mixture was replaced with THF/MeOH (9:1), and the cells flushed for a further 72 h.

The solvent in the combined permeate was removed *in vacuo*, and the conversion analysed by ¹H NMR and HPLC (see graduated method above). The conversion was found to be 61%, while the *ee* of the ester was 58% and the *ee* of the alcohol was 23 %. After purification by flash column chromatography, the isolated yield of the ester from the permeate was 0.28 g (39%), while a further 0.022 g was isolated from contents of the racemisation cell (4%, combined yield isolated yield of 43%).

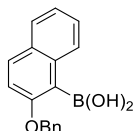
1-Bromo-2-(phenylmethoxy)naphthalene (**101**)^[120]



Large Scale

To a flask equipped with an overhead mechanical stirrer was added 1-bromo-2-naphthol (150 g, 0.67 mol), acetonitrile (1.2 L) and with vigorous stirring, K_2CO_3 (182 g, 1.31 mol). To the resulting suspension was added benzyl bromide (90 mL, 0.75 mol) and the mixture heated at 60 °C for five hours. The suspension was filtered while hot to remove K_2CO_3 and then cooled to allow the product to crystallize. The crude product was filtered and washed with warm acetonitrile/ CH_2Cl_2 . The resulting white solid was recrystallised from hexane: CH_2Cl_2 to give a white solid (150 g, 71%). The mother liqueurs were combined and purified *via* flash column chromatography (hexane: CH_2Cl_2 8:2) to yield further product as a white solid (59.1 g, 28%). The total combined yield of 1-bromo-2-(phenylmethoxy)naphthalene as a white solid was therefore 209.1 g (99%). 1H NMR (400 MHz, $CDCl_3$) δ_H 8.26 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 9.0 Hz, 2H), 7.58 (ddd, J = 8.5, 7.0, 1.2 Hz, 1H), 7.54 (d, J = 7.0 Hz, 2H), 7.44 – 7.38 (3H), 7.34 (t, J = 7.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 5.33 (s, 2H); MS-(ES-API⁺) m/z (rel intensity) 312.80 (30%, M⁺), 314.80 (30%, M⁺). Data consistent with that reported previously.^[120]

2-(Phenylmethoxy)-1-naphthaleneboronic Acid (**102**)^[120]



Small Scale

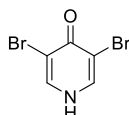
A suspension of 1-bromo-2-(phenylmethoxy)naphthalene **101**^[120] (12.5 g, 39.9 mmol) in diethyl ether (180 mL) was cooled to -78 °C and *n*-BuLi (27.4 mL, 1.6 M, 43.9 mmol) added dropwise. The contents was stirred at -78 °C for 30 min, and 0 °C for 1.5 h. The solution was re-cooled to -78 °C and B(OMe)₃ (8.9 mL, 78.8 mmol) was added. The reaction was stirred at -78 °C for 30 min, and rt overnight. The solution was then quenched with 1 M HCl (200 mL) and stirred at rt for 1.5 h. The organic solvent was removed *in vacuo*, the aqueous layer extracted with CH_2Cl_2 and the combined organic phases dried over Na_2SO_4 , before solvent removal *in vacuo*. The crude product purified by recrystallisation from CH_2Cl_2 to give the boronic acid **102** as a white powder (7.83 g, 71%). 1H NMR (400 MHz, CD_3OD) δ_H 7.88 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.45 – 7.27 (6H), 5.25 (s, 2H); MS-(ES-API⁺) m/z (rel intensity) 279.2 (100%, M+H⁺). Data consistent with that reported previously.^[120]

Large Scale

A suspension of 1-bromo-2-(phenylmethoxy)naphthalene **101**^[120] (60 g, 191 mmol) in diethyl ether (800 mL) was cooled to -78 °C and *n*-BuLi (100 mL, 2.5 M, 248 mmol) added dropwise *via* a dropping funnel,

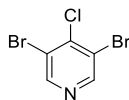
ensuring the solution temperature remained below $-65\text{ }^{\circ}\text{C}$. The contents was stirred at $-78\text{ }^{\circ}\text{C}$ for 25 min, and $0\text{ }^{\circ}\text{C}$ for 1 h. The solution was re-cooled to $-78\text{ }^{\circ}\text{C}$ and B(OMe)_3 (42.5 mL, 382 mmol) was added slowly. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for and left to warm up overnight. The solution was then quenched with 1.5 M HCl (200 mL) and stirred at rt for 1.5 h while a white suspension was formed in the organic phase. The phases were separated and the organic phase filtered. The resulting solid was suspended in CH_2Cl_2 and filtered to provide the boronic acid **14** as a white powder (47.2 g, 89%). Data as above.

3,5-Dibromo-4-pyridone (**114**)^[101]



To a mechanically stirred suspension of 4-pyridone (40 g, 0.42 mol) and KOH (44 g, 0.84 mol) in water (700 mL) was slowly added a solution of bromine (42. mL, 0.84 mol) in water (100 mL) *via* a dropping funnel. The suspension was allowed to stir for one hour until the yellow colour disappeared. The suspension was filtered, washed with water (400 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ solution (500 mL). The resulting solid was dried overnight in a vacuum oven to yield a white powder (89.4 g, 84%) and used without further purification. Mp: $>256\text{ }^{\circ}\text{C}$ (lit.: sublimes at $320\text{ }^{\circ}\text{C}$ ^[337]).

3,5-Dibromo-4-chloropyridine (**115**)^[101]



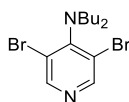
Small Scale

A mixture of 3,5-dibromo-4-pyridone **114** (5g, 19.8 mmol) and PCl_5 (5.14 g, 24.7 mmol) was heated at $160\text{ }^{\circ}\text{C}$ for 3 h. The reaction mixture was cooled to $0\text{ }^{\circ}\text{C}$ and quenched with H_2O (50 mL). The precipitate formed was filtered, dissolved in CH_2Cl_2 , dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2) to give 3,5-dibromo-4-chloropyridine **115** as white needles (3.91 g, 73%). $R_f = 0.6$ (CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 8.66 (s, 2H). Data consistent with that reported previously.^[1]

Large Scale

A mixture of 3,5-dibromo-4-pyridone **114** (62.0 g, 0.24 mol) and PCl_5 (61.3 g, 0.30 mol), was loaded into a three necked flask with two necks attached to nitrogen gas and a third to a trap followed by a Drescher bottle containing 250 mL 8 M NaOH solution. The reaction was heated at $160\text{ }^{\circ}\text{C}$ for 3 h then cooled to $40\text{ }^{\circ}\text{C}$ and quenched with H_2O (200 mL). The aqueous suspension formed was extracted with CH_2Cl_2 , the aqueous layers basified and re-extracted with CH_2Cl_2 , the combined organic layers dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified recrystallisation from CH_2Cl_2 /hexane to give 3,5-dibromo-4-chloropyridine **115** as pale yellow-white needles (52.0 g, 78%). Data as above.

3,5-Dibromo-4-dibutylaminopyridine (**116**)^[122]



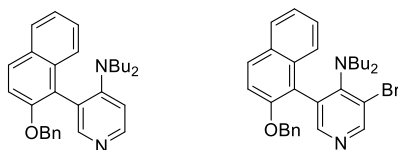
Small Scale

A solution of 3,5-dibromo-4-chloropyridine **115** (3.79 g, 13.9 mmol), dibutylamine (10.9 mL, 64.8 mmol) in NMP (11 mL) with 100 mg 4 Å MS was heated in a sealed high-pressure vessel to 170 °C for 20 h. The mixture was allowed to cool, before diluting with EtOAc (100 mL) and washed with sat. NaHCO₃ solution (100 mL) and water (3 × 100 mL). The organic phase was washed with brine (100 mL) and dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (hexane:CH₂Cl₂ 3:1) to give 3,5-dibromo-4-dibutylaminopyridine **116** as a brown oil (3.65 g, 70%). *R_f* = 0.45 (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 8.53 (s, 2H), 3.37 (m, 4H), 1.45 (m, 4H), 1.30 (dq, *J* = 14.4, 7.3 Hz, 4H), 0.89 (t, *J* = 7.3 Hz, 6H); MS-(ES-API⁺) *m/z* (rel intensity) 364.9 (100%, M+H⁺), 366.9 (40%, M+H⁺), 367.9 (10%, M+H⁺). Data consistent with that reported previously.^[122]

Large Scale

A solution of 3,5-dibromo-4-chloropyridine **115** (40 g, 0.147 mol), dibutylamine (86 mL, 0.516 mol) in (wet) NMP (111 mL) was heated in a sealed high-pressure vessel to 140 °C for 48 h. The mixture was allowed to cool, before diluting with TBME (300 mL) and washed with sat. NaHCO₃ solution (200 mL) and water (3 × 200 mL). The organic phase was washed with brine (300 mL) and dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (hexane→hexane:EtOAc 9:1) to give 3,5-dibromo-4-dibutylaminopyridine **116** as a pale yellow oil that crystallized on standing (46.3 g, 81%). Data as above.

Dibutyl(3-[2-(phenylmethoxy)naphthyl](4-pyridyl)-amine (**150**)^[122] and dibutyl(3-[2-(phenylmethoxy)naphthyl](5-bromo-4-pyridyl)-amine (**150a**)



Small Scale

To a solution of 3,5-dibromo-4-dibutylaminopyridine **116** (100 mg, 0.275 mmol) in toluene (2.7 mL) and ethanol (0.16 mL) was added 2M KOH solution (0.67 mL) and Pd(PPh₃)₄ (15.8 mg, 0.0136 mmol) and boronic acid **102** (133 mg, 0.48 mmol). The mixture was heated at 100 °C for 20 h, cooled to rt and diluted with water (5 mL). The phases were separated, and the aqueous phase extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified flash column chromatography (CH₂Cl₂→CH₂Cl₂:EtOAc 1:1) to give dibutyl[3-[2-(phenylmethoxy)naphthyl](4-pyridyl)]-amine **150** as a yellow oil (72 mg, 31%). *R_f* = 0.25 (EtOAc); ¹H NMR

(400 MHz, CDCl₃) δ_{H} 8.31 (d, J = 6.1 Hz, 1H), 8.06 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.84 – 7.79 (1H), 7.74 – 7.62 (3H), 7.58 – 7.52 (m, 1H), 7.51 – 7.44 (2H), 7.34 – 7.23 (2H), 6.78 (d, J = 6.1 Hz, 1H), 5.17 (s, 2H), 2.90 (m, 4H), 1.24 (m, 2H), 1.05 (m, 2H), 0.84 (m, 4H), 0.63 (t, J = 7.3 Hz, 6H); MS-(ES-API⁺) m/z (rel intensity) 439.2 (100%, M+H⁺) 440.2 (80%). Data consistent with that reported previously.^[122]

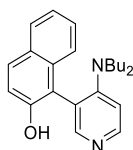
Large Scale

To a mixture of 3,5-dibromo-4-dibutylaminopyridine **116** (20.0 g, 54.8 mmol), boronic acid **102** (19.1 g, 68.6 mmol), KOH (6.0 g) in a three necked flask equipped with an air condenser was added in a glove-box Pd(PPh₃)₄ (3.8 g, 3.29 mmol). The flask was removed from the glove box and dry degassed dioxane (200 mL) and degassed H₂O (20 mL) was added to the flask. The resulting solution was heated at 100 °C for 75 minutes, after which a further portion of boronic acid (7.65 g, 27.5 mmol) in dioxane (20 mL) was added. The solution was allowed to stir at 100 °C for a further 18 h, after which a further portion of boronic acid (3.8 g, 13.6 mmol) was added to the reaction mixture as a solid. The solution was allowed to stir for a further 3 hours, then cooled to rt and diluted with water (100 mL) and EtOAc (500 mL). The phases were separated, and the aqueous phase extracted with EtOAc (200 mL). The combined organic extracts were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude products were purified flash column chromatography (hexane→hexane:EtOAc 1:1→EtOAc) to give:

Dibutyl[3-[2-(phenylmethoxy)naphthyl](4-pyridyl)]-amine **150** as a yellow oil (2.04 g, 8.5 %), data as above.

Dibutyl[3-[2-(phenylmethoxy)naphthyl](5-bromo-4-pyridyl)]-amine **150a** as a yellow oil (16.06 g, 57%). R_f = 0.55 (hexane:EtOAc 9:1); ¹H NMR (400 MHz, CDCl₃) δ_{H} 8.67 (s, 1H), 8.13 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.85-7.80 (1H), 7.41 – 7.33 (4H), 7.33 – 7.25 (3H), 7.20 (d, J = 6.3 Hz, 2H), 5.15 (s, 2H), 2.73 (ddd, J = 9.1, 6.5, 2.8 Hz, 4H), 1.14 (m, 4H), 0.95 (m, 4H), 0.67 (t, J = 7.3 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ_{C} 157.21, 153.18, 152.76, 152.02, 136.83, 135.05, 133.43, 129.93, 129.16, 128.48, 127.99, 127.79, 126.78, 126.63, 125.00, 123.97, 114.67, 109.95, 70.80, 51.48, 30.41, 20.04, 13.79; MS-(ES⁺) m/z (rel intensity) 517.19 (100 %, M+H), 519.19 (95%, M+H); HRMS (ES⁺) calcd. for C₃₀H₃₄N₂OBr (M+H) 517.1855, found 517.1871, (Δ =-3.1 ppm); IR (neat) ν_{max} 3061, 3032 (Ar, C-H) 2956, 2930, 2867 (C-H), 1622 (C=N), 1592, 1560, 1506, 1454 (C=C), 1262 (Ar, C-O).

Dibutyl(3-[2-(hydroxy)naphthyl](4-pyridyl))-amine (**153**)^[122]



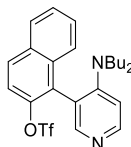
Small Scale

To a solution of dibutyl(3-[2-(phenylmethoxy)naphthyl](4-pyridyl))-amine **150** (71 mg, 0.162 mmol) in EtOAc (0.65 mL) and ethanol (1.28 mL) was added Pd/C (22 mg), and the resulting suspension stirred at rt with H₂ (1 atm) for 24 h. The mixture was filtered through a pad of Celite[®] and concentrated to give the crude product (quantitative conversion by ¹H NMR). *R*_f = 0.2 (EtOAc:MeOH 1:9) Product not fully purified.

