JYU DISSERTATIONS 337

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2,5-Diarylpyrrolidines and Pyroglutamic-Acid-Derived 2-Diarylmethyl-5-Aryl-Pyrrolidines

Their Synthesis and Use in Asymmetric Synthesis

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF MATHEMATICS
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ABSTRACT

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2,5-Diarylpyrrolidines and Pyroglutamic-Acid-Derived 2-Diarylmethyl-5-Aryl-Pyrrolidines: Their Synthesis and Use in Asymmetric Synthesis
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Pyrrolidine is a nitrogen-containing heterocycle, and various natural products contain this five-membered structure. It is also present in chiral organocatalysts, which are used in asymmetric synthesis. Examples of such compounds include proline, the Hayashi–Jørgensen catalyst, 2,5-diarylpyrrolidines and pyroglutamic-acid-derived 2-diarylmethyl-5-aryl-pyrrolidines. The latter two are in the focus of this dissertation, and in Chapters two and three, compendiums of the synthesis strategies and routes of the pyrrolidines are presented. The routes are categorised based on the retrosynthetic scissions, critical for the formation of the 2,5-disubstituted pyrrolidine cores. Lastly, the usefulness of these pyrrolidines in the field of asymmetric synthesis is summarised.

Chapter four describes the method development of an iminium-catalysed Mukaiyama–Michael reaction, the focus being in the organocatalyst optimisation. 2,5-diarylpyrrolidines and pyroglutamic-acid-derived 2-diarylmethyl-5-aryl-pyrrolidines were prioritised in the research. Eventually, an excellent level of enantioselectivity was reached by using a 2,5-diarylpyrrolidine catalyst, equipped with strongly electron-withdrawing substituents.

In the fifth chapter, the above-mentioned reaction was utilised as the key transformation in a total synthesis route of an amino acid, (+)-lycoperdic acid. With another organocatalytic reaction, namely an enamine-catalysed α-chlorination, the full stereocontrol of the stereogenic centers was achieved. The target natural product was synthesised in nine steps from a commercially available compound.

The last chapter compiles together additional studies related to the 2,5-diarylpyrrolidine synthesis and the Mukaiyama–Michael reaction of interest. An alternative way to reduce 1,4-bis(aryl)butane-1,4-diones enantioselectively was studied, and commercially available ketoreductase enzymes gave encouraging results. Studies for replacing acrolein with its diethyl acetal in the studied Mukaiyama–Michael reaction were started with promising results. Lastly, another type of pyrrolidine organocatalyst, which gave eventually the best *er* in the above-mentioned reaction, was found.

Keywords: Mukaiyama–Michael reaction, asymmetric natural product total synthesis, pyrrolidines, organocatalysis, lycoperdic acid

TIIVISTELMÄ

Pyrrolidiini on typpeä sisältävä viisirenkainen yhdiste, joka esiintyy monissa luonnonaineissa. Tämä heterosyklinen rakenne löytyy myös kiraalisista organokatalyyteistä, joita käytetään useissa asymmetrisissä synteesimenetelmissä. Esimerkkejä edellä mainituista yhdisteistä ovat proliini, Hayashi–Jørgensen katalyytti, 2,5-diaryylipyrrolidiinit ja pyroglutamiinihappojohdetut 2-diaryylimetyyli-5-aryylipyrrolidiinit. Tässä väitöskirjassa keskitytään edellä mainituista esimerkeistä kahteen jälkimmäiseen yhdistetyyppiin, joiden kirjallisuudesta tunnetut synteesireitit ja –strategiat esitellään kappaleissa kaksi ja kolme. Reitit on jaoteltu 2,5-disubstituoidun pyrrolidiinirungon syntetisoinnin kannalta ratkaisevassa asemassa olevien retrosynteettisten katkaisujen perusteella. Kappaleiden lopuissa käydään läpi näiden pyrrolidiinien käyttö asymmetrisessä synteesissä.

Kappaleessa neljä käydään läpi iminium-katalysoidun Mukaiyama–Michael reaktion menetelmäkehityksen vaiheita. Työn pääpaino oli reaktiossa käytetyn organokatalyytin rakenteen optimoinnissa. Optimoitaviksi katalyyttirungoiksi valittiin 2,5-diaryylipyrrolidiinin ja pyroglutamihappojohdetun 2-diaryylimetyyli-5-aryylipyrrolidiinin tyyppiset yhdisteet. Tutkitussa reaktiossa saavutettiin lopulta erinomainen enantioselektiivisyys käytettäessä 2,5-diaryylipyrrolidiinikatalyyttiä, jossa oli voimakkaasti elektronitiheyttä puoleensa vetävät ryhmät.

Viidennessä kappaleessa edellä mainittua reaktiota hyödynnettiin erään aminohapon, (+)-lykoperdiinihapon, kokonaissynteesireitissä. Reitissä käytettiin myös toista enantioselektiivistä organokatalyyttistä reaktiota, enamiinikatalysoitua α-kloorausreaktiota. Näiden reaktioiden avulla voitiin täysin kontrolloida kohdemolekyylin stereokeskusten absoluuttisia konfiguraatioita. Luonnonaineen synteesireitin kokonaispituudeksi muodostui lopulta yhdeksän askelta kaupallisesti saatavilla olevasta yhdisteestä laskettuna.

Viimeiseen kappaleeseen on koottu sekä 2,5-diaryylipyrrolidiinien synteesiin että tutkittuun Mukaiyama–Michael reaktioon liittyvien lisäkokeiden tuloksia. Kaupallisesti saatavilla olevilla ketoreduktaasientsyymeillä saatiin lupaavia tuloksia 1,4-bis(aryyli)butaani-1,4-dionien enantioselektiivisessä pelkistyksessä. Akroleiinin dietyyliasetaalin havaittiin olevan lupaava akroleiinin korvaava reagenssi tutkitussa Mukaiyama–Michael reaktiossa. Lisäksi väitöskirjatyön loppuvaiheilla löydettiin uudenlainen pyrrolidiinikatalyytti, jolla saavutettiin paras *er* edellä mainitussa reaktiossa.

Avainsanat: Mukaiyama–Michael-reaktio, asymmetrinen luonnonaineiden kokonaissynteesi, pyrrolidiinit, organokatalyysi, lykoperdiinihappo

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AUTHOR CONTRIBUTIONS

The author of this dissertation has designed and carried out the experiments and analyses presented in this work, and interpreted the related results. This work was also written by the author. The following compounds, present in Chapter 4, were synthesised by former researchers of the group in their previous projects: Dr Gokarneswar Sahoo synthesised catalysts **31a,l,m,p** and Dr Aurelie Claraz the catalysts **32a–d,i–n** and **485**.

The initial studies for catalyst **31k**, diketone **34n** and enzymatic diketone reductions were conducted by a summer trainee Roosa-Maria Willman and BSc-candidates Toni Väisänen and Roope Suvinen, respectively, with the help and under the supervision of the author of this dissertation. The HRMS spectra were measured by Johanna Hiidenheimo and Dr Elina Kalenius.

The publication related to this work was written together with the co-authors.[57]

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Jyväskylä, 26 November 2020
Sami Kortet

ACRONYMS, ABBREVIATIONS, SYMBOLS AND DEFINITIONS

(–)-DIP-Cl	(−)-B-chlorodiisopinocampheylborane
ACN	Acetonitrile
Ac	Acetyl
acac	Acetylacetone
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
Ar	Aryl
BA	Benzoic acid
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
Bz	Benzoyl
Boc	*tert*-butoxycarbonyl
Bu	Butyl
CBS	Corey–Bakshi–Shibata
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
Cbz	Benzyloxycarbonyl
CCD	Charge coupled device
COD	Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadiene
cPr	Cyclopropyl
CSD	Cambridge Structural Database
CuTC	Copper (I) thiophene-2-carboxylate
Cy	Cyclohexyl
Cyp	Cyclopentyl
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBnAD	Dibenzyl azodicarboxylate
DIBAlH	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DCA	Dichloroacetic acid
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density-functional theory
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dr	diastereomeric ratio

EC_{50}	Half maximal effective concentration; the concentration that is required to get a 50% effect.
EDC	*N*-(3-dimethylaminopropyl)-N′-ethylcarbodiimide
EDG	Electron-donating group
er	enantiomeric ratio
ESI–Q–TOF	Electrospray ionisation–quadruple–time-of-flight
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
FT	Fourier Transformation
G*	Reaxys Generic Group; retrieves structures with any group or in which an atom in the group can be linked with an atom in the original structure to form a ring
GH*	Reaxys Generic Group; same as G* but a hydrogen atom can also be retrieved
GC	Gas chromatography
Glc	Glucose
HCV	Hepatitis C virus
HetAr	Heteroaryl
Hex	Hexyl
HMPA	Hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
Ipc	Isopinocampheylborane
IR	Infrared
KHMDS	Hexamethyldisilazane potassium salt
KRED	Ketoreductase
LA	Lewis acid
LED	Light-emitting diode
LDA	Lithium diisopropylamide
LiDBB	Lithium di-*tert*-butylbiphenyl
LiHMDS	Hexamethyldisilazane lithium salt
LC/MS	Liquid chromatography/Mass spectrometer
LUMO	Lowest unoccupied molecular orbital
MCA	Monochloroacetic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesityl
mp	Melting Point
Ms	Mesyl
MS	Molecular sieve *or* mass spectrometer

MTBE	*tert*-butyl methyl ether
n	normal; straight-chain
n.d.	Not determined
NAD^+	Nicotinamide adenine dinucleotide
$NADPH^+$	Nicotinamide adenine dinucleotide phosphate
Naph	Naphthyl
NBA	Nitrobenzoic acid
nbd	2,5-Norbornadiene
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
NSA	Naphtalenesulfonic acid
OAc	Acetate
OMe	Methoxy
ORTEP	Oak Ridge thermal ellipsoid plot
MOM	Methoxymethyl
Pen	Pentyl
Ph	Phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	Propyl
R	A general abbreviation for an atom or a group of atoms
refl.	reflux
rt	Room temperature
s(*ec*)	secondary
S_N2	Substitution nucleophilic bi-molecular
S_NAr	Substitution nucleophilic aromatic
SOMO	Singly occupied molecular orbital
SPS	Solvent purification system
t(*ert*)	tertiary
TBAI	Tetrabutylammonium iodide
$TBAN_3$	Tetrabutylammonium azide
TBS	*tert*-butylsilyl
TCA	Trichloroacetic acid
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tf	Triflyl
TfO	Triflate
TfOH	Triflic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl triflate, triisopropylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography

TMEDA	Tetramethylethylenediamine
TMM	Trimethylenemethane
TMS	Trimethylsilyl
TPSH	2,4,6-Triisopropylbenzenesulfonyl hydrazide
Ts	Tosyl
TS	Transition state
TSA	*para*-toluenesulfonic acid
UV	Ultraviolet

CONTENTS

1 INTRODUCTION TO PYRROLIDINES

Pyrrolidine (**1**) is a five-membered nitrogen-containing heterocycle and a secondary amine (Figure 1). It was isolated from the tobacco plant by Pictet and Court in 1907.[1] It can also be made industrially, for example, from ammonia and 1,4-butanediol.[2] The pyrrolidine core is present in many biologically active molecules (atrasentan[3], dihydrokainic acid[4]), pharmaceuticals* (meropenem[5], gliclazide[6]), natural products**[,7,8] (nicotine, atropine), chiral auxiliaries[9–11] ((*R*,*R*)-**8** and (*R*,*R*)-**9**) and organocatalysts[12,13] ((*R*,*R*)-**10** and (*S*)-**11**).

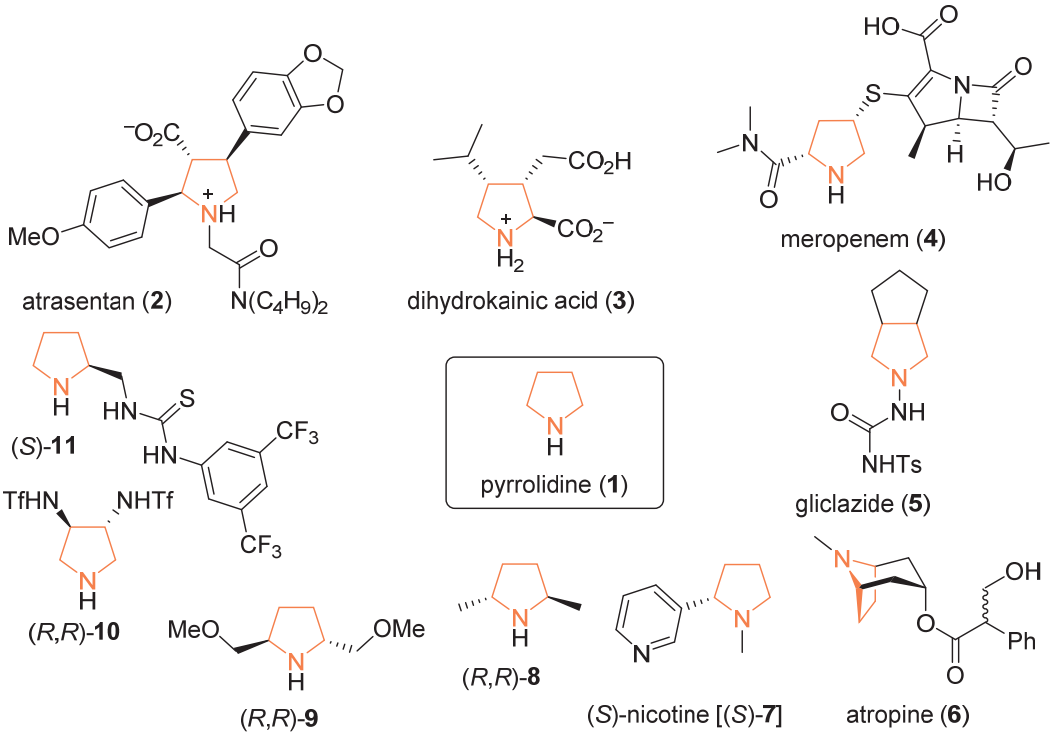


Figure 1: Pyrrolidine and a few example molecules, where the core is present.

* At least 200 approved drugs based on a Reaxys search using pyrrolidine as a substructure.
** ~15 000 structures based on a Reaxys search using pyrrolidine as a substructure.

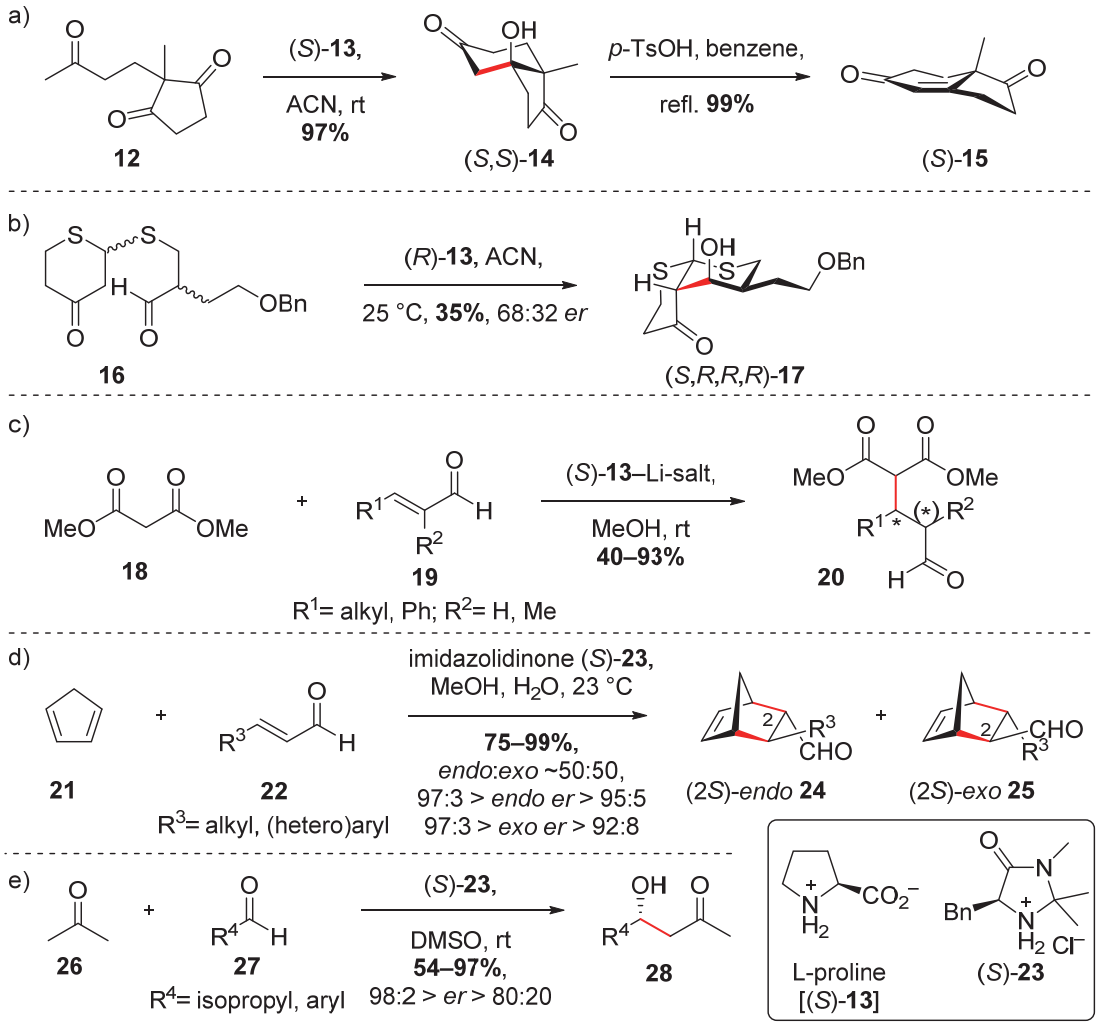
As can be seen from Figure 1 and the Reaxys search results, the possibilities for differently substituted pyrrolidines are vast. However, only 2,5-substituted pyrrolidines, more specifically, 2,5-diarylpyrrolidines and pyroglutamic-acid-derived 2-diarylmethyl-5-arylpyrrolidines, are the focus of this dissertation, due to their potential use in asymmetric organocatalysed reactions.