Large Scale

To a solution of dibutyl(3-[2-(phenylmethoxy)naphthyl](4-pyridyl))-amine **150** and dibutyl[3-[2-(phenylmethoxy)naphthyl](5-bromo-4-pyridyl)]-amine **150a** (8.68 g, 17.1 mmol) and *i*-Pr₂NEt (6 mL, 34.4 mmol) in EtOAc (40 mL), ethanol (80 mL) was added Pd/C (5%) (5 g), and the resulting suspension shaken in a Parr Hydrogenation apparatus at rt with H₂ (60 bar) for 24 h. The mixture was filtered through a pad of Celite[®], the pad washed with EtOAc (100 mL) and combined solution concentrated to give the crude product (quantitative conversion by ¹H NMR), (8.89 g, 150% yield – traces of base still present in the mixture). The solid was taken through to the next reaction without further purification. ¹H NMR (400 MHz, CDCl₃) δ_H 8.37 (d, *J* = 6.0 Hz, 1H), 8.24 (s, 1H), 7.86 – 7.76 (2H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.36 (dddd, *J* = 16.0, 8.3, 6.9, 1.5 Hz, 2H), 7.28 (d, *J* = 8.9 Hz, 1H), 6.92 (d, *J* = 6.0 Hz, 1H), 2.98 (m, 4H), 1.33 (m, 4H), 0.99 (m, 4H), 0.70 (t, *J* = 7.3 Hz, 6H); MS-(ES-API⁺) *m/z* (rel intensity) 349.2 (100%, M+H⁺). Data consistent with that reported previously.^[122]

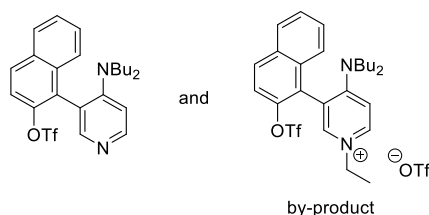
1-[4-(Dibutylamino)-3-pyridyl]-2-naphthyl (trifluoromethyl)sulfonate (**130**)^[122]



To a solution of crude dibutyl(3-[2-(hydroxy)naphthyl](4-pyridyl))-amine **153** (4.28 g, 9.6 mmol), 4-DMAP (0.75 g, 6.2 mmol) and *i*-Pr₂NEt (4.2 mL, 24.7 mmol) in CH₂Cl₂ (60 mL) was added dropwise at 0 °C triflic anhydride (2.4 mL, 14.8 mmol). The solution was stirred at 0 °C for 3 ½ hours, after which it was quenched with sat. NaHCO₃ solution (50 mL), the phases separated and the aqueous phase extracted with further portions of CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude products were purified flash column chromatography (hexane:EtOAc 3:7 → EtOAc) to give triflate **130** as a yellow oil (3.41 g, 74% over two steps). *R*_f = 0.61 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ_H 8.38 (d, *J* = 6.0 Hz, 1H), 8.14 (s, 1H), 7.96 (m, 2H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.57 (dq, *J* = 15.2, 7.3, 6.9 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 6.0 Hz, 1H), 2.89 (ddd, *J* = 15.0, 9.6, 6.0 Hz, 2H), 2.77 (ddd, *J* = 15.0, 9.6, 6.0 Hz, 2H), 1.19 (m, 4H), 0.87 (m, 4H), 0.64 (t, *J* = 7.3 Hz, 6H); MS-(ES-API⁺) *m/z* (rel intensity) 481.2 (100%, M+H⁺). Data consistent with that reported previously.^[122]

1-[4-(Dibutylamino)-3-pyridyl]-2-naphthyl (trifluoromethyl)sulfonate (130) and

1-[4-(dibutylamino)-3-pyridyl-*N*-ethyl]-2-naphthyl (trifluoromethyl)sulfonate triflate salt (157)

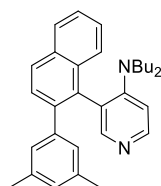


To a solution of crude dibutyl(3-[2-(hydroxy)naphthyl](4-pyridyl))-amine **153** (18.9 g, 38.0 mmol, 70% by mass), 4-DMAP (2.3 g, 19.0 mmol) and *i*-Pr₂NEt (13 mL, 76 mmol) in CH₂Cl₂ (130 mL) was added dropwise at 0 °C triflic anhydride (7.35 mL, 43.7 mmol, 1.15 eq). The solution was stirred at 0 °C for 3 hours, after which a further portion of triflic anhydride (3.8 mL, 22.8 mmol, 0.6 eq) was added. After one hour, the reaction was quenched with sat. NaHCO₃ solution (100 mL), the phases separated and the aqueous phase extracted with further portions of CH₂Cl₂ (3 x 80 mL). The combined organic layers were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude products were purified flash column chromatography (hexane:EtOAc 3:7 → EtOAc→MeOH) to give:

1-[4-(Dibutylamino)-3-pyridyl]-2-naphthyl (trifluoromethyl)sulfonate **130** as a thick brown oil (3.2 g, 19%), data as above.

1-[4-(Dibutylamino)-3-pyridyl-*N*-ethyl]-2-naphthyl (trifluoromethyl)sulfonate triflate salt **157** as a sticky brown oil (10.3 g, 41%). *R*_f = 0.2 (MeOH); ¹H NMR (400 MHz, CDCl₃) δ_H 8.49 (d, *J* = 7.7 Hz, 1H), 8.14 (d, *J* = 9.1 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.80 – 7.64 (2H), 7.67 (s, 1H), 7.48 (d, *J* = 9.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 4.39 (dq, *J* = 14.4, 7.3 Hz, 1H), 4.26 (dq, *J* = 14.4, 7.3 Hz, 1H), 3.19 (br s, 2H), 3.02 (br s, 2H), 1.53 (t, *J* = 7.3 Hz, 3H), 1.32 (br s, 4H), 0.83 (br s, 4H), 0.65 (br s, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ_F -73.96, -78.29; ¹³C NMR (101 MHz, CDCl₃) δ_C 156.04, 144.80, 142.12, 132.78, 132.20, 129.80, 128.82, 128.47, 126.32, 125.98, 123.04, 122.44, 119.86, 119.26, 119.08, 116.67, 114.74, 111.96, 53.87, 52.75, 29.14, 19.63, 15.98, 13.29; MS-(ES⁺) *m/z* (rel intensity) 509.21 (100 %, (M-OTf)⁺), 510.21 (30%, M-OTf+H⁺); HRMS (ES⁺) calcd. for C₂₆H₃₂N₂O₃SF₃ (M-OTf) 509.2086, found 509.2088, (Δ=0.4 ppm); IR (neat) ν_{max} 2962 (C-H), 1647 (C=N), 1537 (C=C), 1253 (Ar, C-O), 1221 (C-F), 1156 (C-N), 1030 (S=O), 831 (S-O).

{3-[2-(3,5-Dimethylphenyl)naphthalen-1-yl]pyridin-4-yl}dibutylamine (DBAP* 66)^[208]



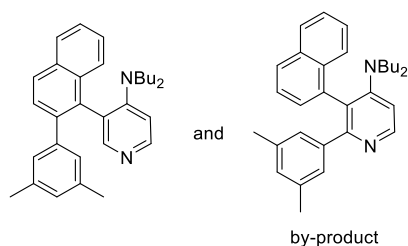
Method A

Following a modified procedure from Spivey^[102], a mixture of triflate **130** (1.0 g, 2.08 mmol), 3,5-dimethylphenyl boronic acid **151** (0.62 g, 4.16 mmol), K₃PO₄ (1.5 g, 7.28 mmol), Pd₂(dba)₃ (57 mg, 0.062 mmol, 3 mol%) and SPhos (70 mg, 0.19 mmol, 9 mol%) was dried *in vacuo* for 10 minutes. The flask was purged with nitrogen (3 x) and dry degassed toluene (12 mL) was added. The reaction was heated to 104 °C for 8 h, after which a further portion of boronic acid was added (0.3 g, 2.00 mmol). The reaction was left to heat for a further 9 h (17 h in total). The solution was cooled to rt and diluted with sat. NaHCO₃ solution (20 mL) and EtOAc (10 mL). The phases were separated, and the aqueous phase extracted with further portions of EtOAc (2 x 10 mL). The combined organic extracts were extracted with brine (30 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (hexane→hexane:EtOAc 1:1→EtOAc) to give {3-[2-(3,5-dimethylphenyl)naphthalen-1-yl]pyridin-4-yl}dibutylamine **66** as a yellow oil (0.61 g, 68 %). R_f = 0.3 (hexane:EtOAc 6:4); ¹H NMR (400 MHz, CDCl₃) δ_H 8.23 (d, *J* = 6.1 Hz, 1H), 8.14 (s, 1H), 7.91 (t, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 6.80 (s, 1H), 6.71 (s, 2H), 6.48 (d, *J* = 6.1 Hz, 1H), 2.78 (ddd, *J* = 14.2, 10.0, 6.0 Hz, 2H), 2.59 (ddd, *J* = 14.2, 10.0, 6.0 Hz, 2H), 0.93 (m, 4H), 0.71 (m, 4H), 0.58 (t, *J* = 7.1 Hz, 6H); MS-(ES-API⁺) *m/z* (rel intensity) 437.2 (100%, M+H⁺), 438.2 (30%). Data consistent with that reported previously.^[208]

Method B

To a solution of bromide **159** (0.157 g, 0.30 mmol) in EtOH (5.3 mL) and EtOAc (2.6 mL) was added Et₃N (60 μL, 0.43 mmol), 10% Pd/C (140 mg). The reaction vessel was evacuated and flushed with hydrogen, and stirred vigorously for 48 h with a 1 atm H₂ atmosphere. The solution filtered through Celite[®] and the solvent removed *in vacuo*. The resulting oil was diluted with EtOAc and washed with sat. NaHCO₃ solution (10 mL), dried over Mg₂SO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (hexane→hexane:EtOAc 1:1→EtOAc) to give DBAP* **66** as a yellow oil (98 mg, 74 %). Data as above.

**{3-[2-(3,5-Dimethylphenyl)naphthalen-1-yl]pyridin-4-yl}dibutylamine (DBAP* 66)^[208] and
{(3-naphthalen-1-yl)(2-(3,5-dimethylphenyl)pyridin-4-yl)dibutylamine (158)}**



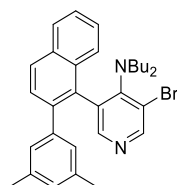
Following a modified procedure from Spivey,^[102] a mixture of triflate **130** (3.54 g, 7.39 mmol), 3,5-dimethylphenyl boronic acid (2.2 g, 14.67 mmol), K₃PO₄ (5.4 g, 25.4 mmol), Pd₂(dba)₃ (0.2 g, 0.218 mmol,

3 mol%) and SPhos (0.25 g, 0.609 mmol, 9 mol%) was dried *in vacuo* for 10 minutes. The flask was purged with nitrogen (3 x) and dry degassed toluene (40 mL) was added. The reaction was stirred for 15 minutes at room temperature, before being heated to 104 °C for 16 h. The solution was cooled to rt and diluted with sat. NaHCO₃ solution (50 mL) and EtOAc (40 mL). The phases were separated, and the aqueous phase extracted with further portions of EtOAc (2 x 40 mL). The combined organic extracts were extracted with brine (100 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (hexane→hexane:EtOAc 1:1→EtOAc) to give:

{3-[2-(3,5-Dimethylphenyl)naphthalen-1-yl]pyridin-4-yl}dibutylamine **66** as a yellow oil (1.73 g, 54%), data as above.

{(3-Naphthalen-1-yl)(2-(3,5-dimethylphenyl)pyridin-4-yl)}dibutylamine **158** as an orange oil (1.14 g, 35%). *R_f* = 0.5 (hexane:EtOAc 6:4); ¹H NMR (400 MHz, CDCl₃) δ_H 8.49 (d, *J* = 5.8 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.36 – 7.30 (2H), 7.17 (dd, *J* = 7.0, 1.1 Hz, 1H), 6.89 (d, *J* = 5.8 Hz, 1H), 6.58 (s, 3H), 2.75 (qdd, *J* = 14.0, 9.4, 5.8 Hz, 4H), 1.95 (s, 6H), 1.19 (m, 2H), 1.08 (m, 2H), 0.92 (m, 4H), 0.70 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ_C 160.51, 156.86, 148.48, 136.61, 136.18, 133.42, 132.23, 129.18, 128.18, 127.94, 127.34, 126.62, 126.33, 125.54, 125.27, 111.70, 77.34, 77.22, 77.02, 76.70, 51.73, 29.34, 20.98, 20.08, 13.76; MS-(ES⁺) *m/z* (rel intensity) 437.29 (100 %, M+H), HRMS (ES⁺) calcd. for C₃₁H₃₇N₂ (M+H⁺) 437.2957, found 437.2951, (Δ= -1.4 ppm); IR (neat) ν_{max} 2960, 2926, 2867 (C-H), 1620 (C=N), 1596, 1572 (C=C), 1155 (C-N).

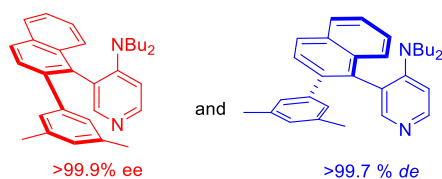
{3-[2-(3,5-Dimethylphenyl)naphthalen-1-yl]-5-bromo-pyridin-4-yl}dibutylamine (**159**)



3,5-Dibromo-4-dibutylaminopyridine **116** (500 mg, 1.375 mmol), 2-(3,5-dimethylphenyl)-1-naphthylboronic acid **137** (1.518 g, 5.5 mmol, 4 eq), KOH (0.154 g, 2.75 mmol) and Pd(PPh₃)₄ (159 mg, 0.1375 mmol) were loaded into a 20 mL microwave vial. The vial was purged with argon; dry degassed dioxane (6 mL) and water (0.5 mL) was added and the mixture was heated to 100 °C for 3 days. The reaction was monitored by ¹H NMR analysis, and after 3 days a further portion of Pd(PPh₃)₄ (80 mg, 0.0688 mmol) was added. After a further 2 days the reaction was cooled to rt, diluted with water (10 mL) and EtOAc (30 mL). The phases were separated, and the aqueous phase extracted with EtOAc (20 mL). The combined organic extracts were dried over Na₂SO₄ and the solvent removed *in vacuo*. The crude product was purified flash column chromatography (hexane→hexane:EtOAc (1:1)→EtOAc) to give dibutyl[3-[2-(3,5-dimethylphenyl)naphthyl][5-bromo-4-pyridyl]]-amine **159** as a yellow oil (157 mg, 22%). *R_f* = 0.44 (hexane:EtOAc 9:1); ¹H NMR (400 MHz, CDCl₃) δ_H 8.58 (s, 1H), 8.26 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H),

7.91 (d, $J = 8.0$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.50 (ddd, $J = 8.0, 6.8, 1.2$ Hz, 1H), 7.42 (ddd, $J = 8.4, 6.8, 1.2$ Hz, 1H), 2.41 (m, 4H), 2.22 (s, 6H), 1.04 (dddd, $J = 15.7, 9.4, 7.2, 5.1$ Hz, 2H), 0.93 (m, 2H), 0.84 (m, 4H), 0.63 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 155.84, 153.42, 152.71, 141.40, 140.76, 138.77, 137.33, 136.21, 132.91, 132.49, 132.36, 128.66, 128.52, 128.00, 127.93, 126.47, 126.29, 125.91, 118.74, 51.36, 30.44, 21.25, 19.97, 13.66; MS-(ES^+) m/z (rel intensity) 515.21 (100%, $\text{M}+\text{H}$), 517.21 (95%, $\text{M}+\text{H}^+$); HRMS (ES^+) calcd. for $\text{C}_{31}\text{H}_{36}\text{N}_2\text{Br}$ ($\text{M}+1$) 515.2062, found 515.2054, ($\Delta = -1.6$ ppm); IR (neat) ν_{max} 2957, 2928, 2867 (C-H), 1600, 1558, 1503, 1456 (C=C), 1259, 1095 (C-N).