1.1 Pyrrolidines in asymmetric organocatalysis

Asymmetric organocatalysis is a rather young sub-field of synthetic organic chemistry. Before the 2000s, "asymmetric organocatalysis" was barely a term describing the field due to the low number of publications at that time. The organocatalytic transformations were seen as esoteric, without much of a broader concept behind them.[14]

The foundations of asymmetric organocatalysis could be traced back to some key publications published over the decades before the breakthrough. One of the highly asymmetric seminal examples of organocatalysed reactions was the L-proline-catalysed Hajos–Parrish–Eder–Sauer–Wiechert reaction, developed in 1970s (Scheme 1a).[15,16] Another noteworthy application was the D-proline catalysed enantioselective aldol reaction of a chiral intermediate (*S*,*R*,*R*,*R*)-**17**, which was used in the total synthesis of erythromycin by Woodward and co-workers in the early 1980s (Scheme 1b).[17,18] In 1991, Yamaguchi and co-workers published the first asymmetric iminium ion catalysed reactions, which were Michael additions between enones and dimethyl malonate (Scheme 1c).[19,20]

The true blossoming of the field began only after 2000, when MacMillan[21] and List,[22] with their co-workers, published their papers on iminium-catalysed Diels–Alder reactions (Scheme 1d) and enamine-catalysed aldol reactions (Scheme 1e), respectively. These reactions were catalysed by imidazolidinone (*S*)-**23** and L-proline ((*S*)-**13**). The utility of these successes in enantioselective reactions was immediately recognised, and even more importantly, the researchers began to understand the underlying concepts of the field. Terms such as iminium- and enamine catalysis or HOMO-, SOMO- and LUMO-activation modes helped everyone in the field when developing novel catalysts and stereoselective reactions.[14]



Scheme 1: Early and the "breakthrough" examples of organocatalysed reactions. a) Hajos–Parrish–Eder–Sauer–Wiechert reaction.[15,16] b) D-proline catalysed enantioselective aldol-reaction to make a chiral intermediate (*S*,*R*,*R*,*R*)-**17**.[17] c) Michael additions between enones and dimethyl malonate.[19] d) Organocatalysed Diels–Alder reactions.[21] e) Intermolecular aldol reactions.[22] The bonds formed in the reactions are highlighted with red color.

1.1.1 Pyrrolidines beyond proline

Proline is widely available as both enantiomers at low cost*, which partly explains its popularity as an organocatalyst. In addition, it has the acid–base bifunctionality inserted in the pyrrolidine core, which differentiates it from the other proteinogenic amino acids.[23] Proline is important also in another sense, since it can be used as the chiral pool starting material, when other C2-substituted pyrrolidine organocatalysts are synthesised. For example, the Hayashi–Jørgensen-type[24,25] catalysts (*S*)-**29**[**,26,27] and (*S*)-**30** are synthesised from proline (Figure 2).[28,29] However, numerous amounts of chiral organocatalysts, which are not straightforwardly synthesisable from proline, also employ

* L-proline 19 €/25 g and D-proline 139 €/25 g in TCI Europe (July 2020).

** The corresponding prolinol is also known from the Corey–Itsuno (or Corey–Bakshi–Shibata) reduction.[26,27]

pyrrolidine as the core structure. These include *trans*-2,5-diarylpyrrolidines **31**, which are the corner stones of this thesis' subject and will be discussed more thoroughly in the upcoming chapters. The purpose of this dissertation is not to go through all the pyrrolidine catalyst types, and the already existing reviews and their references about the subject should be consulted in case of interest.[20,30–32]

As with proline, there are a plethora of examples in the literature, where Hayashi–Jørgensen-type amines have been successfully used in the asymmetric organocatalysis, namely in enamine- and iminium ion catalysed reactions.[33–35] However, even these compounds are not applicable in every situation, which can be noticed from the above literature examples, as well as from our group's synthesis efforts.[36,37] The reasons are more or less case dependant, but they might relate to the lack of a substituent on the C5 position of the ring, meaning that an additional steric bulk near the reaction centre is missing. The fine-tuning of the electronics of the catalysts is also limited due to the absence of this substituent.

The development of new catalyst types is thus important. This quest has prompted us to invent novel differently substituted *trans*-2-diarylmethyl-5-arylpyrrolidines **32** and *trans*-2,5-diarylpyrrolidines **31** (Figure 2) for our studies in the field of iminium ion catalysis.

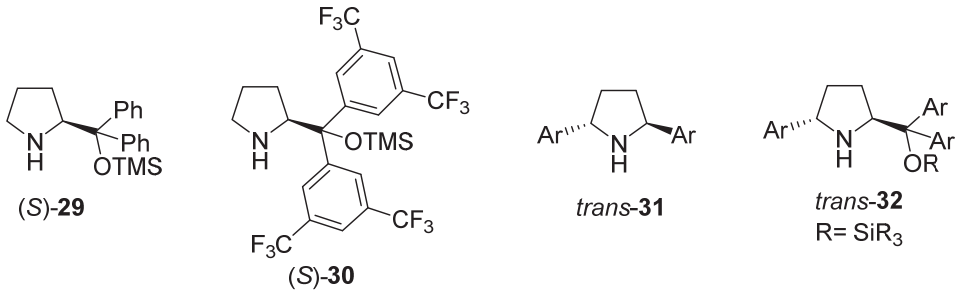


Figure 2: Jørgensen–Hayashi-type pyrrolidine catalysts (*S*)-**29** and (*S*)-**30** and general cores for *trans*-2,5-diarylpyrrolidine **31** and *trans*-2-diarylmethyl-5-arylpyrrolidine **32**.

The choice of the five-membered ring system*[,20,38] in our and others' studies can be justified both by theoretical terms and by simple historical aspects. Without a doubt, proline has had its influence on the catalyst structures, thus acting as the "common ancestor" for many. Additionally, when research groups focus on a certain core and gain both success and valuable knowledge of the system over the years, it might be natural to use the familiar setup.

The catalytic processes, where a pyrrolidine and (α,β-unsaturated) aldehydes and ketones form enamines and iminium ions, provide another reason for the choice of the five-membered ring. When the iminium is formed, an *exo* double bond is created, and the nitrogen atom of the catalyst changes its hybridisation from sp^3 to sp^2. Brown and co-workers noticed that the *exo* double bonds are more stable in five-membered rings than in the six-membered equiv-

* Primary amines, amino acids, morpholine- and BINOL-type amines are also well-known organocatalysts.[20,32,38]

alent and thus more readily adopt sp^2-hybridised atoms into the ring.[39] This probably also allows a better delocalisation of the nitrogen lone pair with the π-system, which is a part of a functioning HOMO-raising and LUMO-lowering catalysis.[38]

As previously stated, *trans*-2,5-diarylpyrrolidines **31** and *trans*-2-diarylmethyl-5-arylpyrrolidines **32** are in the focus in this dissertation. The choice of the 2,5-substitution pattern over the others can be further justified with the fact that these substituents are the closest ones to the reactive centre and thus, hypothetically, have a more pronounced effect on the bond-forming event than the substituents of the other carbons would.

To get a consistent picture of the subject background, the synthesis strategies to the above-mentioned pyrrolidines, as well as their use in synthesis are compiled together in Chapters 2 and 3. To best of the author's knowledge, this is the first compendium dedicated to the synthesis strategies of 2,5-diarylpyrrolidines. In addition, no preceding overall review articles about their use in asymmetric synthesis exists. The following literature examples are as comprehensive as possible, and any omissions of publications are purely coincidental and unfortunate.

In Chapter 4, the syntheses of a handful of novel pyrrolidine catalysts and the challenges related to them are presented. In addition, a development of a pyrrolidine-catalysed Mukaiyama–Michael reaction will be demonstrated. In Chapter 5, the above-mentioned reaction is used in an asymmetric total synthesis route of a natural product (+)-lycoperdic acid. In Chapter 6, additional studies related to the pyrrolidine catalyst synthesis and the Mukaiyama–Michael reaction are presented.

2 2,5-DIARYLPYRROLIDINES

Many synthesis routes for 2,5-diarylpyrrolidines have been published over the years. Some of them target the pyrrolidines as the final products, but there are also routes where the pyrrolidines are used as advanced intermediates diverging into more complex targets. Our literature review includes both achiral and chiral as well as both *cis*- and *trans*-substituted 2,5-diarylpyrrolidines. Even though the racemic pyrrolidines are not useful in asymmetric catalysis, presenting these approaches as well makes it possible to give a more comprehensive picture of the applicable methods.

Our searches about the subject were made using the Reaxys database, and they included three different 2,5-substituted pyrrolidine cores (Figure 3a). In addition to 2,5-diarylpyrrolidines, we included 2,5-diheteroarylpyrrolidines, as well as the mixed aryl–heteroaryl-substituted compounds.

We divided the routes based on the critical disconnections that were needed to furnish the substituted pyrrolidine cores. We named these C_α-N-, C_α–C_{Aryl}-, C_α–C_β- and mixed disconnection strategies, indicating the place of the retrosynthetic cleavage, as depicted in Figure 3b.

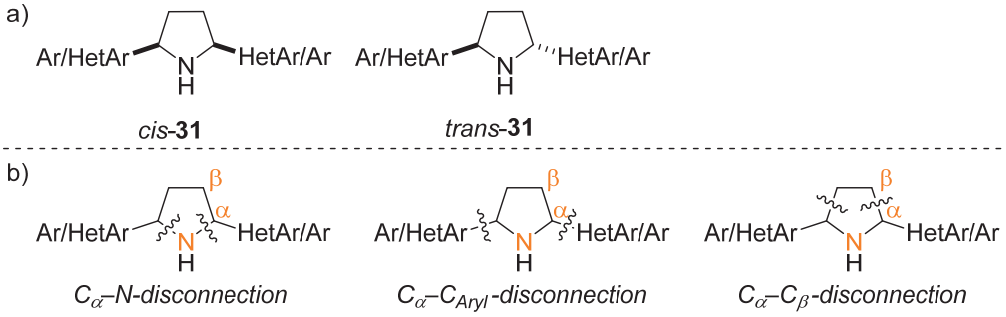


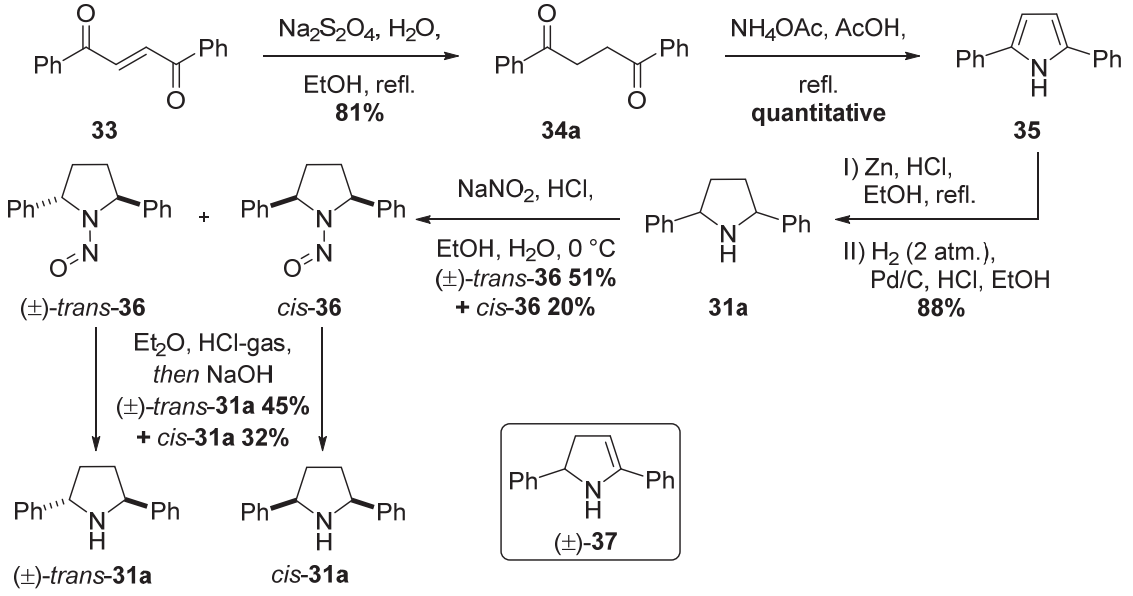
Figure 3. a) 2,5-pyrrolidines included in the literature search. b) Disconnection strategies used in the division of the found routes.

2.1 2,5-diarylpyrrolidine synthesis strategies

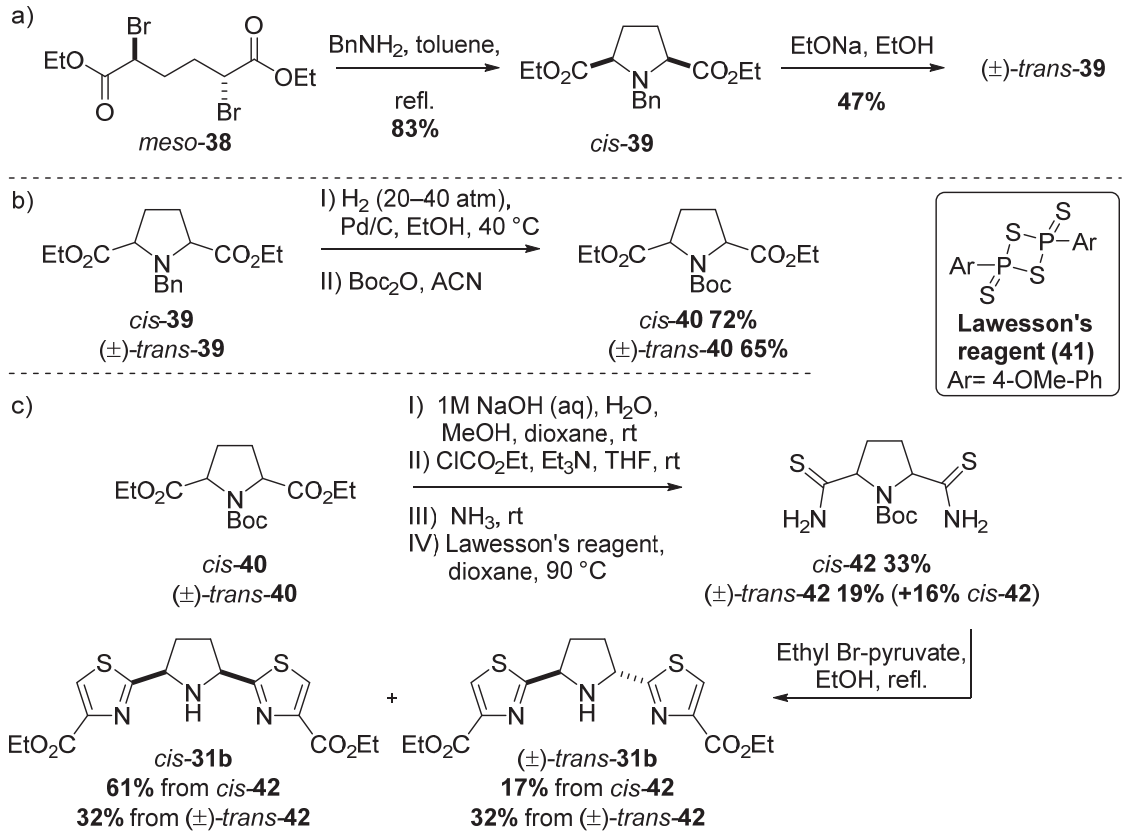
2.1.1 C_α–N disconnection strategy

The first example of the C_α-N disconnection strategy in the synthesis of 2,5-diarylpyrrolidines was published by Overberger and co-workers in 1969.[40] It also belongs to one of the first reported synthesis routes for the studied pyrrolidine system. The racemic route started with a dithionate reduction of *trans*-1,2-dibenzoylethylene (**33**) to 1,4-diketone **34a** in an 81% yield (Scheme 2). It was followed by the formation of pyrrole **35** in quantitative yield, using Paal-Knorr pyrrole synthesis.[41,42] The pyrrole was then reduced to pyrrolidine **31a** with zinc. However, Pd-catalysed hydrogenation was needed to confirm the complete reduction of the ring because some unreacted pyrroline (±)-**37** was left after the zinc reduction. Despite this, the authors were able to achieve 2,5-diphenylpyrrolidine (**31a**) in very good yield as a mixture of stereoisomers.

To get diastereopure pyrrolidines, the authors synthesised the corresponding nitroso compounds **36** (Scheme 2). The diastereomers were then separated successfully by recrystallisation, giving *trans*-(±)-**36** in a 51% yield and *cis*-**36** in a 20% yield. The nitrosopyrrolidines were finally liberated from the nitroso-group by acidic treatment, giving the corresponding diastereopure pyrrolidines in poor yields.[40]



Scheme 2: Synthesis route to *cis*- and *trans*-**31a** by Overberger and co-workers.[40]



Scheme 3: A synthesis route to thiazolylpyrrolidines **31b** by Hashimoto and co-workers. a) Synthesis of both diastereomers of **39** and their b) hydrogenation and Boc protection. c) Final steps of the route.[43]

In 2002, Hashimoto and co-workers published a synthesis route for thiazolylpyrrolidine **31b**, which was used in the synthesis of thiostrepton antibiotics (see also subsection 2.2.3).[43] They started the route by synthesising *cis*-**39** with a high-yielding cascade reaction between *meso*-**38** and benzylamine (Scheme 3a).[44] *cis*-**39** could be epimerised to (±)-*trans*-**39**, but in a poor, 47% yield.[45] Both of the diastereomers **39** were deprotected *via* hydrogenation and Boc protected to give compounds **40** with good yields (Scheme 3b).[46]

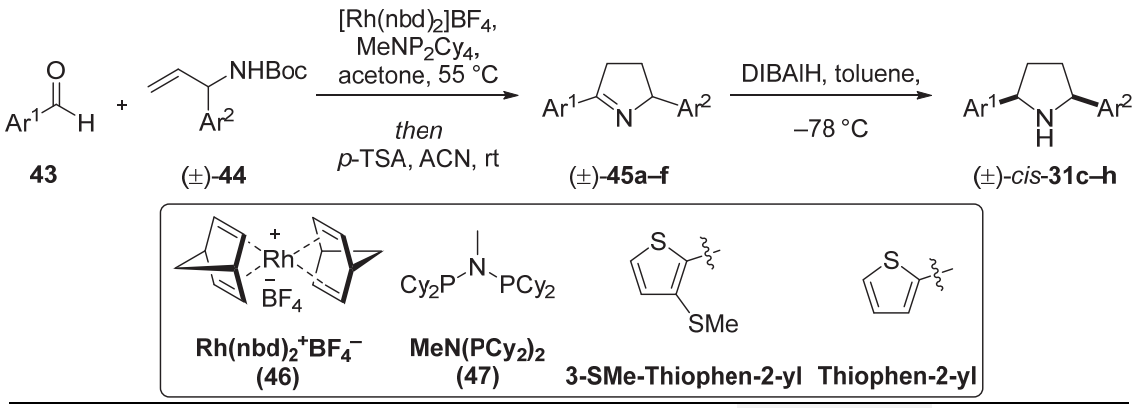
Both diastereomeric pyrrolidines **40** were then saponified and converted to mixed anhydrides, which reacted with ammonia to give the corresponding amides (Scheme 3c). The amides were transformed to thioamides **42** with Lawesson's reagent. In the case of the *cis*-diastereomer, the four-reaction sequence was completed without epimerisation, with a 33% yield. The formation of the *trans*-isomer **42** was not as high yielding because of the epimerisation that took place in the course of the sequence, resulting in practically a 50:50 *dr*.[43]