Resolution of **DBAP*** **66**^[121,338]



As described by Richardson^[338]: To a solution of **DBAP*** **66** (racemic, 6.2 g, 74% by mass, 10.5 mmol) in 2-propanol (50 mL) was added 4-methyldibenzoyl-(2*S*,3*S*)-(-)-tartaric acid (4.1 g, 11 mmol, 1.05 eq). The solution was stirred for 5 minutes and the solvent blown off overnight, forming a salt (10.4 g, 74% by mass, 9.35 mmol, 89% yield). The resulting salt was dissolved in 4-methyl-2-pentanone (MIBK) (38.5 mL), and the solution stirred for 5 minutes and left overnight to recrystallise. The solids were filtered, washed with further portions of MIBK (2 x 10 mL), and the solids air dried, providing the enantiomer (-)-**DBAP***.4-methyldibenzoyl-(2*S*,3*S*)-(-)-tartaric acid salt (in 97.5% *de* (2.8 g, 100% by mass, 3.4 mmol, 36% yield). The filtrate was “free-based” using an SCX-2 column, eluting with 250 mL MeOH followed by 250 mL 7*N* NH_3/MeOH . The basic fractions were collected and the solvent removed *in vacuo* to provide (+)-**DBAP*** catalyst (3.2 g, 79% by mass, 5.8 mmol).

As carried out at Imperial College^[121,338]: (-)-**DBAP***.4-methyldibenzoyl-(2*S*,3*S*)-(-)-tartaric acid salt (500 mg, 0.61 mmol) was recrystallised from hot *i*-PrOH to yield the pure salt (-)-**DBAP***.4-methyldibenzoyl-(2*S*,3*S*)-(-)-tartaric acid salt (>99.9% *de*, 322 mg, 64%). 325 mg of this salt (0.39 mmol) was dissolved in $\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$ (10:1, 5 mL), stirred overnight at room temperature and the solvent removed *in vacuo*. The residue was purified by a plug of silica gel, eluting with EtOAc, providing (-)-**DBAP*** in 99.9% *ee* (123 mg, 0.28 mmol, 71%). Total yield of (-)-**DBAP*** from initial salt formation at 18% for this batch. Sign of optical rotation determined by Mohan from CD measurement and assigned here according to residence time in HPLC.^[297] Other spectroscopic data as above.

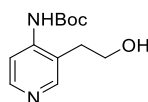
The filtrate from Richardson was purified by flash column chromatography (hexane→EtOAc) to yield (+)-**DBAP*** **66** (1.99 g, ~95% by mass, 4.34 mmol, 46% from initial salt formation). The *ee* of this mixture was

² Absolute configuration of catalyst has not been established.

~85%, as analysed by chiral HPLC at Imperial College, although the impurities could have effected this value. This was resolved following the procedure from Richardson with the opposite enantiomer of the acid, 4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid. Thus, to a solution of (+)-DBAP* (1.99 g, ~95% by mass, 4.34 mmol) in *i*-PrOH (16 mL) was added 4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid (1.67 g, 4.34 mmol, 1.0 eq). The solution was stirred for 5 minutes and the solvent removed *in vacuo*, forming a pale yellow fluffy solid (~4 g). The solid was triturated with MIBK (60 mL) and stirred for one hour, after which the solids were filtered, washed with further portions of MIBK (2 x 8 mL) and air dried, providing (+)-DBAP*.4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid salt as a white solid in 97.5% *de* (2.45 g, 3.0 mmol, 69%). The solids were triturated again as above from MIBK, providing (+)-DBAP*.4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid salt as a white solid in 98.5% *de* (2.09 g, 2.5 mmol, 85%). The salt was recrystallised from hot *i*-PrOH to yield the pure salt (+)-DBAP*.4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid salt (>99.8% *de*, 1.40 g, 67%). The mother liqueurs from the second suspension and the recrystallisation were combined and recrystallised from *i*-PrOH, providing a further portion of the pure (+)-DBAP*.4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid salt (>99.7% *de*, 0.3 g, 14%). Total yield of (+)-DBAP*.4-methyldibenzoyl-(2*R*,3*R*)-(+)-tartaric acid salt from initial salt formation at 22%. Sign of optical rotation determined by Mohan from CD measurement and assigned here according to residence time in HPLC.^[297]

HPLC conditions: OD-H column (100 x 250 mm), 35 °C, flow: 4 mL/min, eluent: hexane:(EtOAc:Et₂NH (99:1)) (90:10), detection: 254 nm. (-)-DBAP*: 11 minutes. (+)-DBAP*: 18 minutes

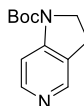
4-(*tert*-Butoxycarbonylamino)-3-(2-hydroxyethyl)-pyridine (**96**)^[120]



To a solution of 4-(*tert*-butoxycarbonylamino)-pyridine **95**^[120] (2.0 g, 10.28 mmol) in THF (26 mL) at -78 °C was added *t*-BuLi (1.6 M, 15.42 mL, 24.68 mmol) over 40 min. The suspension was stirred at -78 °C for 20 min, and -15 °C for 2 h. In a separate flask, to a solution of 2-bromoethanol (1.08 mL, 15.42 mmol) in THF (20 mL) at -78 °C was added *n*-BuLi (2.5 M, 7.4 mL, 18.50 mmol). After 10 min, the solution was transferred to the carbamate, and the mixture allowed to warm to room temperature over 2 h. The reaction was then quenched with water (4 mL) at -78 °C, and the organic solvent removed *in vacuo*. The residue was partitioned between water and CH₂Cl₂, and the phases separated. The aqueous layer was extracted with further portions of CH₂Cl₂ (3 x 20 mL), and the combined organic extracts washed with brine (30 mL), dried over Na₂SO₄ and the organic solvent removed *in vacuo*. The crude product was dissolved in CH₂Cl₂ and passed through a short plug of silica with EtOAc. Fractions containing the product were concentrated, and 4-(*tert*-butoxycarbonylamino)-3-(2-hydroxyethyl)-pyridine **96** removed as a solid by filtration. The mother liqueur was then purified by flash column chromatography (EtOAc) to give further portions of 4-(*tert*-butoxycarbonylamino)-3-(2-hydroxyethyl)-pyridine **96** as a pale yellow solid (1.75 g, 72%). *R_f* = 0.15

(EtOAc); ^1H NMR (400 MHz, CDCl_3) 8.47 (s, 1H), 8.35 (d, $J = 5.6$ Hz, 1H), 8.25 (s, 1H), 7.96 (d, $J = 5.6$ Hz, 1H), 3.99 (t, $J = 5.5$ Hz, 2H), 2.86 (t, $J = 5.5$ Hz, 2H), 1.55 (s, 9H). Data consistent with that reported previously.^[120]

1-(*tert*-Butoxycarbonyl)-5-azaindoline (**97**)^[120]



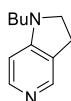
To a solution of 4-(*tert*-butoxycarbonylamino)-3-(2-hydroxyethyl)-pyridine **96** (1.21 g, 5.08 mmol), Et_3N (1.55 mL, 11.1 mmol) in CH_2Cl_2 (15 mL) at -10°C was added methanesulfonyl chloride (0.43 mL, 5.59 mmol). The reaction was left to stir for 1 h at rt, at which point the reaction was washed with NaHCO_3 (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and the organic solvent removed *in vacuo*. The compound was purified by flash column chromatography (EtOAc) to give 1-(*tert*-butoxycarbonyl)-5-azaindoline **97** as a light yellow oil that solidifies upon standing (1.03 g, 92 %). $R_f = 0.2$ (EtOAc); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.34 (d, $J = 5.5$ Hz, 1H), 8.31 (s, 1H), 7.68 (br s, 1H), 4.01 (t, $J = 8.8$ Hz, 2H), 3.14 (t, $J = 8.8$ Hz, 2H), 1.58 (s, 9H). Data consistent with that reported previously.^[120]

5-Azaindoline (**132**)^[297]



THF (70 mL) was cooled to 0°C , and LiAlH_4 (1.12 g, 29.7 mmol) added. A solution of 1-(*tert*-butoxycarbonyl)-5-azaindoline **97** (1.49 g, 6.76 mmol) in THF (20 mL) was added dropwise, and the resulting solution stirred at 0°C for 15 min, and at reflux for 2.5 h. The reaction was cooled to 0°C and quenched with water (1 mL), 2 M NaOH solution (2×1 mL) and water (3×1 mL). The resulting mixture was stirred until no grey colour was observed, diluted with diethyl ether, dried with Na_2SO_4 and filtered, and the solvent removed *in vacuo* to give a yellow oil that solidified upon standing. The compound was purified by recrystallisation from EtOAc, and the mother liqueur purified by flash column chromatography (EtOAc) to give 5-azaindoline **132** as a yellow solid (0.53 g, 66%). $R_f = 0.15$ (CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.16 (s, 1H), 8.12 (d, $J = 5.4$ Hz, 1H), 6.48 (d, $J = 5.4$ Hz, 1H), 4.17 (s, 1H), 3.67 (t, $J = 8.6$ Hz, 2H), 3.08 (t, $J = 8.6$ Hz, 2H); MS-(ES-API $^+$) m/z (rel intensity) 121.0 (100%, $\text{M}+\text{H}^+$). Data consistent with that reported previously.^[297]

1-Butyl-5-azaindoline (**133**)^[297]



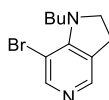
Method A (Small Scale)

To a suspension of NaH (0.88 g, 22 mmol) in THF (50 mL) was added a solution of 5-azaindoline **132** (0.53 g, 4.4 mmol) in THF (10 mL), and the reaction heated to 40 °C for 40 min. The solution was then cooled to -15 °C, 15-crown-5 (1.31 mL, 6.6 mmol) added, and stirred for 20 min. After adding bromobutane (0.57 mL, 5.3 mmol) and tetrabutylammonium iodide (0.33 g, 0.9 mmol), the resulting solution was heated at 40 °C for 3 h. The reaction was cooled to 0 °C, quenched with sat. NaHCO₃ solution (50 mL) and the organic solvent removed *in vacuo*. The aqueous phase was extracted with EtOAc (3 x 30 mL), washed with brine (50 mL), dried over Na₂SO₄, and the solvent removed *in vacuo*. The compound was purified by flash column chromatography (EtOAc:Et₃N 99:1→97:1) to give 1-butyl-5-azaindoline **133** as a yellow oil (0.50 g, 64%). *R*_f = 0.31 (EtOAc: Et₃N, 97:3); ¹H NMR (400 MHz, CDCl₃) δ_H 8.10 (d, *J* = 5.5 Hz, 1H), 8.02 (s, 1H), 6.25 (d, *J* = 5.5 Hz, 1H), 3.51 (t, *J* = 8.7 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 2H), 3.02 (t, *J* = 8.7 Hz, 2H), 1.57 (tt, *J* = 8.0, 6.7 Hz, 2H), 1.38 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); MS-(ES-API⁺) *m/z* (rel intensity) 177.0 (100%, M+H⁺). Data consistent with that reported previously.^[297]

Method B (Large Scale)

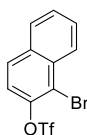
To a suspension of 5-azaindoline **132** (20 g, 168 mmol) in THF (500 mL) was added butyraldehyde (22.4 mL, 252 mmol) and acetic acid (19 mL, 336 mmol). The resulting solution was allowed to stir for 1 h, after which sodium triacetoxyborohydride (50 g, 236 mmol) was added portionwise and the reaction allowed to stir for a further 4 h. The solution was quenched with sat. NaHCO₃ solution (200 mL) and extracted with EtOAc (2 x 500 mL). The aqueous layer was basified with KOH to pH = 10, and extracted again with EtOAc (1 x 500 mL). The combined organic extracts were dried over Na₂SO₄, and the solvent removed *in vacuo* to give a yellow oil which was not purified further and taken straight through to the next reaction (27.64 g, 94% crude yield). Data as above.

7-Bromo-1-butyl-5-azaindoline (**134**)^[297]



To a solution of 1-butyl-5-azaindoline **133** (0.50 g, 2.84 mmol) in CH₂Cl₂ at -1 °C was added solid NBS (0.56 g, 3.12 mmol), and the resulting solution stirred at -1 °C for 24 h. The solvent was removed *in vacuo*, and the compound purified by flash column chromatography (EtOAc:Et₃N 99:1→97:1) to give 7-bromo-1-butyl-5-azaindoline **134** as a dark brown oil (0.54 g, 75%). *R*_f = 0.31 (EtOAc:Et₃N, 97:3); ¹H NMR (400 MHz, CDCl₃) 8.14 (s, 1H), 7.88 (s, 1H), 3.66 – 3.57 (4H), 3.01 (t, *J* = 9.1 Hz, 2H), 1.61 (m, 2H), 1.39 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); MS-(ES) *m/z* (rel intensity) 255.05 (100%, M+H⁺), 257.05 (90%). Data consistent with that reported previously.^[297]

1-Bromo-2-naphthol triflate (**135**)^[297]



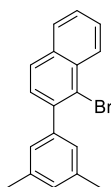
Small Scale

To a solution of 1-bromo-2-naphthol **100** (2.78 g, 11.90 mmol) in pyridine (10 mL) in a two-necked flask was added a solution of 4-DMAP (0.14 g, 1.19 mmol) in pyridine (2.5 mL). The solution was cooled to 0 °C and triflic anhydride (2.51 mL, 11.90 mmol) was added dropwise over 30 min. The resulting solution was stirred at 0 °C for 2.5 h before quenching with 1 M HCl (150 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were extracted with sat. NaHCO₃ solution (100 mL), dried over Na₂SO₄ and the organic solvent removed *in vacuo*. The compound was purified by flash column chromatography (petroleum ether→petroleum ether:EtOAc 9:1) to give the triflate **135** as a yellow oil which solidifies in the freezer (3.92 g, 93%). *R*_f = 0.4 (Petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ_H = 8.36 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.73 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.65 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 1H). Data consistent with that reported previously.^[297]

Large Scale

To a solution of 1-bromo-2-naphthol **100** (50 g, 224 mmol) in CH₂Cl₂ (250 mL) in a two-necked flask was added pyridine (2.6 mL, 448 mmol). The solution was cooled to 0 °C and triflic anhydride (45.2 mL, 269 mmol) was added slowly by dropping funnel over 60 min. The resulting solution was stirred at rt for 2 h before quenching with NaHCO₃ and extracted with CH₂Cl₂ (100 mL). The combined organic extracts were dried over Na₂SO₄ and the organic solvent removed *in vacuo* to give the triflate **135** as a brown oil which solidified in the freezer and was used without further purification (80 g, >99%). Data as above.