Finally, the desired thiazolylpyrrolidines **31b** were furnished by using Hantzsch's thiazole synthesis (Scheme 3c).[47] A mixture of diastereomers (*dr* 78:22) was obtained, even with a diastereomerically pure starting material *cis*-**42**. However, this was not detrimental in general, since the researchers did not need diastereomerically pure **31b** in the thiostrepton synthesis. The synthesis of stereoisomerically pure *trans*-**31b** would probably have been possible by using

a chiral pyrrolidine *trans*-**39** available, for example, *via* kinetic resolution,[48] but the risk of epimerisation at some point of the route would still be huge.[43]

In 2016, Willis and co-workers synthesised racemic unsymmetrical 2,5-diarylpyrrolidines with a hydroacylation–cyclisation–reduction sequence (Table 1). The essential atoms of the pyrrolidine core were formed with a rhodium-catalysed hydroacylation reaction between aldehydes and allylic amines.[49]

Table 1: A synthesis route to pyrrolidines **31** by Willis and co-workers.[49]

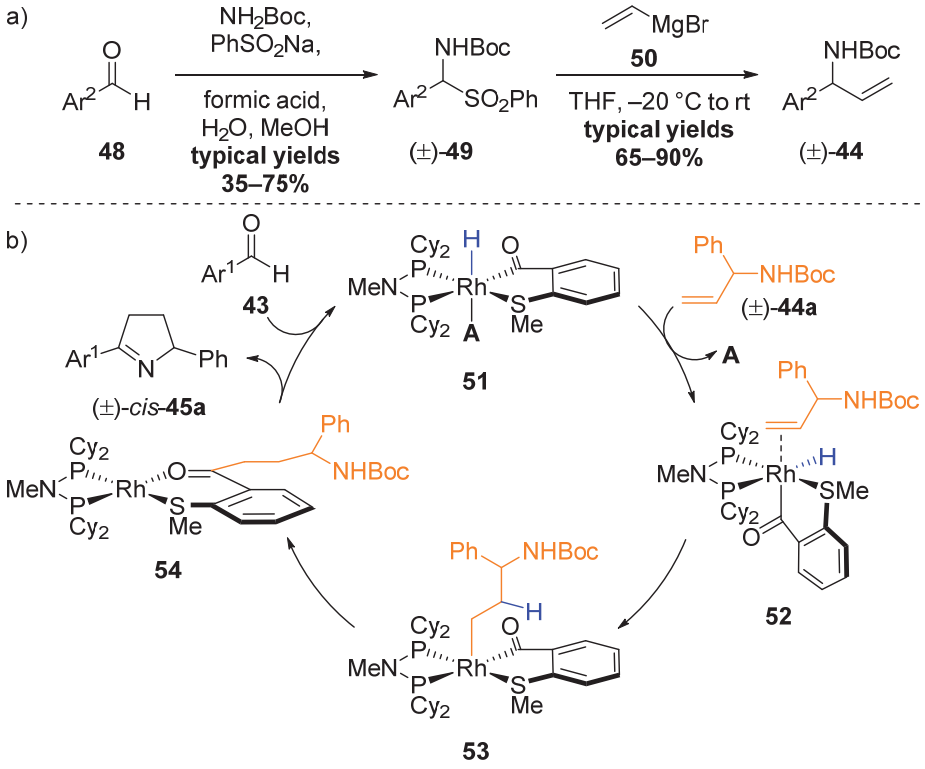


Entry	Ar^1	Ar^2	Yield (%)[a]	Yield (%)[b]
1	2-SMe-Ph	Ph	**a**: 84	**c**: 90 (68)[c]
2	4-Br-2-SMe-Ph	Thiophen-2-yl	**b**: 82	**d**: 77
3	2,4-diSMe-Ph	Ph	**c**: 87	**e**: –
4	3-SMe-Thiophen-2-yl	Ph	**d**: 76	**f**: 96
5	3-SMe-Thiophen-2-yl	4-OMe-Ph	**e**: 90	**g**: 90
6	4-Br-2-SMe-Ph	4-CF_3-Ph	**f**: 86	**h**: 92

a) Yield of the dihydropyrrolidines **45a–f**. b) Yield of the *cis*-pyrrolidines **31c–h**. c) Yield of the isolated *trans*-isomer **31c** in parentheses after a reaction with $NaBH_4$ in acetic acid at room temperature (*dr* 75:25).

The reaction worked well with allylamine compounds (±)-**44** substituted with both electron-rich and -poor aryls, as well as with heteroaryls (Table 1). There was also a slight variation in the aldehyde **43**, such as moderately electron-poor Br-substituted aryl (Table 1, entries 2 and 6) and thiophenyl (Table 1, entries 4 and 5). The hydroacylation step was followed by an acidic Boc deprotection, causing a cyclisation to dihydropyrroles **45**. The yields were very good (90% at best).[49]

The substrate scope of the method was rather limited, even though many allylamine substrates **44** were available within two steps from an arylaldehyde **48** *via* amido-sulfone formation and a nucleophilic addition reaction (Scheme 4a).[50–52] A possible poor commercial availability of *o*-SMe-Ph aldehydes **43** and the additional steps required to prepare them might raise the barrier to use the method in a wider context.



Scheme 4: a) Synthesis of the allylamine substrates.[50–52] b) A proposed shortened catalytic cycle of the hydroacylation reaction.[49,53] **A**=acetone.

The crucial part of the key transformation was the need for a diphosphine ligand **47** with a small bite angle (∠ P-Rh-P). It was hypothesised to promote both the hydroacylation reaction over a competing decarbonylation of the aldehyde and the formation of linear products over branched ones. In addition, a directing group in the *ortho* position of the aldehydes was a necessity. Its role was to chelate the rhodium–ligand complex to the aldehyde substrate and thus form a hydride complex **51** (Scheme 4b). This complex coordinated with the allylamine substrate (**52**), leading to hydride insertion (**53**) and reductive elimination, providing the final hydroacylation product ((±)-*cis*-**45a**).[49,53] Fortunately, the *o*-SMe-group could be removed *via* one-pot reduction prior to the cyclisation reaction.[54]

The final reduction with DIBAlH favoured the formation of *cis*-pyrrolidines **31** exclusively, due to the bulky reductant attacking the imine from the sterically less demanding side, i.e. *trans* to the Ar^2 (Table 1). However, the diastereoselectivity could be inverted to favour the *trans*-isomer by using $NaBH_4$ in acidic conditions. This was demonstrated with the synthesis of (±)-*trans*-**31c** in a good 68% yield and with 75:25 *dr*.[49] Even though chiral pyrrolidines were not synthesised in this study, it would, in principle, be possible with this method by starting with enantiopure allylamine **44** compounds.

One of the most widely used routes to chiral *trans*-2,5-diarylpyrrolidines is the one developed by Chong and co-workers.[55] Chronologically, it is the second asymmetric route for the pyrrolidines of interest. It was invented to solve the problems associated with pyrrolidines (*R*,*R*)-**8** (low boiling point, difficult to

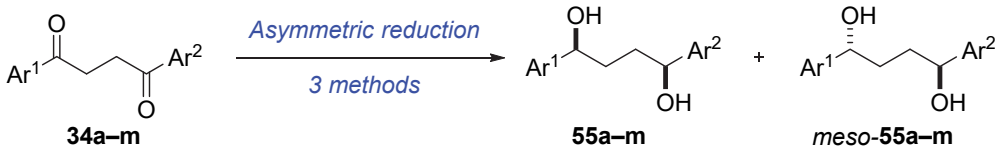
recover) and (*R*,*R*)-**9** (complex synthesis routes, expensive commercially) and to get more stereoselectivity in asymmetric reactions with the help of large phenyl substituents (Figure 1, Chapter 1).

The route starts with the preparation of 1,4-diarylbutane-1,4-diones **34** (Scheme 5), which have been accessed in multiple ways. The strategies used in the 2,5-diarylpyrrolidine context have included Friedel-Crafts reaction between a suitable aryl and fumaryl chloride (**34a,i**), followed by a double bond reduction.[55,56] The most popular way, however, has been a Rongalite-mediated coupling of substituted 2-bromoacetophenones, which has enabled the synthesis of symmetrical diketones in varying yields (**34a,b,d–e,g,l**).[36,37,56–58] In addition, Kulinkovich's activated cyclopropyl method with substituted acetophenones (**34c,m**), as well as nucleophilic substitution between an organolithium reagent and suitable 1,4-diamidebutane (**34j,k**), have been used.[59–62]

Only a few unsymmetrical diketones have been utilised in 2,5-diarylpyrrolidine synthesis. To make diketone **34h**, a Grignard addition to a suitable Weinreb amide, followed by an indium-homoenolate formation and a palladium coupling of the homoenolate with benzoyl chloride, were required.[56,63] In another example, Kulinkovich's reaction was used in the synthesis of diketone **34f**.[57,64]

In the seminal 2,5-diarylpyrrolidine paper by Chong and co-workers, the diketone **34a** was reduced to diol (*S*,*S*)-**55a** with a chiral borane reagent (–)-DIP-Cl ((–)-**56**) in a 93% yield and with a >99:1 *er* (Scheme 5).[55] Later, Steel and co-workers replaced the stoichiometric reductant with a catalytic CBS reaction,[26,27] which utilised an oxazaborolidine catalyst (*R*)-**57**, prepared *in situ* from a chiral (*R*)-Ph_2-pyrrolidin-2-yl methanol and $B(OMe)_3$.[65] They were able to synthesise (*R*,*R*)-1,4-diphenylbutane-1,4-diol ((*R*,*R*)-**55a**) in a 96% yield and with high stereoselectivities (>99:1 *er*, >97.5:2.5 *dr*). This method has become the most widely used route in the context of 2,5-diarylpyrrolidine synthesis, enabling the reduction of aryl diketones with both electron-withdrawing and mildly electron–donating substituents. However, the diastereoselectivities have deviated from excellent, directly detected after HPLC analysis[66] or indirectly from the isolated amounts of *cis*-**59** diastereomers after the next steps, which originate from the *meso*-diols **55**.

Usually, the unwanted diastereomer has been successfully separated after the later steps, but there are also exceptions.[56,59] To overcome the diastereoselectivity problems of CBS reduction, Yamada and co-workers developed a borohydride reduction, where the stereoinformation was transferred by a chiral cobalt complex (*S*,*S*)-**58** (Scheme 5).[59] They were able to synthesise diols (*R*,*R*)-**55a**, (*R*,*R*)-**55i** and (*R*,*R*)-**55m** in good to excellent yields with brilliant stereoselectivities. It is noteworthy that the reduction of diketone (*R*,*R*)-**55m** with (–)-DIP-Cl[67] was impractical, and with CBS reduction completely unachievable.[65] Despite the great results, Yamada's method has not gained more popularity in the 2,5-diarylpyrrolidine context, probably because the complex (*S*,*S*)-**58** is not commercially available and requires preceding synthesis steps,[68] whereas both enantiomers of Ph_2-pyrrolidin-2-yl methanol are readily available.



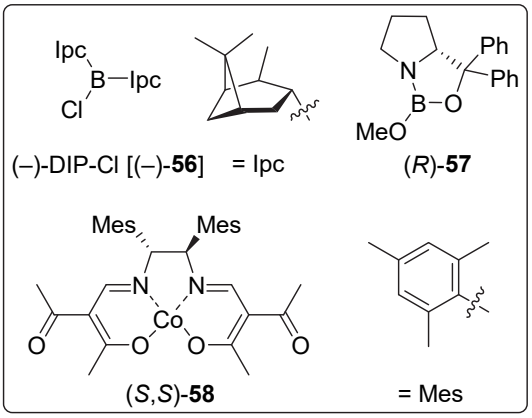
Label	Ar^1	Ar^2
a	Ph	Ph
b	3,5-$(CF_3)_2$-Ph	3,5-$(CF_3)_2$-Ph
c	4-Cl-3-NO_2-Ph	4-Cl-3-NO_2-Ph
d	4-NO_2-Ph	4-NO_2-Ph
e	4-CF_3-Ph	4-CF_3-Ph
f	3,5-$(CF_3)_2$-Ph	Ph
g	4-F-Ph	4-F-Ph
h	3,5-Me_2-Ph	Ph
i	4-*t*-Bu-Ph	4-*t*-Bu-Ph
j	3,5-Me_2-Ph	3,5-Me_2-Ph
k	3,5-*i*-Pr_2-Ph	3,5-*i*-Pr_2-Ph
l	2-Me-Ph	2-Me-Ph
m	2-naphthyl	2-naphthyl

Asymmetric reduction methods

(–)-DIP-Cl reduction:
(–)-**56**, THF, –78 °C to rt
55a: 93%, >99:1 *er*, >98:2 *dr*
55k: (n.d.)

CBS reduction:
(*R*)-**57**, BH_3•SMe_2, THF, rt
55a: 96%, >99:1 *er*, >97.5:2.5 *dr*
55b–j, l: 74–99%

Co-complex–borohydride reduction:
(*S*,*S*)-**58**, $NaBH_4$, tetrahydrofurfuryl alcohol, EtOH, $CHCl_3$, –40 °C *or* –20 °C
55a, i, m: 75%–quant., >99:1 *er*, >94:6 *dr*

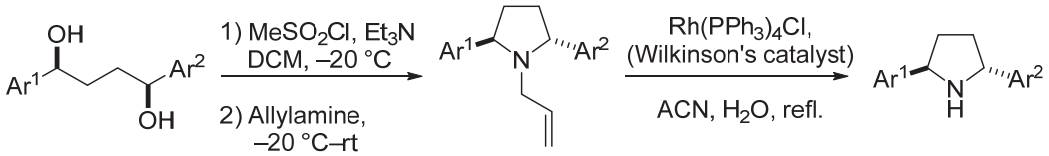


Scheme 5: Asymmetric reduction methods used in the 2,5-diarylpyrrolidine synthesis routes. Yields are sums of the diastereomer mixtures. (–)-DIP-Cl reduction by Chong *et al.*,[55] CBS reduction by Steel *et al.*,[65] also used by others,[37,56,57,60,61] and Co-complex catalysed borohydride reduction by Yamada *et al*.[59] The stereochemistry is represented with bold bonds instead of wedge bonds to describe the relative stereochemistry rather than absolute stereochemistry.

Chong and co-workers continued the synthesis by dimesylating the diol (*S*,*S*)-**55a** and treating it with ammonia in several conditions to get the desired pyrrolidine (*R*,*R*)-**59a** directly.[55] Unfortunately, the reaction gave only 33% of the expected product and was contaminated with the corresponding tetrahydrofuran side product. A reaction with allylamine, however, provided the wanted *trans*-*N*-allylamine pyrrolidine (*R*,*R*)-**59a** in a 71% yield (Table 2, entry 1). Chong and Steel noticed that the dimesylate was rather unstable when isolated. To circumvent the problems arising from this, Yamada and co-workers tried the S_N2-cascade with allylamine in the same pot, without the isolation of the dimesylate, getting (*S*,*S*)-**59a** in a 71% yield, but as a mixture of diastereomers.[59] Later, Pihko and co-workers isolated *cis*-**59a** and (*S*,*S*)-**59a** in 12% and 74% yields, re-

spectively, confirming that a partial epimerisation took place during the reaction.[36]

Table 2: The formation of *trans*-2,5-diarylpyrrolidines from chiral diols.



55a–m *trans*-**59a–m** *trans*-**31a, i–t**

Entry	Yield (%)[a]	*dr*	Yield (%)[b]	*er*[c]	Ref
1	**a**: 74 (71)[d]	86:14	**a**: 98	>99:1	36,55
2	**b**: 52 (70)[d]	80:20	**i**: 91	99:1	56,57
3	**c**: 39	n.d.	**j**: 74	n.d.	60
4	**d**: 59[d, e]	83:17	**k**: 96	99:1	57
5	**e**: 59	n.d.	**l**: 70	99:1	56
6	**f**: 64	82:18	**m**: 88	99:1	57
7	**g**: 75	82:18	**n**: 95	99:1	57
8	**h**: 74	n.d.	**o**: 82	>99:1	37
9	**i**: 58	n.d.	**p**: 85 (75)	>99:1 (95:5)	56,59
10	**j**: n.d.	n.d.	**q**: 44[f]	n.d.	61
11	**k**: n.d.	n.d.	**r**: 41[f]	n.d.	62
12	**l**: 62[g]	87:13	**s**: 67[e]	85:15	56
13	**m**: 74[g]	n.d.	**t**: 63	>99:1	59

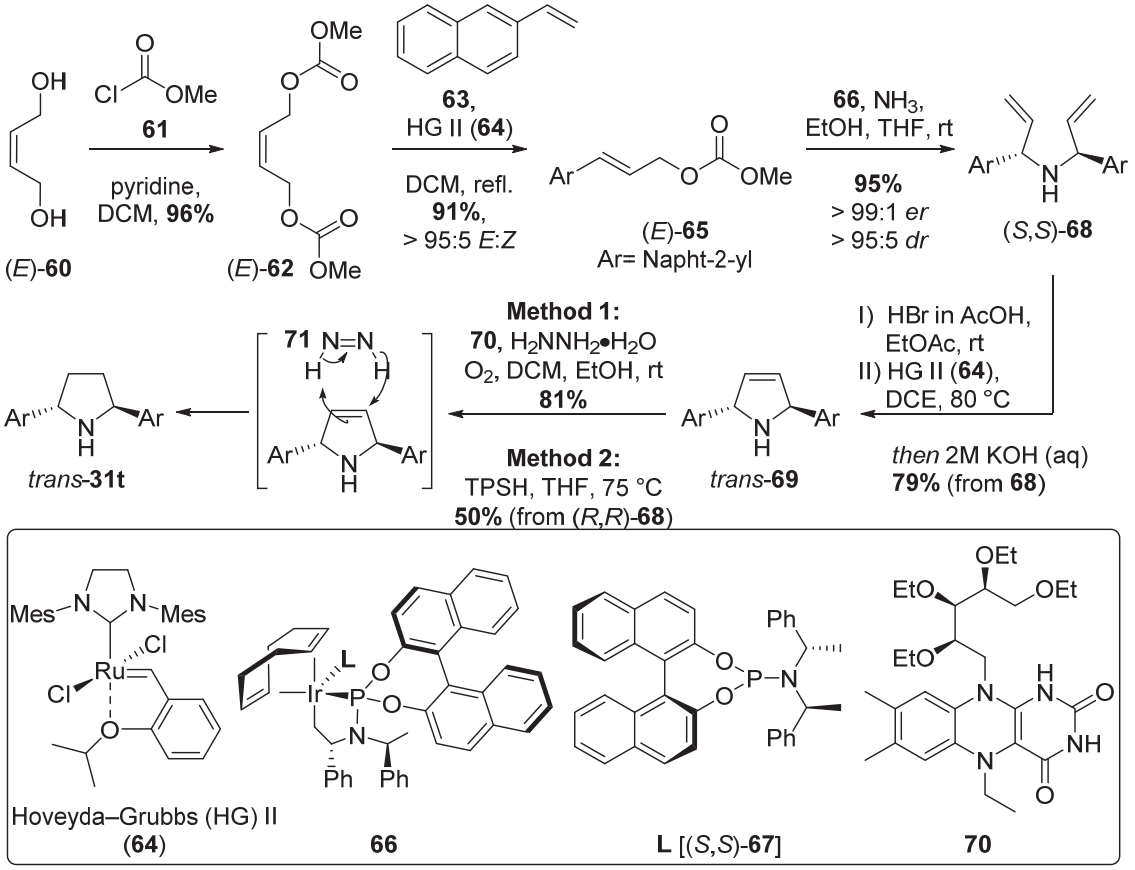
a) Yields of the *trans*-*N*-allyl 2,5-diarylpyrrolidines **59** from the corresponding diol (see the matching label letter from Scheme 5). b) Yields of the *trans*-2,5-diarylpyrrolidines **31** (see the correct substitution patterns *via* the compounds **59**). c) *er* of the *trans*-2,5-diarylpyrrolidines **31**. d) Yield when the parent dimesylate was isolated prior to the S_N2-cascade. e) Poor yields were obtained when the reaction was done in one pot (see Section 4.3). f) Overall yield from the parent diketone. g) The diastereomers were inseparable.