1-Bromo-2-(3,5-dimethylphenyl)naphthalene (**136**)^[297]



Small Scale

To a mixture of Mg turnings (1.28 g, 0.053 mol) in diethyl ether (40 mL) was added a crystal of I₂. The reaction was left to discolour, upon which 1-bromo-3,5-dimethyl benzene (5.98 g, 0.044 mol) was added slowly while heating at reflux. Once the reaction had started, the mixture was left to react at room temperature overnight.

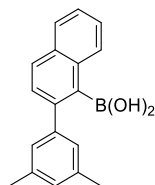
A solution of 1-bromo-2-naphthol triflate **135** (3.92 g, 11.0 mmol) and PdCl₂(dppp) (0.13 g, 0.22 mmol) in diethyl ether (80 mL) was heated at reflux for 5 min. The Grignard reagent was added slowly over 1 h, and refluxed for a further 1.5 h. The reaction was quenched with NH₄Cl, filtered through a Celite[®] pad and

washed with diethyl ether. The aqueous phase was extracted with diethyl ether (3×50 mL), dried over Na_2SO_4 , and the solvent removed *in vacuo*. The compound was purified by flash column chromatography (hexane:EtOAc 99:1), and recrystallised from hexane to give 1-bromo-2-(3,5-dimethylphenyl)naphthalene **136** as an off-white solid (2.28 g, 70%). $R_f = 0.2$ (hexane); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.43 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 8.1$ Hz, 1H), 7.64 (ddd, $J = 8.5, 6.9, 1.4$ Hz, 1H), 7.56 (ddd, $J = 8.1, 6.9, 1.2$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.10 (s, 2H), 7.08 (s, 1H), 2.41 (s, 6H). Data consistent with that reported previously.^[297]

Large Scale

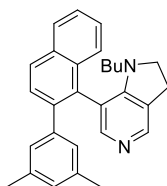
A solution of 1-bromo-2-naphthol triflate **135** (27 g, 76 mmol) and $\text{PdCl}_2(\text{dppp})$ (0.99 g, 1.71 mmol) in THF (45 mL) was heated at 55 °C for 5 min. A solution of 3,5-dimethylphenyl magnesium bromide (200 mL, 0.5 M in THF, 100 mmol) was added slowly over 1 h, and refluxed for 5 h. A further portion of the Grignard reagent (115 mL, 57.5 mmol) was added to the reaction and refluxed for a further 16 h. The reaction was quenched with NH_4Cl (200 mL), extracted with diethyl ether (3×300 mL), filtered through a Celite[®] pad and washed with diethyl ether. The combined organic fractions were dried over Na_2SO_4 , and the solvent removed *in vacuo*. The compound was recrystallised from hexane to give 1-bromo-2-(3,5-dimethylphenyl)naphthalene **136** as an off-white solid (15.4 g, 65%). Data as above.

2-(3,5-Dimethylphenyl)-1-naphthylboronic acid (**137**)^[297]



A solution of 1-bromo-2-(3,5-dimethylphenyl)naphthalene **136** (2.28g, 7.33 mmol) in diethyl ether (60 mL) was cooled to -78 °C, and *n*-BuLi (2.5 M, 3.52 mL, 8.79 mmol) was added dropwise. The reaction was allowed to stir at -78 °C for 30 min, and then warmed to 0 °C over 1.5 h. The reaction was then cooled again to -78 °C, and $\text{B}(\text{OMe})_3$ (1.63 mL, 14.65 mmol) was added dropwise, after which the reaction was stirred at rt for 17 h. The resulting solution was quenched with 1 M HCl (80 mL) at 0 °C and stirred for 45 min. The aqueous phase was extracted with diethyl ether (3×30 mL), and the combined organic phases washed with brine (50 mL), dried over Na_2SO_4 and the organic solvent removed *in vacuo*. The residue was triturated with pentane to give the boronic acid **137** as a white solid. The pentane filtrate was then purified by flash column chromatography (hexane:EtOAc 4:1→3:1) to give further portions of the boronic acid **137** as a white solid (1.1 g, 50%). $R_f = 0.24$ (hexane:EtOAc 4:1); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.16 (d, $J = 8.2$ Hz, 1H), 7.90 (t, $J = 8.6$ Hz, 2H), 7.63 – 7.44 (3H), 7.18 (s, 2H), 7.06 (s, 1H), 4.57 (s, 2H), 2.40 (s, 6H); MS-(ES) m/z (rel intensity) 232 (100%, $\text{M}-\text{B}(\text{OH})_2 + \text{H}^+$), 276 (30%, M^+). Data consistent with that reported previously.^[297]

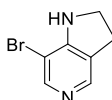
1-Butyl-7-[2-(3,5-dimethylphenyl)naphthalene-1-yl]-5-azaindoline (5-Azy* 131)^{3[297]}



7-Bromo-1-butyl-5-azaindoline **134** (100 mg, 0.39 mmol), 2-(3,5-dimethylphenyl)-1-naphthylboronic acid **137** (0.43 g, 1.56 mmol), KOH (0.39 g, 7.05 mmol), PEPPSI-*i*-Pr (26 mg, 0.039 mmol) were loaded into a 5 mL microwave vial and dried overnight over P₂O₅. The vial was purged with argon; dry degassed xylene (4.5 mL) was added and the reaction was stirred at room temperature for 15 min. The vial was heated in a microwave, for 10 min at 76 °C, 10 min at 100 °C, 15 min at 150 °C, and 35 min at 180 °C. The reaction was diluted with brine (5 mL) and sat. NaHCO₃ solution (5 mL), phase separated, and the aqueous phases extracted with EtOAc. The combined organic phases were filtered through Celite[®], dried over Na₂SO₄ and the solvent removed *in vacuo*. The compound was purified by flash column chromatography (EtOAc→EtOAc:Et₃N 95:5) to give 1-butyl-7-[2-(3,5-dimethylphenyl)naphthalene-1-yl]-5-azaindoline **131** as a yellow solid (114 mg, 72%). *R*_f = 0.2 (EtOAc:Et₃N, 95:5); ¹H NMR (400 MHz, CDCl₃) δ_H 7.97 (s, 1H), 7.92 (t, *J* = 8.7 Hz, 2H), 7.77 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.2, 6.8, 1.5 Hz, 1H), 6.87 (s, 2H), 6.83 (s, 1H), 3.49 (m, 1H), 3.35 (td, *J* = 9.9, 9.4, 6.6 Hz, 1H), 3.04 (ddd, *J* = 16.5, 10.2, 6.6 Hz, 1H), 2.95 (m, 1H), 2.52 (m, 2H), 2.23 (s, 6H), 1.12 (m, 1H), 0.80 (m, 1H), 0.62 (m, 1H), 0.47 (m, 1H), 0.33 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 155.89, 151.85, 142.43, 141.40, 140.14, 137.11, 133.28, 132.63, 132.19, 128.30, 128.23 (2C), 128.02, 127.68 (2C), 127.21, 126.50, 125.92, 125.05, 114.00, 52.03, 47.64, 29.97, 29.83, 25.57, 21.44, 19.61, 13.34; MS-(ES⁺) *m/z* (rel intensity) 407.25 (100 %, M+H⁺); HRMS (ES⁺) calcd. for C₂₉H₃₁N₂ (M+1) 407.2503, found 407.2487, (Δ=3.9 ppm). Data consistent with that reported previously.^[297]

HPLC conditions: OD-H column (100 x 250 mm), 35 °C, flow: 4 mL/min, eluent: hexane:(EtOAc:Et₂NH (99:1)) (85:15), detection: 254 nm. (-)-5-Azy* : 14 minutes. (+)-5-Azy*: 19 minutes. Sign of optical rotation determined by Mohan from CD measurement and assigned here according to residence time in HPLC.^[297]

7-Bromo-5-azaindoline (161)^[339]

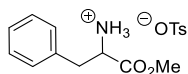


To a solution of 5-azaindoline **132** (5 g, 42.0 mmol) in CH₂Cl₂ (120 mL) at -1 °C was added solid NBS (8.22 g, 46.2 mmol), and the resulting solution stirred at -1 °C for 24 h. The solution was extracted with Na₂S₂O₃ solution (100 mL), sat. NaHCO₃ solution (100 mL), dried with Na₂SO₄ and filtered, and the solvent removed *in vacuo* to give a dark orange solid that required no further purification (3.52 g, 42%). ¹H NMR (400 MHz,

³ Absolute configuration of catalyst has not been established.

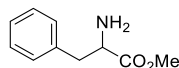
CDCl₃) δ_{H} 8.21 (s, 1H), 8.05 (s, 1H), 4.46 (s, 1H), 3.76 (t, $J = 8.7$ Hz, 3H), 3.22 (t, $J = 8.7$ Hz, 2H); MS-(ES-API⁺) m/z (rel intensity) 199.0(100%, M+H⁺), 201.00 (100%, M+H⁺). Data consistent with that reported previously.^[324,339]

(±)-Phenylalanine methyl ester tosylate Salt (139.OTs)^[3]



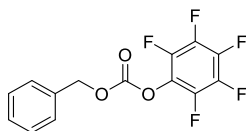
A solution of (±)-phenylalanine (1.5 g, 9.1 mmol) and tosic acid (2.57 g, 13.5 mmol) in methanol (1.9 mL) and benzene (35 mL) was heated at reflux in a Dean-Stark apparatus for 16 h. The organic solvent was removed *in vacuo*, and the viscous oil triturated with CH₂Cl₂ to give a white solid, which was filtered and washed with diethyl ether. The product was dried *in vacuo* to give (±)-phenylalanine methyl ester tosylate salt **29** as a white solid (2.55 g, 80%). ¹H NMR (400 MHz, DMSO-*d*₆) δ_{H} 8.40 (s, 2H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.39 – 7.29 (3H), 7.23 (2H), 7.12 (d, $J = 8.0$ Hz, 2H), 4.35 (s, 1H), 3.69 (s, 3H), 3.09 (m, 2H), 2.30 (s, 3H); MS-(ES⁺) m/z (rel intensity) 180.10 (60%, M-OTs+H⁺) 221.13 (60%) 223.18 (100%). Data consistent with that reported previously.^[3]

(±)-Phenylalanine methyl ester (139)^[340]



(±)-Phenylalanine methyl ester hydrochloride (0.2 g, 0.93 mmol) and K₂CO₃ (0.2 g) were dissolved in water (3 mL) and shaken vigorously. The aqueous layer was extracted with EtOAc (5 mL x 3), dried over Na₂SO₄, and the solvent removed *in vacuo* to give the free-based (±)-phenylalanine methyl ester **139** as a pale yellow oil (0.13 g, 80%) which was stored in the freezer and used within one week. ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.45 – 7.03 (5H), 3.76 (dd, $J = 7.9, 5.2$ Hz, 1H), 3.74 (s, 3H), 3.12 (dd, $J = 13.5, 5.2$ Hz, 1H), 2.89 (dd, $J = 13.5, 7.9$ Hz, 1H), 1.70 (s, 2H); MS-(ES⁺) m/z (rel intensity) 180.10 (100%, M+H⁺) 208.04 (40%) 221.13 (70%). Data consistent with that reported previously.^[340]

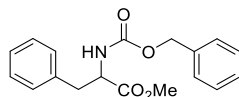
Benzyl pentafluorophenol carbonate (146)^[3]



Following a procedure from Davey^[3]: to a solution of pentafluorophenol (3.0 g, 16.3 mmol) and quinoline (1.92 mL, 16.3 mmol) in CH₂Cl₂ (25 mL) was added dropwise benzyloxycarbonyl chloride (1.92 mL, 13.0 mmol), and the resulting solution stirred at rt overnight. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography (petroleum ether:EtOAc 20:1) to give to give the carbonate **146** as a clear colourless oil which crystallised on standing (4.3 g, 65%). $R_f = 0.31$ (petroleum ether:EtOAc 20:1); ¹H NMR (400 MHz, CDCl₃) δ_{H} 7.51 – 7.34 (5H), 5.35 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) 151.31, 133.70,

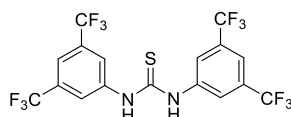
129.21, 128.84 (2C), 128.55 (2C), 72.13; ^{19}F NMR (377 MHz, CDCl_3) δ_{F} -152.96 (d, $J = 18.4$ Hz), -157.38 (t, $J = 21.7$ Hz), -161.94 (t, $J = 19.9$ Hz); MS-(Cl^-) m/z (rel intensity) 91 (100%) 108 (92%) 336 (25%, $\text{M}+\text{NH}_4^+$); HRMS (Cl^-) calcd. for $\text{C}_{14}\text{H}_{11}\text{NO}_3\text{F}_5$ ($\text{M}+\text{NH}_4^+$) 336.0659, found 336.0647, ($\Delta = -3.6$ ppm). Data consistent with that reported previously.^[3]

(±)-*N*-Benzyloxycarbonyl phenylalanine methyl ester (149)^[341]



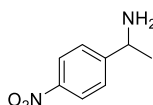
Following a procedure from Davey^[3]: to an ice-cold solution of (±)-phenylalanine methyl ester hydrochloride (0.6 g, 2.8 mmol) and Et_3N (0.86 mL, 6.2 mmol) in CH_2Cl_2 (10 mL) was added benzyl chloroformate (0.48 mL, 3.4 mmol) dropwise. The reaction was allowed to stir at room temperature for 16 h, after which it was diluted with CH_2Cl_2 (10 mL), washed with NaHCO_3 (10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo* to yield a white solid. This was purified by flash column chromatography (hexane:EtOAc 5:1) to yield a colourless solid **149** (0.52 g, 60%). $R_f = 0.25$ (hexane:EtOAc 5:1); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.43 – 7.20 (8H), 7.11 (dd, $J = 7.8, 1.7$ Hz, 2H), 5.23 (d, $J = 8.2$ Hz, 1H), 5.11 (m, 2H), 4.68 (m, 1H), 3.74 (s, 3H), 3.13 (qd, $J = 13.9, 5.9$ Hz, 2H); MS-(ES^+) m/z (rel intensity) 270.15 (40%) 314.13 (100%, $\text{M}+\text{H}^+$) 331.16 (35%). Data consistent with that reported previously.^[341]

***N,N'*-bis[3,5-bis(Trifluoromethyl)phenyl]thiourea (166)**^[316]



To a solution of 3,5-trifluoromethyl aniline (0.31 mL, 2.11 mmol) in THF (5 mL) was added 3,5-(trifluoromethyl)phenyl isothiocyanate (0.4 mL, 2.12 mmol), and the reaction heated to 50 °C for 80 h. The organic solvent was removed *in vacuo* to give a yellow oil, which was purified by flash column chromatography (petroleum ether: CH_2Cl_2 7:3) to give *N,N'*-bis-[3,5-bis(trifluoromethyl)phenyl]thiourea **32** as a white solid (1.05 g, >99%). $R_f = 0.4$ (petroleum ether: CH_2Cl_2 7:3); ^1H NMR (400 MHz, CDCl_3) δ_{H} = 10.65 (s, 2H), 8.20 (s, 4H), 7.87 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 180.57, 141.15, 130.33 (q, $J = 32.8$ Hz), 124.11, 123.16 (q, $J = 1084.4$), 119.08; MS-(ES^+) m/z (rel intensity) 498 (100%) 499 (28%). Data consistent with that reported previously.^[316]

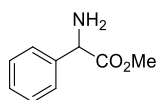
(±)- α -Methyl-4-nitrobenzylamine (169)^[342]



A procedure was adapted from the method of Saigo^[318] as follows: to a solution of 4-nitroacetophenone (1.0 g, 6 mmol) in MeOH (15 mL) was added ammonium acetate (5.82 g, 75.6 mmol) in one portion, and the

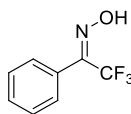
solution stirred for 2 h. Sodium cyanoborohydride (0.26g, 4.24 mmol) was added in one portion, and the resulting solution stirred for 48 h. The reaction was quenched with 6 M HCl (5 mL), and washed with Et₂O. The aqueous layer was basified with KOH to pH=10, and washed with CH₂Cl₂ (3 x 10 mL). The combined organic phases were dried over Na₂SO₄ and the solvent removed *in vacuo* to yield crude product, which was purified by flash column chromatography (hexane:CH₂Cl₂ 3:1→CH₂Cl₂) to yield (±)-α-methyl-4-nitrobenzylamine **169** (0.48 g, 47%). *R_f* = 0.15 (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 8.19 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 4.27 (q, *J* = 6.6 Hz, 1H), 1.99 (s, 2H), 1.41 (d, *J* = 6.6 Hz, 3H); MS-(ES⁺) *m/z* (rel intensity) 167.08 (42 %, M+H⁺) 208.10 (100%); HRMS (ES⁺) calcd. for C₈H₁₁N₂O₂ (M+1) 167.0813, found 167.0821, (Δ=-4.8 ppm). Data consistent with that reported previously.^[21]

(±)-Phenylglycine methyl ester (**170**)^[343]

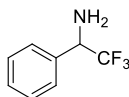


To a solution of (±)-phenylglycine (0.5 g, 3.3 mmol) in methanol (5 mL) at 0 °C was added dropwise thionyl chloride (0.35 mL, 4.9 mmol) and the resulting solution was stirred at rt for 48 hours. The solvent was removed *in vacuo*, the residue slurried in Et₂O, filtered and dried to give phenylglycine methyl ester hydrochloride salt in quantitative yield. The salt was dissolved in water (10 mL) and K₂CO₃ and the solution washed with EtOAc. The combined organic layers were dried over Na₂SO₄ and the solvent removed *in vacuo* to yield (±)-phenylglycine methyl ester **170** as a yellow solid (0.32 g, 60% yield). ¹H NMR (400 MHz, CDCl₃) δ_H 7.47 – 7.28 (5H), 4.64 (s, 1H), 3.71 (s, 3H), 2.10 (s, 2H); MS-(ES⁺) *m/z* (rel intensity) 166.09 (83 %, M+H⁺) 207.11 (100%); HRMS (ES⁺) calcd. for C₉H₁₂NO₂ (M+1) 166.0870, found 166.0869, (Δ=1.2 ppm). Data consistent with that reported previously.^[344]

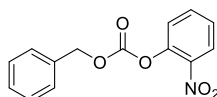
(*E*)- and (*Z*)-α-Trifluoromethylbenzyloxime (**178**)



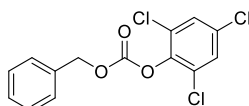
Following a procedure from Masher^[320]: to a solution of 2,2,2-trifluoroacetophenone (1.85 mL, 13.3 mmol) in water (9 mL) was added NH₂OH.HCl (1.67 g, 24.0 mmol), sodium acetate (2.49 g, 30.6 mmol) and enough EtOH to yield a homogeneous mixture. The resulting solution was heated at 85 °C for 3 h. EtOH was removed *in vacuo*, the water layer extracted with Et₂O (3 x 10 mL) and the combined organic phases dried over Na₂SO₄ and the solvent removed *in vacuo* to yield α-trifluoromethylbenzyloxime **178** in quantitative yield (0.54 g, >99%). ¹H NMR (400 MHz, CDCl₃) δ_H 8.52 (br s, 1H), 7.63 – 7.39 (5H). Data consistent with that reported previously, (*E*)/(*Z*)-stereochemistry undefined.^[320] This material was not purified further and taken straight through to the reduction.

(±)- α -Trifluoromethylbenzylamine (171)^[345]

Following a procedure from Masher^[320]: Oxime **178** (2.4 g, 13.3 mmol) was dissolved in Et₂O (4 mL) and AcOH (4 mL), and to the resulting solution was added Pd/C (0.70 g), and the mixture was stirred at rt with H₂ (1 atm) for 17 h. The mixture was then filtered through Celite[®], washed with 2 M NaOH solution (10 mL), dried over Na₂SO₄ and the solvent removed *in vacuo* at rt. The crude product was purified by distillation (100 °C, 19 mbar) to yield (±)- α -trifluoromethylbenzylamine **171** (1.62 g, 70%). ¹H NMR (400 MHz, CDCl₃) δ _H 7.54 – 7.33 (5H), 4.40 (q, *J* = 7.5 Hz, 1H), 1.80 (s, 2H); ¹⁹F NMR (377 MHz, CDCl₃) δ _F -76.70 (d, *J* = 7.4 Hz); MS-(ES⁺) *m/z* (rel intensity) 176.07 (25%, M+H⁺) 200.07 (53%) 217.08 (100%); HRMS (ES⁺) calcd. for C₈H₉NF₃ (M+1) 176.0693, found 176.0687, (Δ =3.4 ppm). Data consistent with that reported previously.^[345]

Benzyl 2-nitrophenol carbonate (180)^[322]

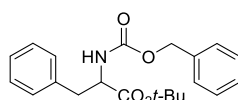
To a solution of nitrophenol (0.5 g, 3.6 mmol) in THF at 0 °C was added dropwise benzyloxycarbonyl chloride (0.53 mL, 3.8 mmol) and Hünig's base (0.74 mL, 4.3 mmol), and the resulting solution stirred at rt for 16 h. The solvent was removed *in vacuo*, and the residue diluted with EtOAc. The solution was washed with 1 M aq. Citric acid (5 mL), sat. NaHCO₃ solution (10 mL), 2 M NaOH solution (10 mL), dried over Na₂SO₄ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (petroleum ether:EtOAc 9:1) to give the carbonate **180** as a yellow solid (0.46 g, 46%). *R*_f = 0.25 (petroleum ether:EtOAc 9:1); ¹H NMR (400 MHz, CDCl₃) δ _H 8.14 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.68 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.49 – 7.38 (6H), 7.35 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.34 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ _C 152.65, 144.44, 135.09, 134.43, 129.05, 128.86, 128.67, 127.14, 126.14, 125.00, 71.42; MS-(CI⁺) *m/z* (rel intensity) 91 (100%) 291 (12%, M+NH₄⁺); HRMS (CI⁺) calcd. for C₁₄H₁₅N₂O₅ (M+NH₄) 291.0981, found 291.0994, (Δ =4.5 ppm); IR (neat) ν _{max} 3075, 3035 (Ar C-H), 1762 (C=O), 1210 (C-O), 733 (C-Cl); Mp: 44.0 – 46.8 °C.

Benzyl trichlorophenol carbonate (181)^[346]

A procedure was adapted from the method of Frankel^[346] and Davey^[3] as follows: to a solution of trichlorophenol (3.0 g, 15.2 mmol) and quinoline (1.79 mL, 15.2 mmol) in CH₂Cl₂ (30 mL) was added dropwise benzyloxycarbonyl chloride (1.7 mL, 12.1 mmol), and the resulting solution stirred at rt for 48 h. The solution was washed with NaHCO₃ (10 mL), 2 M NaOH solution (10 mL), dried over Na₂SO₄ and the

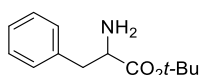
solvent removed *in vacuo*. The residue was purified by flash column chromatography (petroleum ether:EtOAc 9:1) to give the carbonate **181** as a yellow oil (1.96 g, 49%). R_f = 0.4 (petroleum ether:EtOAc 9:1); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.49 – 7.35 (5H), 7.39 (s, 2H), 5.34 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) 151.50, 143.08, 134.42, 132.50, 129.76, 129.06, 128.85, 128.49, 71.54; MS-(Cl^+) m/z (rel intensity) 108 (52%) 291 (52%) 348 (100%, $\text{M}+\text{NH}_4^+$) 350 (98%); HRMS (Cl^+) calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{Cl}_3$ ($\text{M}+\text{NH}_4^+$) 347.9961, found 347.9975, (Δ =4.0 ppm); IR (neat) ν_{max} 1765 (C=O), 1528 (N=O, as), 1347 (NO, s) 1206 (C-O); Mp: 62.0 – 65.2 °C.

(±)-*N*-Benzyloxycarbonyl phenylalanine *tert*-butyl ester (185**)**^[347] [CAS: 7670-20-4]



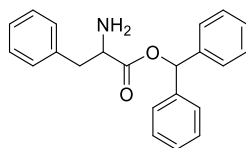
To a solution of (±)-*N*-benzyloxycarbonyl phenylalanine (2.0 g, 6.7 mmol) and di-*tert*-butyl dicarbonate (2.92 g, 13.4 mmol) in *tert*-butanol (10 mL) was added 4-DMAP (0.245 g, 2.0 mmol) in one portion. The reaction was stirred at 35 °C for 3 h, and at rt for a further 16 h. The solution was diluted with CH_2Cl_2 , washed with sat. NaHCO_3 solution (10 mL), water (10 mL) and brine (10 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:EtOAc 9:1) to give (±)-*N*-benzyloxycarbonyl phenylalanine *tert*-butyl ester **185** as a pale yellow oil that crystallised on standing (2.01 g, 84%). R_f = 0.26 (hexane:EtOAc (9:1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.43 – 7.11 (10H), 5.27 (d, J = 8.0 Hz, 1H), 5.12 (m, 2H), 4.56 (dt, J = 8.0, 6.0 Hz, 1H), 3.11 (d, J = 6.0 Hz, 2H), 1.42 (s, 9H); MS-(ES^+) m/z (rel intensity) 300.12 (90%, $\text{M}-t\text{-Bu}+\text{H}^+$) 356.13 (25%, $\text{M}+\text{H}^+$) 378.16 (100%, $\text{M}+\text{Na}^+$) 419.19 (50%). Data consistent with that reported previously.^[14]

(±)-Phenylalanine *tert*-butyl ester (186**)**^[348] [CAS: 16874-17-2]



To a solution of (±)-*N*-benzyloxycarbonyl phenylalanine *tert*-butyl ester **185** (1.0 g, 2.8 mmol) in EtOAc (65 mL) was added 10 % Pd/C (100 mg). The reaction vessel was evacuated and flushed with hydrogen, and stirred for 17 h with a 1 atm H_2 atmosphere. The solution filtered through Celite® and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:EtOAc 5:1) to give (±)-phenylalanine *tert*-butyl ester **186** as a yellow oil (0.55 g, 90%). R_f = 0.13 (hexane:EtOAc (5:1)); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.44 – 7.17 (5H), 3.65 (dd, J = 7.7, 5.7 Hz, 1H), 3.08 (dd, J = 13.5, 5.7 Hz, 1H), 2.89 (dd, J = 13.5, 7.7 Hz, 1H), 1.56 (s, 2H) 1.47 (s, 9H); MS-(ES^+) m/z (rel intensity) 166.09 (95%) 207.11 (100%) 222.15 (58%, $\text{M}+\text{H}^+$). Data consistent with that reported previously.^[348]

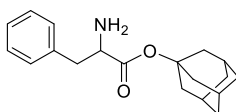
(±)-Phenylalanine diphenylmethyl ester (**187**)



Following a procedure from Fruton^[325] and Schroeder^[327], (±)-phenylalanine (0.5 g, 3.02 mmol) and *p*-toluenesulfonic acid monohydrate (0.55 g, 3.17 mmol) were dissolved in water (30 mL) and heated/stirred to obtain a clear solution. The solvent was removed *in vacuo*, and the tosyl salt was recrystallised from hot acetone (0.55 g, 1.62 mmol, 54%).

To a solution of benzophenone hydrazone (0.37 g, 1.88 mmol) in petroleum ether (7.5 mL) was added Ag₂O (0.45 g, 1.95 mmol) and MgSO₄ (0.3 g). The solution was stirred for 30 minutes in a water bath, cooling occasionally to keep at 30 °C. The suspension was filtered through a sinter funnel to remove the Ag₂O and MgSO₄, to yield a bright purple solution of diphenyldiazomethane. The tosyl salt was dissolved in DMF (2 mL) and the diphenyldiazomethane solution added to the reaction. The resulting solution was stirred for 10 minutes, and quenched with 1 M citric acid. The aqueous solution was basified with sat. NaHCO₃ solution (20 mL), and extracted with CH₂Cl₂ to yield the free (±)-phenylalanine diphenylmethyl ester. The resulting oil was purified by flash column chromatography (hexane:EtOAc 4:1) to give (±)-phenylalanine diphenylmethyl ester **187** as a yellow oil that crystallised on standing. (0.39 g, 73%). *R_f* = 0.1 (Hexane:EtOAc (4:1)); ¹H NMR (400 MHz, CDCl₃) δ_H 7.42 – 7.21 (13H), 7.16 – 7.09 (2H), 6.95 (s, 1H), 3.89 (dd, *J* = 7.4, 5.6 Hz, 1H), 3.16 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.95 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.56 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_C 174.16, 139.83, 139.75, 136.91, 129.35, 128.55, 128.03, 127.27, 127.15, 126.80, 77.44, 55.89, 40.82; MS-(ES⁺) *m/z* (rel intensity) 167.08 (70 %) 332.16 (100%, M+H⁺); HRMS (ES⁺) calcd. for C₂₂H₂₂NO₂ (M+1) 332.1651, found 332.1654, (Δ=0.9 ppm); IR (neat) ν_{max} 1734 (C=O), 1264, 1224 (C-O), 703 (N-H); Mp: 74.4 – 76.9 °C.