The one-pot dimesylation–S_N2 cascade has since been used successfully to synthesise *trans*-*N*-allylamine pyrrolidines with both electron-poor (**59b–g, m**, Table 2, entries 2–7, 13)[56,57] and mildly electron–rich (**59h-l,** Table 2, entries 8–12)[37,56,59,61,62] substituents. The yields were very good (75% at best), except for **59c**[60], and the diastereomers have been separable in most of the examples. In the case of 3,5-$(CF_3)_2$-Ph- and 4-NO_2-Ph-substituted compounds, the dimesylate was stable enough to be isolated as a crude product, and dissolving the dimesylate in DMF, followed by the addition of allylamine, gave better yields than the one-pot approach. Lastly, compounds bearing aryls with electron-donating substituents, as well as a Ph-substitution, are seemingly cumbersome starting materials for this route, probably due to the instability of the formed dimesylates, even in solutions (see also Section 4.3). This instability might lead

to a loss of diastereomeric purity prior the nucleophilic additions, which indicates a change from the S_N2 reaction type to S_N1.[66,67]

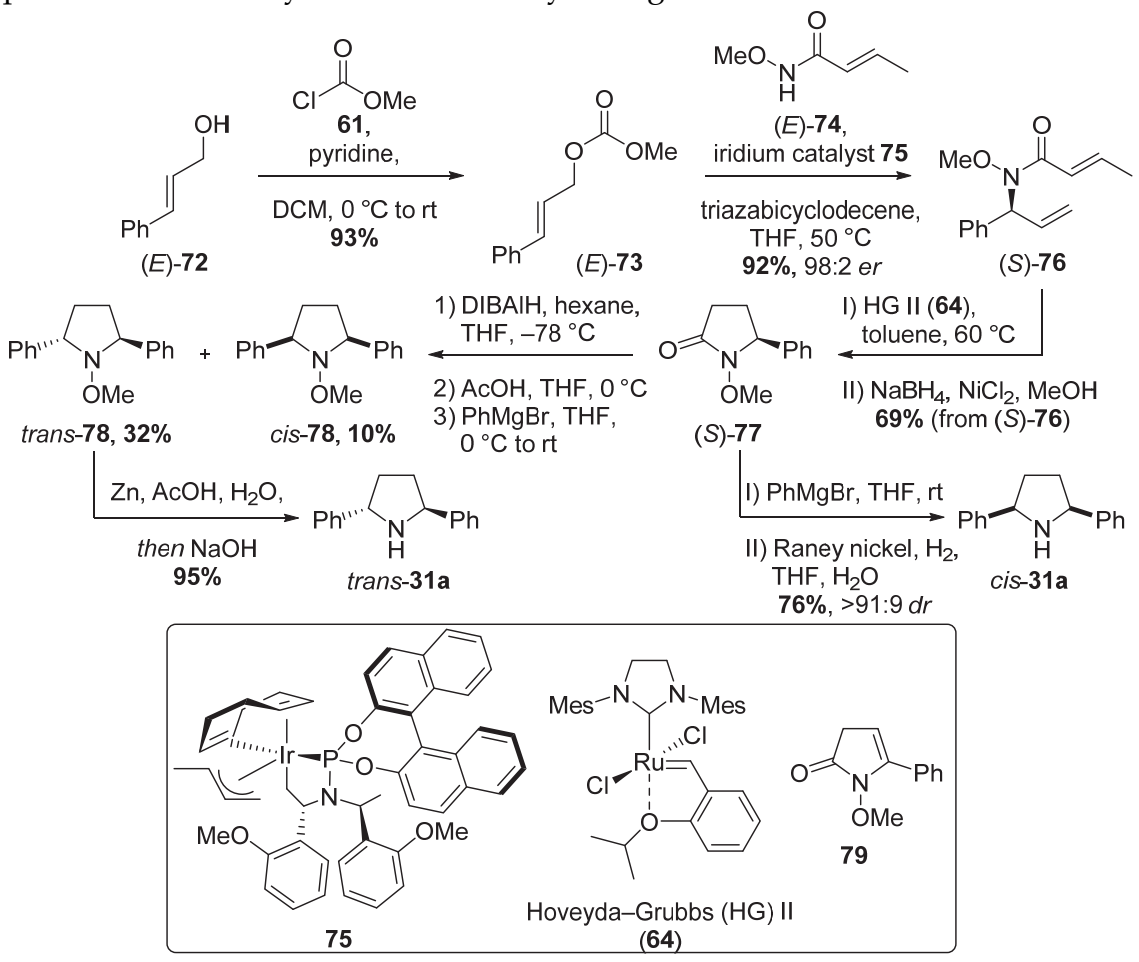
The allyl group was cleaved off in the final step with Wilkinson's catalyst to give the *trans*-2,5-diarylpyrrolidines **31** in good to excellent yields (Table 2). The *er*'s of the compounds were brilliant (>99:1), except for the only *ortho*-substituted example (*S*,*S*)-**31s** (Table 2, entry 12). Since the *er* was closely related to the enantioselectivity of the asymmetric reduction, another method would probably have been more suitable in this case. The synthesis of pyrrolidines (*R*,*R*)-**31i**, (*R*,*R*)-**31k** and (*S*,*S*)-**31n** will be discussed in more detail in Chapter 4 of this dissertation.

In 2010, Teichert and Feringa developed an enantioselective synthesis route for 2-naphthyl-substituted *trans*-pyrrolidine (*S*,*S*)-**31t**.[69] They commenced the work by first synthesising dimethyl carbonate (*E*)-**62** from (*E*)-diol **60**,[70,71] followed by a cross-metathesis reaction between 2-vinylnaphthalene (**63**) and (*E*)-**62**, with excellent yield and *E*/*Z*-selectivity (>95:5, Scheme 6). The stereocenters of (*S*,*S*)-**31t** were then set by an asymmetric iridium-catalysed double allylation reaction, applying the method of Hartwig and co-workers.[72] In this reaction, ammonia attacked first the benzylic carbon of (*E*)-**65**, the methyl carbonate leaving in an S_N2' manner. This was followed by a quick second allylation reaction between the allylamine intermediate and (*E*)-**65**, furnishing (*S*,*S*)-**68** with a 95% yield and excellent stereoselectivities.



Scheme 6: Enantioselective synthesis route to *trans*-(2*S*,5*S*)-2,5-dinaphth-2-ylpyrrolidine ((*S*,*S*)-**31t**) by Teichert and Feringa.[69]

The diolefin was cyclised to *trans*-dihydropyrrole **69** in another metathesis reaction with a 79% yield (Scheme 6). To facilitate the reaction, the researchers had to use the bromide salt of (*S*,*S*)-**68** as a starting material because of the unsuitability of free amine with Hoveyda–Grubbs catalyst **64**. In the final step, the double bond of *trans*-**69** was reduced with diimide, formed *in situ* from hydrazine by oxidisation with a riboflavin derivative **70**.[73] The reaction gave *trans*-**31t** in very a good, 81% yield, without epimerisation taking place.[69] Later, Trost and Mata changed the reduction step by replacing hydrazine and riboflavin **70** to 2,4,6-triisopropylbenzenesulfonyl hydrazide (TPSH), which proved to be a method almost equally effective as its predecessor.[74] Overall, the synthesis route offered a good alternative for the approach developed by Yamada and co-workers[59], even though the method required some prior synthesis steps to prepare the active catalyst **66** under strictly inert glove-box conditions.