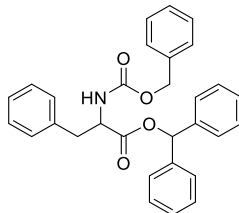
(±)-Phenylalanine adamantyl ester (**188**)



To a solution of (±)-*N*-benzyloxycarbonyl phenylalanine adamantyl ester **190** (0.39 g, 0.86 mmol) in EtOAc (20 mL) was added 10 % Pd/C (30 mg). The reaction vessel was evacuated and flushed with hydrogen, and stirred for 17 h with a 1 atm H₂ atmosphere. The solution filtered through Celite[®] and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:EtOAc 5:1) to give (±)-phenylalanine adamantyl ester **188** as a yellow oil (0.19 g, 77%). *R_f* = 0.05 (hexane:EtOAc 9:1); ¹H NMR (400 MHz, CDCl₃) δ_H 7.42 – 7.13 (5H), 3.62 (dd, *J* = 7.6, 5.6 Hz, 1H), 3.05 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.86 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.17 (s, 3H), 2.08 (m, 6H), 1.87 (s, 2H) 1.67 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ_C 174.06, 137.57, 129.43, 128.42, 126.66, 81.25, 56.32, 41.28, 41.25, 36.14, 30.84; MS-(ES⁺) *m/z* (rel intensity) 300.19 (100 %, M+H⁺) 341.22 (50%); HRMS (ES⁺) calcd. for C₁₉H₂₆NO₂ (M+1) 300.1964, found

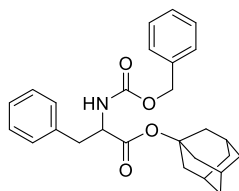
30.1958, (Δ =-2.0 ppm); IR (neat) $\nu_{\max}$ 2913, 2854 (C-H), 1725 (C=O), 1265 (C-O), 735 (N-H); Mp: 42.9 – 45.3 °C.

(±)-*N*-Benzyloxycarbonyl phenylalanine diphenylmethyl ester (189)



A procedure was adapted from the method of Steglich^[326] as follows: To a solution of DCC, (±)-*N*-benzyloxycarbonyl phenylalanine (0.5 g, 1.72 mmol) and diphenylmethanol (0.95 g, 5.16 mmol, 3 eq.) in CH₂Cl₂ (5 mL) at 0 °C was added DCC (0.38 g, 1.85 mmol, 1.1 eq.) and 4-DMAP (0.018 g, 0.15 mmol, 0.1 eq.). The reaction was stirred at 0 °C for 5 minutes, and at rt 20 h. The solution was filtered, stirred with 1 M HCl (10 mL) overnight, washed with sat. NaHCO₃ solution (10 mL), dried over Na₂SO₄, and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:EtOAc 9:1) to give the product and diphenylmethanol. The mixture was re-subjected to purification by column chromatography (hexane:CH₂Cl₂ 6:4) to give (±)-*N*-benzyloxycarbonyl phenylalanine diphenylmethyl ester **189** as a yellow oil (0.42 g, 54%). R_f = 0.4 (hexane:EtOAc 4:1); ¹H NMR (400 MHz, CDCl₃) δ_H 7.46 – 7.27 (18H), 7.18 (dt, J = 14.1, 6.9 Hz, 2H), 6.91 (s, 1H), 5.23 (d, J = 8.3 Hz, 1H), 5.11 (m, 2H), 4.83 (dt, J = 8.3, 5.8 Hz, 1H), 3.15 (dt, J = 14.0, 5.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ_C 170.61, 155.61, 139.39, 136.22, 135.33, 129.37, 128.61, 128.53, 128.24, 128.19, 128.09, 128.04, 127.59, 127.02, 126.96, 78.13, 67.00, 54.79, 38.04; MS-(ES⁺) m/z (rel intensity) 483.2301 (100%, M+NH₄⁺); HRMS (ES⁺) calcd. for C₃₀H₃₁N₂O₄ (M+NH₄) 483.2284, found 483.2301, (Δ =3.5 ppm); IR (neat) $\nu_{\max}$ 3424 (br, N-H), 3030 (Ar C-H), 1711 (C=O), 1245 (C-O), 1043 (C-N) 740, 697 (N-H); Mp: 83.2 – 87.5 °C.

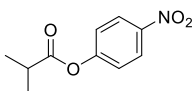
(±)-*N*-Benzyloxycarbonyl phenylalanine adamantyl ester (190)



A procedure was adapted from the method of Steglich^[326] as follows: To a solution of DCC, (±)-*N*-benzyloxycarbonyl phenylalanine (0.5 g, 1.72 mmol) and 1-adamantonol (0.75 g, 5.16 mmol, 3 eq.) in CH₂Cl₂ (3 mL) at 0 °C was added DCC (0.38 g, 1.85 mmol, 1.1 eq.) and 4-DMAP (0.018 g, 0.15 mmol, 0.1 eq.). The reaction was stirred at 0 °C for 5 minutes, and at rt 20 h. The solution was filtered, stirred with 1 M HCl (5 mL) overnight, washed with sat. NaHCO₃ solution (10 mL), dried over Na₂SO₄, and the solvent removed *in vacuo*. The resulting oil was purified by flash column chromatography (hexane:EtOAc 9:1) to give (±)-*N*-benzyloxycarbonyl phenylalanine adamantyl ester **190** as a yellow oil (0.42 g, 54%). R_f = 0.32

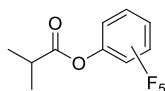
(hexane:EtOAc 9:1); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.41-7.22 (8H), 7.15 (d, $J = 6.4$ Hz, 2H), 5.21 (d, $J = 8.0$ Hz, 1H), 5.11 (m, 2H), 4.53 (dt, $J = 8.0, 5.8$ Hz, 1H), 3.09 (d, $J = 5.8$ Hz, 2H), 2.16 (s, 3H), 2.05 (s, 6H), 1.65 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 170.18, 155.58, 136.42, 136.08, 129.56, 128.50, 128.38, 128.09, 126.92, 82.37, 66.82, 55.20, 41.22, 38.42, 36.06, 30.85; MS-(ES^+) m/z (rel intensity) 434.23 (100 %, $\text{M}+\text{H}^+$) 456.21 (50%, $\text{M}+\text{Na}^+$) HRMS (ES^+) calcd. for $\text{C}_{27}\text{H}_{32}\text{NO}_4$ ($\text{M}+1$) 434.2331, found 434.2328, ($\Delta = -0.7$ ppm); IR (neat) ν_{max} 3340 (br, N-H), 2911, 2853 (C-H), 1718 (C=O), 1254, 1207 (C-O), 1052 (C-N) 747, 698 (N-H); Mp: 59.6 – 61.6 $^{\circ}\text{C}$.

***p*-Nitrophenyl isobutyrate (191)**^[349]

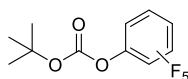


A procedure was adapted from the method of Davey^[3] as follows: To an ice-cold solution of pentafluorophenol (0.75 g, 5.4 mmol) and Et_3N (0.83 mL, 6.0 mmol) in CH_2Cl_2 (10 mL) was added isobutyryl chloride (0.42 mL, 6.0 mmol) dropwise. The resulting solution was allowed to stir at room temperature for 3 h, after which it was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL), brine (10 mL) and the solvent removed *in vacuo*. The resulting solid was purified by flash column chromatography, eluting with hexane to give ester **191** as a white solid (0.9 g, 79%). $R_f = 0.4$ (hexane:EtOAc 9:1); ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.29 (d, $J = 9.1$ Hz, 2H), 7.29 (d, $J = 9.1$ Hz, 2H), 2.87 (hept, $J = 7.0$ Hz, 1H), 1.36 (d, $J = 7.0$ Hz, 6H); MS-(APCI^+) m/z (rel intensity) 180 (100%); HRMS (APCI^+) calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_2\text{N}$ ($\text{M}+\text{NH}_3-\text{NO}_2$ decomposition product) 180.09, found 180.1014, ($\Delta = 2.8$ ppm). Data consistent with that reported previously.^[349]

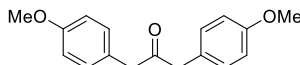
Pentafluorophenyl isobutyrate (192)^[350]



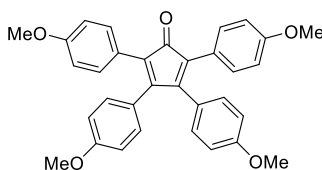
A procedure was adapted from the method of Davey^[3] as follows: To an ice-cold solution of pentafluorophenol (1.0 g, 5.4 mmol) and Et_3N (0.83 mL, 6.0 mmol) in CH_2Cl_2 (10 mL) was added isobutyryl chloride (0.42 mL, 6.0 mmol) dropwise. The resulting solution was stirred at room temperature for 3 hours, after which it was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL), brine (10 mL) and the solvent removed *in vacuo*. The resulting solid was purified by flash column chromatography, eluting with hexane to give ester **192** as a white solid (200 mg, 15%). $R_f = 0.7$ (hexane); ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.94 (hept, $J = 7.0$ Hz, 1H), 1.36 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 173.04, 33.77, 18.80; ^{19}F NMR (377 MHz, CDCl_3) δ_{F} -153.52 (d, $J = 18.4$ Hz), -158.59 (t, $J = 21.7$ Hz), -162.76 (t, $J = 20.0$ Hz). Data consistent with that reported previously.^[350]

***tert*-Butyl pentafluorophenyl carbonate (193)**^[329]

Following a procedure from Chandrasekaran^[329]: to an ice-cold solution of pentafluorophenol (0.92 g, 5 mmol) and 4-DMAP (0.61 g, 5 mmol) in CH₂Cl₂ (15 mL) was added di-*tert*-butyldicarbonate (1.09 g, 5 mmol) dropwise. The solution was allowed to stir at room temperature for 5 h, after which it was diluted with CH₂Cl₂ (20 mL), washed with sat. citric acid solution (30 mL), water (30 mL), brine (30 mL) and the solvent removed *in vacuo*. The resulting solid was purified by flash column chromatography, eluting with hexane:CH₂Cl₂ (10→100%) to give carbonate **193** as a white solid (1.07 g, 75%). *R*_f = 0.8 (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 1.59 (s, 9H); ¹⁹F NMR (377 MHz, CDCl₃) δ_F -41.81 (d, *J* = 17.2 Hz, 2F), -46.70 (t, *J* = 21.7 Hz, 1F), -50.80 – -50.99 (2F). Data consistent with that reported previously.^[349]

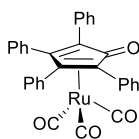
1,3-bis(4-Methoxyphenyl)-2-propanone^[230]

Following a procedure from Bäckvall^[230]: To a solution of 4-methoxyphenyl acetic acid in dry CH₂Cl₂ was added 4-DMAP (2.8 g, 22.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) hydrochloride (6.7 g, 35.1 mmol). The resulting solution was allowed to stir for 48 h, after which it was diluted with H₂O (30 mL), washed with 1 M HCl (2 x 30 mL), sat. NaHCO₃ solution (30 mL), dried over Mg₂SO₄ and the organic solvent removed *in vacuo*. The resulting yellow solid was used without further purification (3.44 g, 72%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.09 (d, *J* = 8.6 Hz, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 3.83 (s, 6H), 3.67 (s, 4H). Data consistent with that reported previously.^[351]

2,3,4,5-Tetrakis(4-methoxyphenyl)cyclopentadienone^[230]

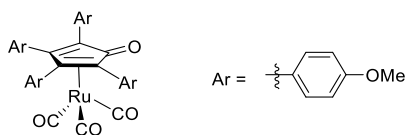
Following a procedure from Bäckvall^[230]: To a solution of 1,3-bis(4-methoxyphenyl)-2-propanone (3.44 g, 12.7 mmol) and 1,2-di(4-methoxyphenyl)benzyl (3.44 g, 12.7 mmol) in EtOH (47 mL) was added 2 M NaOH solution (34.4 mL) slowly. The resulting solution was heated at 80 °C for 2 hours, during which a black precipitate was formed. After 2 hours, the precipitate was filtered, washed with EtOH (30 mL) and hexane (50 mL) and dried *in vacuo*, to yield the product as a dark greenish black solid (5.7 g, 89%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.21 (d, *J* = 8.8 Hz, 4H), 6.88 (d, *J* = 8.7 Hz, 4H), 6.81 (d, *J* = 8.8 Hz, 4H), 6.74 (d, *J* = 8.7 Hz, 4H), 3.81 (s, 21H). MS-(ES⁺) *m/z* (rel intensity) 505 (100%, M+H⁺). Data consistent with that reported previously.^[351]

Tricarbonyl (2,3,4,5-tetrakis-cyclopentadienone) Ruthenium (203a)



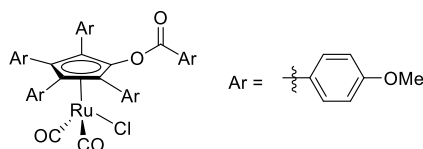
A procedure was adapted from the method of Park^[234] as follows: A suspension of 2,3,4,5-tetrakis-cyclopentadienone (1.8 g, 4.68 mmol) and $\text{Ru}_3(\text{CO})_{12}$ (1.0 g, 1.56 mmol) in dry toluene (15 mL) was heated under argon at 130 °C for 24 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (Hexane: CH_2Cl_2 1:1 $\rightarrow$ CH_2Cl_2 $\rightarrow$ EtOAc) to yield the product as a dark yellow solid (2.25 g, 85%). R_f = 0.15 (CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.52 – 7.43 (4H), 7.29 – 7.15 (9H), 7.12 (t, J = 7.6 Hz, 4H), 7.06 (d, J = 7.3 Hz, 4H); MS-(Maldi⁺) m/z (rel intensity) 871.4 (25%, $\text{M}-3\text{CO}+\text{cyclopentadienone}^+$), 973.3 (100%, $2\text{M}-6\text{CO}^+$). *NB.* The product was not isolated by Park.

Tricarbonyl (2,3,4,5-tetrakis(4-methoxyphenyl)cyclopentadienone) Ruthenium (203b)^[234]



A procedure was adapted from the method of Park^[234] as follows: A suspension of 2,3,4,5-tetrakis(4-methoxyphenyl)cyclopentadienone (0.68 g, 1.35 mmol) and $\text{Ru}_3(\text{CO})_{12}$ (0.28 g, 0.45 mmol) in dry toluene (5 mL) was heated under argon at 130 °C for 48 h. The resulting yellow suspension was filtered to remove any unreacted any $\text{Ru}_3(\text{CO})_{12}$ and purified by flash column chromatography (Hexane: CH_2Cl_2 2:1 to CH_2Cl_2 to EtOAc) to yield the product as a dark yellow solid (0.626 g, 67%). R_f = 0.15 (CH_2Cl_2) ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.43 (d, J = 8.8 Hz, 4H), 7.00 (d, J = 8.7 Hz, 4H), 6.81 (d, J = 8.8 Hz, 4H), 6.68 (d, J = 8.7 Hz, 4H), 3.82 (s, 6H), 3.78 (s, 6H). MS-(Maldi⁺) m/z (rel intensity) 505.2 (30%, $\text{Cyclopentadienone}+\text{H}^+$) 1213 (80%, $2\text{M}-6\text{CO}^+$). *NB.* The product was not isolated by Park.

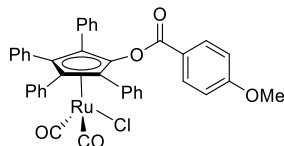
Chlorodicarbonyl (2,3,4,5-tetrakis(4-methoxyphenyl)cyclopentadienone) Ruthenium (II) (84)



A procedure was adapted from the method of Park^[234] as follows: A solution of tricarbonyl (2,3,4,5-tetrakis(4-methoxyphenyl)cyclopentadienone) ruthenium (0.64 g, 0.93 mmol) and 4-methoxy benzoyl chloride (0.32 g, 1.86 mmol) in dry toluene (5 mL) was heated under argon at 110 °C for 20 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (Hex $\rightarrow$ CH_2Cl_2 $\rightarrow$ EtOAc) to yield ruthenium catalyst **84** as a bright yellow solid (0.6015 g, 77%). R_f = 0.4 (CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.95 (d, J = 8.9 Hz, 2H), 7.27 (d, J = 8.9 Hz, 4H), 7.01 (d, J = 8.8 Hz, 4H), 6.90 (d, J = 8.9 Hz,

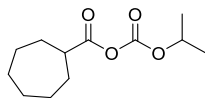
2H), 6.72 (d, $J = 8.9$ Hz, 4H), 6.67 (d, $J = 8.8$ Hz, 4H), 3.87 (s, 3H), 3.77 (s, 6H), 3.75 (s, 6H). MS-(Maldi⁺) m/z (rel intensity) 741 (100%, M-2CO-Cl⁺). Data consistent with that reported previously.^[234]

Chlorodicarbonyl (2,3,4,5-tetrakis-cyclopentadienone) Ruthenium (II) (202)



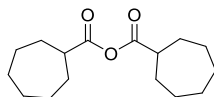
A procedure was adapted from the method of Park^[234] as follows: A solution of tricarbonyl (2,3,4,5-tetrakis-cyclopentadienone) ruthenium (1.96 g, 3.45 mmol) and 4-methoxy benzoyl chloride (1.17 g, 6.90 mmol) in dry toluene (10 mL) was heated under argon at 100 °C for 6 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (Hexane→CH₂Cl₂→EtOAc) to yield ruthenium catalyst **202** as a bright yellow solid (1.8 g, 75%). $R_f = 0.2$ (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.94 (d, $J = 8.9$ Hz, 2H), 7.37 (d, $J = 6.6$ Hz, 4H), 7.28 – 7.17 (8H), 7.14 (t, $J = 7.7$ Hz, 4H), 7.10 – 7.05 (4H), 6.89 (d, $J = 8.9$ Hz, 2H), 3.87 (s, 3H); MS-(Maldi⁺) m/z (rel intensity) 621 (55%, M-Cl-2CO⁺), 677 (10%, M-Cl⁺), 846 (2M-2CO-cyclopentadiene⁺). Data consistent with that reported previously.^[234]

Cycloheptylcarboxylic (isopropyl carbonic) anhydride (200)



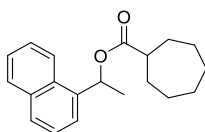
A procedure was adapted from the method of Fu^[291] as follows: cycloheptane carboxylic acid (1.55 mL, 10.5 mmol) was added to a solution of anhydrous Et₂O (30 mL) and Et₃N (2.4 mL, 17.4 mmol) at room temperature. To this solution was added dropwise isopropyl chloroformate (19.2 mL, 19.2 mmol; 1.0 M in toluene; Aldrich). The reaction mixture was stirred for 4 hours. The organic layer was washed with sat. NaHCO₃ solution (3 x 30 mL), and brine (3 x 30 mL). The organic solvent was evaporated *in vacuo*, to provide acyl carbonate **201** as a clear pale yellow oil which was used without further purification (2.0 g, 60% yield). ¹H NMR (400 MHz, CDCl₃) δ_H 5.02 (hept, $J = 6.3$ Hz, 1H), 2.62 (tt, $J = 9.2, 4.5$ Hz, 1H), 2.03 (dddd, $J = 10.5, 6.0, 4.5, 3.2$ Hz, 2H), 1.82 – 1.69 (4H), 1.63 – 1.49 (6H), 1.38 (d, $J = 6.3$ Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ_C 171.27, 148.97, 74.13, 44.86, 30.09, 28.23, 26.12, 21.47; MS-(ES⁺TOF) m/z (rel intensity) 143 (65%) 292 (100%, M+CH₃CN+Na⁺) 330 (75%); HRMS (ES⁺) calcd. for C₁₄H₂₃NO₄Na (M+CH₃CN+Na adduct) 292.1525, found 292.1531, ($\Delta = 2.1$ ppm); IR (neat) ν_{max} 2934, 2857 (C-H), 1807, 1745 (C=O), 1068, 988 (C-O).

Dicycloheptane carboxylic anhydride^[297]



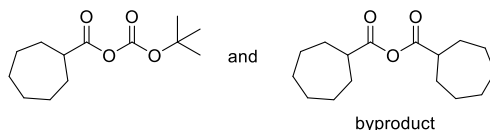
Following the procedure for dicyclohexane carboxylic anhydride **207**, to a solution of DCC (0.725 g, 3.51 mmol) in CH₂Cl₂ (5 mL) was added a solution of cycloheptane carboxylic acid (0.96 mL, 7.03 mmol) in CH₂Cl₂ (3 mL) at 0 °C. The solution was stirred at rt for 24 hours, during which a white precipitate was formed. The solution was filtered, washed with 2 M NaOH solution (2 x 10 mL) and brine (10 mL), and the solvent removed *in vacuo* to yield the anhydride as a clear oil (0.63 g, 67%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.60 (tt, *J* = 9.1, 4.5 Hz, 2H), 2.08 – 1.92 (4H), 1.85 – 1.66 (8H), 1.67 – 1.41 (12H); ¹³C NMR (101 MHz, CDCl₃) δ_C 172.68, 45.77, 30.05, 28.28, 26.16. Data consistent with that reported previously.^[297]

(±)-1-(1-Naphthyl)ethyl cycloheptylcarboxylic acetate (**201**)



Prepared according to general procedure for KR using (±)-1-(1-naphthylethanol) **26** and dicycloheptane carboxylic anhydride, isolated as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ_H 8.11 (d, *J* = 8.3 Hz, 1H), 7.89 (m, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 6.9 Hz, 1H), 7.59 – 7.46 (3H), 6.67 (q, *J* = 6.6 Hz, 1H), 2.57 (ddd, *J* = 13.7, 9.4, 4.3 Hz, 1H), 1.98 (m, 2H), 1.82 – 1.65 (4H), 1.72 (d, *J* = 6.6 Hz, 3H), 1.64 – 1.42 (6H); ¹³C NMR (101 MHz, CDCl₃) δ_C 176.23, 137.68, 133.82, 130.33, 128.85, 128.32, 126.20, 125.63, 125.35, 123.26, 123.13, 68.93, 45.25, 30.82 (2 C), 28.33, 28.27, 26.36, 26.33, 21.66; MS-(CI) *m/z* (rel intensity) 155 (100%) 172 (60%) 296 (10%, M⁺) 314 (30%, M+NH₄⁺); HRMS (CI⁺) calcd. For C₂₀H₂₈NO₂ (M+NH₄ adduct) 314.2120, found 314.2127, (Δ=2.2 ppm); IR (neat) ν_{max} 2927, 2856 (C-H), 1727 (C=O), 1155 (C-O).

Cycloheptylcarboxylic (*tert*-butyl carbonic) anhydride (**204**) and dicycloheptane carboxylic anhydride

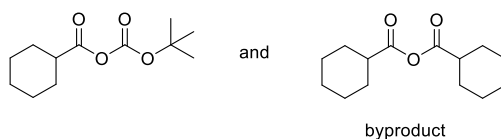


Cycloheptane carboxylic acid (0.36 mL, 2.65 mmol) was added to a solution of anhydrous Et₂O (5 mL) and pyridine (0.39 mL, 4.8 mmol) at room temperature. To this solution was added Boc anhydride in one go (0.88 g, 4.03 mmol). The reaction mixture was stirred for 40 hours. The reaction was quenched with sat. NaHCO₃ solution (10 mL) and stirred for 30 minutes. The organic layer was washed with sat. NaHCO₃ solution (3 x 10 mL), 1 M NaOH solution (10 mL), brine (10 mL) and dried over Na₂SO₄. The organic solvent was evaporated *in vacuo*, to provide a clear pale yellow oil (0.641 g) comprising an inseparable mixture of cycloheptylcarboxylic (*tert*-butyl carbonic) anhydride (**204**, 33% by ¹H NMR in C₆D₆⁴) and dicycloheptane carboxylic anhydride (67% by ¹H NMR in C₆D₆). ¹H NMR (400 MHz, C₆D₆) δ_H [cycloheptylcarboxylic (*tert*-butyl carbonic) anhydride **204**]: 2.28 (tt, *J* = 9.2, 4.5 Hz, 1H), 1.77 (dddd, *J* = 8.0, 7.2, 3.5, 1.8 Hz, 2H), 1.62 – 1.56 (2H), 1.48 – 1.38 (2H), 1.33-1.27 (4H), 1.21 (s, 9H), 1.19-1.1 (2H);

⁴ The two compounds can be distinguished by ¹H NMR in C₆D₆ but not in CDCl₃ due to overlapping peaks.

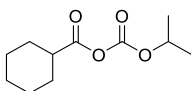
[dicycloheptane carboxylic anhydride]: 2.39 (tt, $J = 9.2, 4.6$ Hz, 2H), 1.84 (ddt, $J = 14.8, 7.4, 3.7$ Hz, 4H), 1.67 (ddt, $J = 14.8, 10.4, 4.6$ Hz, 4H), 1.60 – 1.37 (4H), 1.30 (dt, $J = 6.1, 3.2$ Hz, 8H), 1.26–1.22 (4H); ^{13}C NMR (101 MHz, C_6D_6) δ_{C} [cycloheptylcarboxylic (*tert*-butyl carbonic) anhydride **204**] 172.19, 147.28, 84.18, 44.40, 29.89, 28.02, 26.79, 25.84; [dicycloheptane carboxylic anhydride]: 172.19, 45.56, 29.89, 28.14, 25.91; MS-(ES^+ -TOF) m/z (rel intensity) 284 (25%) 306 (30%, $(\text{M}+\text{CH}_3\text{CN}+\text{Na})^+$) 330 (100% (Anhydride+ $\text{CH}_3\text{CN}+\text{Na})^+$); HRMS (ES^+) calcd. for $\text{C}_{15}\text{H}_{25}\text{NO}_4\text{Na}$ ($\text{M}+\text{CH}_3\text{CN}+\text{Na}$ adduct) 306.1681, found 306.1683, ($\Delta=0.7$ ppm); IR (neat) ν_{max} 2929, 2859 (C-H), 1807, 1754 (C=O), 1117, 1070 (C-O).

Cyclohexylcarboxylic (*tert*-butyl carbonic) anhydride (**205**)



Cyclohexane carboxylic acid (3.45 g, 26.5 mmol) was added to a solution of anhydrous Et_2O (50 mL) and pyridine (3.9 mL, 48 mmol, 9 eq.) at room temperature. To this solution was added Boc anhydride in one go (7.31 g, 33.5 mmol, 1.26 eq.). The reaction mixture was stirred for 40 hours. The reaction was quenched with sat. NaHCO_3 solution (50 mL) and stirred for 30 minutes. The organic layer was washed with sat. NaHCO_3 solution (3 x 50 mL) three times, 1 M NaOH solution (50 mL), brine (50 mL) and dried over Na_2SO_4 . The organic solvent was evaporated *in vacuo*, to provide a clear pale yellow oil (3.9 g) comprising an inseparable mixture of cyclohexylcarboxylic (*tert*-butyl carbonic) anhydride (**205**, 77% by ^1H NMR in C_6D_6 ⁵) and dicyclohexane carboxylic anhydride (**207**, 23% by ^1H NMR in C_6D_6). ^1H NMR (400 MHz, C_6D_6) δ_{H} [cyclohexylcarboxylic (*tert*-butyl carbonic) anhydride **205**]: 2.04 (tt, $J = 10.8, 3.7$ Hz, 1H), 1.75 – 1.68 (2H), 1.45 – 1.31 (5H), 1.21 (s, 9H), 1.07 – 0.81 (3H); [dicyclohexane carboxylic anhydride **207**]: 2.15 (tt, $J = 10.8, 3.7$ Hz, 2H), 1.80 (ddt, $J = 14.6, 4.4, 2.1$ Hz, 4H), 1.57 – 1.45 (4H), 1.45 – 1.31 (6H), 1.04 – 0.81 (6H); ^{13}C NMR (101 MHz, C_6D_6) δ_{C} [cyclohexylcarboxylic (*tert*-butyl carbonic) anhydride **205**]: 170.50, 147.26, 84.17, 42.54, 28.22, 26.79, 25.34, 24.84; [dicyclohexane carboxylic anhydride **207**]: 171.37, 43.68, 28.28, 25.44, 24.96; MS-(ES^+ -TOF) m/z (rel intensity) 281 (25%) 292 (40%, $(\text{M}+\text{CH}_3\text{CN}+\text{Na})^+$) 302 (100% (Anhydride+ $\text{CH}_3\text{CN}+\text{Na})^+$); HRMS (ES^+) calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_4\text{Na}$ ($\text{M}+\text{CH}_3\text{CN}+\text{Na}$ adduct) 292.1525, found 292.1527, ($\Delta=0.7$ ppm); IR (neat) ν_{max} 2933, 2857 (C-H), 1807, 1749 (C=O), 1118, 1068 (C-O).

Cyclohexyl (*isopropyl carbonic*) anhydride (**206**)

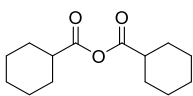


A procedure was adapted from the method of Fu^[291] as follows: Cyclohexane carboxylic acid (1.0 g, 7.8 mmol) was added to a solution of anhydrous Et_2O (35 mL) and Et_3N (2.4 mL, 17.6 mmol) at room temperature. To this solution was added dropwise *isopropyl chloroformate* (15.6 mL, 15.6 mmol; 1.0 M in

⁵ The two compounds can be distinguished by ^1H NMR in C_6D_6 but not in CDCl_3 due to overlapping peaks.

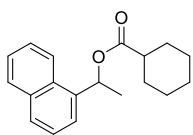
toluene; Aldrich). The reaction mixture was stirred for 4 hours. The organic layer was washed with sat. NaHCO_3 solution (3 x 30 mL), and brine (3 x 30 mL). The organic solvent was evaporated *in vacuo*, to provide acyl carbonate **206** as a clear pale yellow oil which was used without further purification (1.12 g, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ_{H} 5.01 (hept, $J = 6.3$ Hz, 1H), 2.44 (tt, $J = 11.0, 3.7$ Hz, 1H), 2.00 (ddt, $J = 12.2, 3.7, 2.3$ Hz, 2H), 1.80 (ddd, $J = 9.7, 4.4, 2.3$ Hz, 2H), 1.70 – 1.63 (1H), 1.52 (dddd, $J = 13.6, 11.0, 7.8, 3.1$ Hz, 2H), 1.37 (d, $J = 6.3$ Hz, 6H), 1.35 – 1.19 (3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 170.40, 148.92, 77.35, 77.03, 76.71, 74.54, 74.13, 43.97, 43.08, 28.39, 25.59, 25.53, 25.17, 25.11, 21.46; MS-(ES^+ TOF) m/z (rel intensity) 143 (80%) 208 (78%) 278 (100%) 302 (90%); HRMS (ES^+) calcd. for $\text{C}_{13}\text{H}_{21}\text{NO}_4\text{Na}$ ($\text{M} + \text{CH}_3\text{CN} + \text{Na}$ adduct) 278.1368, found 278.1379, ($\Delta = 1.1$ ppm); IR (neat) ν_{max} 2935, 2858 (C-H), 1797, 1754 (C=O), 1069, 1018 (C-O).

Dicyclohexane carboxylic anhydride (**207**)^[352]



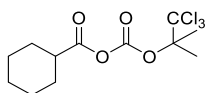
A procedure was adapted from the method of Mohan^[297] as follows: to a solution of DCC (3.2 g, 15.6 mmol) in CH_2Cl_2 (12 mL) was added a solution of cyclohexane carboxylic acid (4.0 g, 31.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The solution was stirred at rt for 24 hours, during which a white precipitate was formed. The solution was filtered, washed with 2 M NaOH solution (2 x 30 mL) and brine (30 mL), and the solvent removed *in vacuo* to yield anhydride **207** as a clear yellow oil (2.6. g, 72%). ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.43 (tt, $J = 11.1, 3.8$ Hz, 2H), 1.98 (ddd, $J = 12.2, 3.8, 1.6$ Hz, 4H), 1.80 (ddt, $J = 9.5, 4.9, 3.0$ Hz, 4H), 1.72 – 1.60 (2H), 1.59 – 1.41 (4H), 1.40 – 1.16 (6H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 171.88, 43.98, 28.42, 25.59, 25.18. Data consistent with that reported previously.^[352]

(±)-1-(1-Naphthyl)ethyl cyclohexyl acetate (**208**)



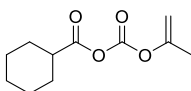
Prepared according to general procedure for KR using (±)-1-(1-naphthylethanol) **26** and dicyclohexane carboxylic anhydride **207**, isolated as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.09 (d, $J = 8.3$ Hz, 1H), 7.88 (m, 1H), 7.81 (d, $J = 8.3$ Hz, 1H), 7.61 (d, $J = 7.0$ Hz, 1H), 7.57 – 7.44 (3H), 6.65 (q, $J = 6.6$ Hz, 1H), 2.38 (tt, $J = 11.3, 3.6$ Hz, 1H), 1.95 (dddd, $J = 16.2, 12.3, 3.6, 2.0$ Hz, 2H), 1.81 – 1.72 (2H), 1.70 (d, $J = 6.6$ Hz, 3H), 1.65 (m, 1H), 1.49 (m, 2H), 1.28 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 175.32, 137.70, 133.81, 130.30, 128.87, 128.33, 126.21, 125.64, 125.36, 123.25, 123.09, 77.35, 77.23, 77.03, 76.71, 68.93, 43.42, 29.04, 28.99, 25.78, 25.46, 21.70; MS-(APCI^+) m/z (rel intensity) 155 (100%); HRMS (APCI^+) calcd. for $\text{C}_{12}\text{H}_{11}$ ($\text{M} - \text{CO}_2\text{C}_6\text{H}_{11}$ decomposition product) 155.09, found 155.0850, ($\Delta = 3.3$ ppm); IR (neat) ν_{max} 2932, 2855 (C-H), 1727 (C=O), 1169 (C-O). CDCl_3

Cyclohexylcarboxylic (2,2,2-trichloro-1,1-dimethylethyl carbonic) anhydride (**209**)



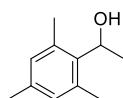
A procedure was adapted from the method of Fu^[291] as follows: to an ice-cold solution of cyclohexane carboxylic acid (0.39 g, 3.05 mmol) and Et₃N (0.64 mL, 4.6 mmol) in anhydrous Et₂O (25 mL) was added dropwise a solution of 2,2,2-trichloro-1,1-dimethylethyl chloroformate (0.95 g, 3.96 mmol) in Et₂O (5 mL). The reaction mixture was stirred for 2 hours. The organic layer was washed with sat. NaHCO₃ solution (3 x 30 mL), and brine (3 x 30 mL). The organic solvent was evaporated *in vacuo*, to provide acyl carbonate **209** as a white solid (0.8 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ_H 2.48 (tt, *J* = 10.9, 3.5 Hz, 1H), 2.01 (s, 6H), 2.04-1.94 (2H) 1.86-1.75 (2H), 1.71-1.63 (1H), 1.61 – 1.45 (2H), 1.40-1.23 (3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 170.20, 146.67, 91.66, 42.94, 28.34, 25.50, 25.03, 20.92; MS-(Cl⁺) *m/z* (rel intensity) 128 (100%, C₇H₁₂O₂, cyclohexane carboxylic acid) 145 (95%, C₇H₁₁O₂ + NH₄⁺), 256 (30%), 348 (30%, M+NH₄⁺); HRMS (Cl⁺) calcd. for C₁₂H₂₁NO₄Cl₃ (M+NH₄ adduct) 348.0536, found 348.0543, (Δ=2.0 ppm); IR (neat) ν_{max} 2935, 2858 (C-H), 1804, 1760 (C=O), 1085, 1069 (C-O), 801 (C-Cl); Mp: 53.5 – 58.5 °C.

Cyclohexyl (*isopropenyl* carbonic) anhydride (**210**)



A procedure was adapted from the method of Fu^[291] as follows: To an ice-cold solution of cyclohexane carboxylic acid (0.39 g, 3.05 mmol) and Et₃N (0.64 mL, 4.57 mmol) in anhydrous Et₂O (30 mL) was added dropwise *isopropenyl* chloroformate (0.5 mL, 4.57 mmol). The reaction mixture was stirred at 0 °C for 90 minutes. The organic layer was washed with sat. NaHCO₃ solution (3 x 30 mL), and brine (3 x 30 mL). The organic solvent was evaporated *in vacuo*, to provide acyl carbonate **210** as a clear oil containing ~10% anhydride impurity (**207**) which was used without further purification (0.57 g, 88%). ¹H NMR (400 MHz, CDCl₃) δ_H 4.93 (s, 1H), 4.81 (s, 1H), 2.53 – 2.44 (1H), 2.10 – 1.91 (2H), 2.04 (s, 3H) 1.87 – 1.75 (2H), 1.72 – 1.63 (1H), 1.62 – 1.45 (2H), 1.41 – 1.20 (3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 169.87, 152.77, 147.15, 102.72, 43.12, 28.36, 25.50, 25.07, 18.78; MS-(Cl⁺) *m/z* (rel intensity) 128 (100%, C₇H₁₂O₂, cyclohexane carboxylic acid) 145 (55%, C₇H₁₁O₂ + NH₄⁺) 230 (60%, M+NH₄⁺); HRMS (Cl⁺) calcd. for C₁₁H₂₀NO₄ (M+NH₄ adduct) 230.1392, found 230.1387, (Δ=-2.2 ppm); IR (neat) ν_{max} 2934, 2858 (C-H), 1808, 1762 (C=O), 1676 (C=C), 1085, 1069 (C-O).

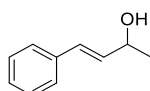
(±)-1-(2,4,6-Trimethyl-phenyl)-1-ethanol (**217**)^[353]



A procedure was adapted from the method of Ausmees^[297] as follows: to a solution of 2,4,6-trimethylacetophenone (1.02 mL, 6.16 mmol) in ethanol (30 mL) was added NaBH₄ (0.34 g, 9.25 mmol) at 0

°C. The resulting yellow solution was stirred at 50 °C for 24 h, after which it was cooled to 0 °C and quenched with aq. NH₄Cl solution (50 mL). The resulting white suspension was extracted with CH₂Cl₂ (3 x 50 mL), the combined organic extracts dried over Na₂SO₄ and the solvent removed *in vacuo*. The resulting clear oil was purified by column chromatography eluting with hexane:EtOAc (0→10%) to yield the alcohol **217** as a white solid (0.86 g, 84%). ¹H NMR (400 MHz, CDCl₃) δ_H 6.85 (s, 2H), 5.40 (q, *J* = 6.8 Hz, 1H), 2.45 (s, 6H), 2.28 (s, 3H), 1.71 (s, 1H), 1.56 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 137.64, 136.45, 135.66, 130.15, 67.51, 21.62, 20.70, 20.53. Data consistent with that reported previously.^[353]

(±)-(E)-4-Phenylbut-3-en-2-ol (226)^[354]



Following a procedure from Leadbeater^[354]: To a solution of cinnamaldehyde (1.9 mL, 15 mmol) in THF (42 mL) at 0 °C was added methyl magnesium chloride (3.0 M in THF, 6.25 mL, 18.75 mmol). The solution was allowed to stir at 0 °C for two hours before quenching dropwise with 1 M HCl (35 mL). The resulting solution was diluted with Et₂O (30 mL) and partitioned. The aqueous layer was extracted with a further portion of Et₂O (30 mL), the organic extracts combined and washed with sat. NaHCO₃ solution (50 mL), water (50 mL), brine (50 mL) and dried over MgSO₄. The solvent was removed *in vacuo* to yield **226** as a dark yellow oil which was purified by distillation (100 °C, 3 mbar) to yield a clear oil which crystallised on standing to a white crystalline solid (1.76 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ_H 7.44 – 7.39 (m, 2H), 7.36 (ddd, *J* = 7.7, 6.7, 1.3 Hz, 2H), 7.32 – 7.25 (m, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.31 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.52 (pd, *J* = 6.4, 1.3 Hz, 1H), 1.68 (s, 1H), 1.42 (d, *J* = 6.4 Hz, 3H); MS-(APCI) *m/z* (rel intensity) 131 (100%, M-OH⁺); HRMS (APCI⁺) calcd. For C₁₀H₁₁⁺ (M-OH⁺) 131.0855, found 131.0857, (Δ=1.32 ppm). Data consistent with that reported previously.^[354]

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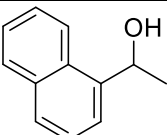
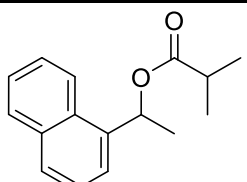
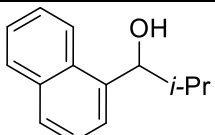
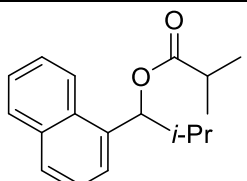
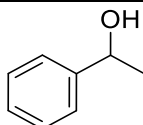
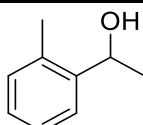
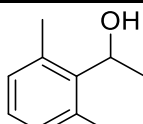
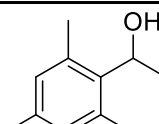
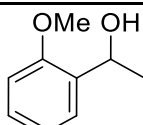
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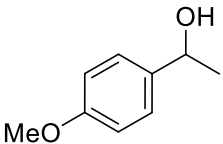
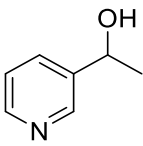
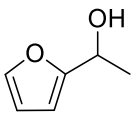
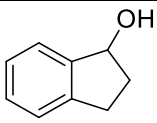
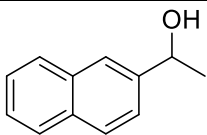
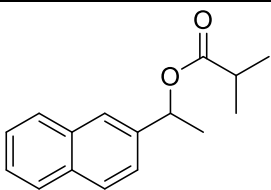
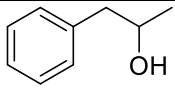
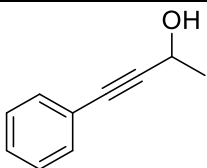
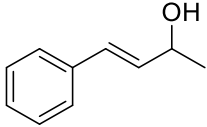
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8 Appendices

8.1 HPLC Methods:

Entry	Substrate	Column	Conditions	Retention Time (R) isomer (min)	Retention Time (S) isomer (min)
1		OD-H	Hex: <i>i</i> -PrOH (90:10) 1mL/min 20 °C, 280 nm	19.2	11.9
2		OD-H	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 280 nm	6.7	9.3
3		OD-H	Hex: <i>i</i> -PrOH (90:10) 1mL/min 20 °C, 280 nm	16.1	8.1 ^a
4		OD-H	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 280 nm	5.5	7.1 ^a
5		OD-H	Hex: <i>i</i> -PrOH (98:2) 1mL/min 20 °C, 210/215 nm	19	26
6		IA	Hex: <i>i</i> -PrOH (98:2) 1mL/min 20 °C, 254nm	13	15.5 ^a
7		OD-H	Hex: <i>i</i> -PrOH (97:3) 1mL/min 20 °C, 254nm	7.2	6.0 ^a
8		IA	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 254nm	13.8	15.9 ^a
9		OD-H	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 254nm	32.8	30.2 ^a

10		OD-H	Hex: <i>i</i> -PrOH (99.9:1.2) 1mL/min 20 °C, 254nm	46.5	50.5 ^a
11		OJ-H	Hex: <i>i</i> -PrOH (95:5) 1mL/min 20 °C, 254 nm	23.5	17.8 ^a
12		OD-H	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 210/215 nm	28	31 ^a
13		OD-H	Hex: <i>i</i> -PrOH (97:3) 1mL/min 20 °C, 254nm	18.4	15.8 ^a
14		OD-H	Hex: <i>i</i> -PrOH (90:10) 1mL/min 20 °C, 280 nm	11.8	10.9 ^a
15		OD-H	Hex: <i>i</i> -PrOH (99:1) 1mL/min 20 °C, 280 nm	5.7	6.7 ^a
16		OD-H	Hex: <i>i</i> -PrOH (98.5:1.5) 1mL/min 20 °C, 254nm	18.9	16.6 ^a
17		OD-H	Hex: <i>i</i> -PrOH (90:10) 1mL/min 20 °C, 280nm	8.1	20.3 ^a
18		OD-H	Hex: <i>i</i> -PrOH (97:3) 1mL/min 20 °C, 254 nm	27	47 ^a

^aAcylation of *R* or *S* enantiomer assumed from analogy to substrates where configuration of acylated enantiomer is known. In the cases above, it has been assumed that the *R* enantiomer is always acylated, by analogy with 1-phenylethanol and 1-(1-naphthyl)ethanol.^[105]