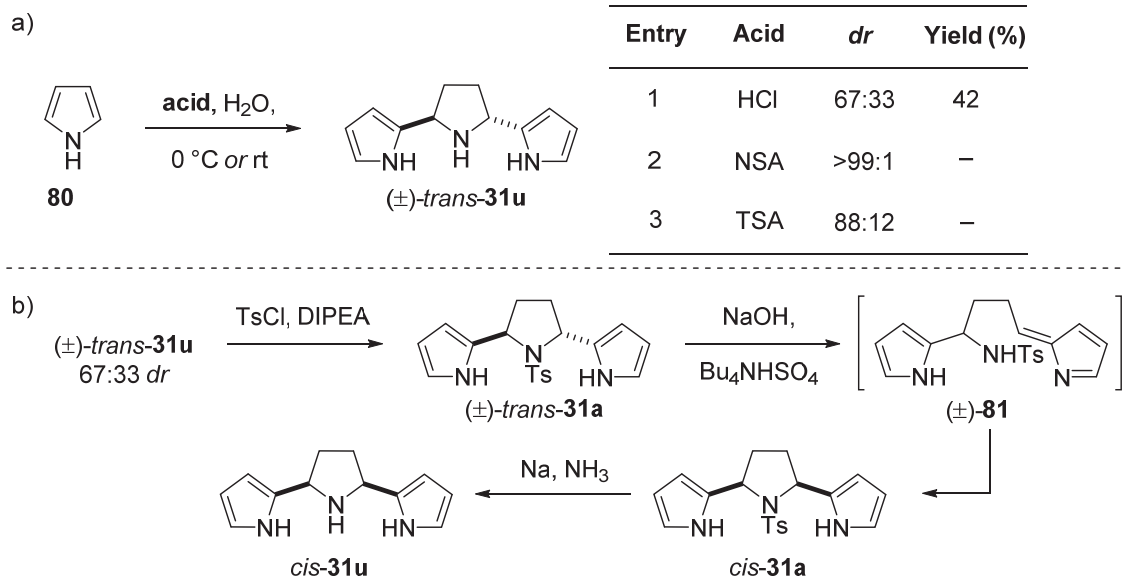
Scheme 7: Synthesis route for both diastereomers of 2,5-diphenylpyrrolidine by Helmchen and co-workers.[75]

The last presented example of the C_α-N disconnection strategy was published in 2013 by Helmchen and co-workers, who used an approach similar to Teichert and Feringa's.[69,75] They started their novel six-step synthesis route by letting (*E*)-methyl carbonate **73**, available in one step from alcohol (*E*)-**72**,[76] react in an iridium-catalysed allylic amination in a 92% yield and with excellent enantiose-

lectivity (Scheme 7). Instead of ammonia, Helmchen *et al*. used methoxyamide (*E*)-**74** as a nucleophile, which made it possible to avoid a double allylation reaction. After ring-closing metathesis, the formed crude lactam was reduced to methoxy-pyrrolidone (*S*)-**77** with $NaBH_4$ in the presence of nickel, which ensured that no double bond migration to pyrrolidone **79** occurred.[75]

The treatment of pyrrolidine (*S*)-**77** with phenylmagnesium bromide, followed by reduction and hydrogenolysis reactions with Raney nickel, provided *cis*-**31a** in a 76% yield and a 91:9 *dr* (Scheme 7). In order to get *trans*-**31a**, the researchers diverged from (*S*)-**77** and reduced it to the corresponding hemiaminal. After an elimination reaction, the formed iminium ion reacted with PhMgBr to give *trans*-**78**. The sequence of transformations was not high yielding, and some *cis*-**78** was also formed, showing the weak point of the route. Finally, *trans*-**31a** was obtained after a reductive cleavage with zinc in acidic conditions, in excellent yield.[75]

2.1.2 C_α–C_{Aryl} disconnection



Entry	Acid	*dr*	Yield (%)
1	HCl	67:33	42
2	NSA	>99:1	–
3	TSA	88:12	–

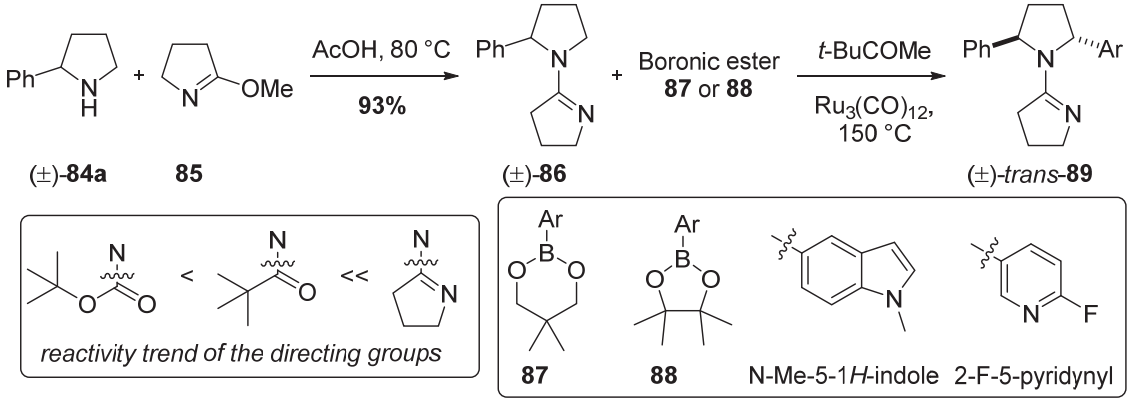
Scheme 8. a) Dennstedt–Zimmermann synthesis route to pyrrolidine (±)-*trans*-**31u** under varying acidic conditions.[77–79] b) Synthesis of *cis*-**31u** from (±)-*trans*-**31u**.[80]

The first synthesis example employing a C_α–C_{Aryl} disconnection strategy was published by Dennstedt and Zimmermann in 1888. The authors synthesised pyrrolidine **31u** by an HCl-catalysed trimerisation reaction of pyrrole (**80**).[77] However, its structure was not confirmed before the year 1957, when Potts and Smith synthesised (±)-*trans*-**31u** in a 42% yield.[78] The reaction favoured the formation of the *trans*-diastereomer (*dr* 67:33), which was later confirmed by Joule and co-workers in 1997.[80] The diastereoselectivity was enhanced by Schulz and co-workers, who used bulky naphtalenesulfonic acid (NSA) and *para*-toluenesulfonic acid (TSA) as acids.[79,80] Unfortunately, the origin of the excellent diastereoselectivity was not discussed in the paper.

Joule and co-workers invented a clever way to epimerise the *trans*-isomer to *cis*-**31u**. Monotosylation of a 67:33 diastereomeric mixture of (±)-*trans*-**31u**, followed by a basic treatment, furnished *cis*-**31a** with a quantitative conversion. The authors hypothesised that the bulky tosyl group forced the pyrrole rings to the opposite sides in relation to it. This minimised the sterical clash between the groups and thus made the *cis*-product the thermodynamic one. Finally, the tosyl group was cleaved off with sodium in liquid ammonia quantitatively.[80]

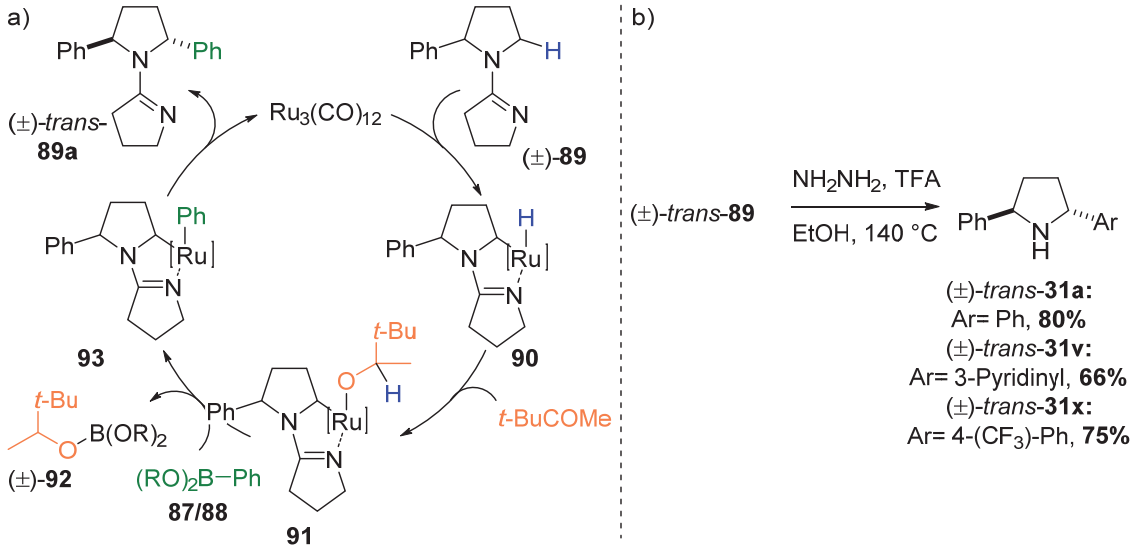
In 2006, Sames and co-workers developed a method where the C5 position of 2-phenylpyrrolidine (±)-**86** was directly arylated, using a ruthenium catalysed reaction (Table 3). To facilitate this regioselective transformation, a cleavable directing group was attached to the pyrrolidine nitrogen. From a handful of choices, a cyclic amidine outperformed both the Boc and pivaloyl groups in reactivity and was thus chosen. The differences in reactivity were not thoroughly discussed, but possibly, both the stronger Lewis basicity of the directing heteroatom and minimised sterical hindrance favoured the amidine group over others. The substrate (±)-**86** was also easily synthesised in an excellent, 93% yield in a reaction between a racemic 2-phenylpyrrolidine ((±)-**84a**) and 2-methoxy-1-pyrrolidine (**85**).[81]

Table 3: Sames' route to racemic (un)symmetrical *trans*-2,5-diarylpyrrolidines **89**.[81]



Entry	Ar	Yield (%)[a]	*dr*[b]	Boronic ester
1	**a**: Ph	76 (68)[c]	75:25	**87**
2	**b**: 4-CF_3-Ph	76	75:25	**87**
3	**c**: 4-COMe-Ph	45	–	**87**
4	**d**: 4-OMe-Ph	70	80:20	**87**
5	**e**: 2-Me-Ph	62	86:14	**87**
6	**f**: *N*-Me-5-1*H*-indole	62	83:17	**88**
7	**g**: 3-pyridinyl	72	75:25	**88**
8	**h**: 2-F-5-pyridynyl	63	75:25	**88**

a) Yields of the pyrrolidines (±)-*trans*-**89**. b) *dr* corresponds to the *trans*:*cis* ratio of isolated pyrrolidines **89**. c) A yield from a reaction with pinacol boronic ester **88** in parentheses.



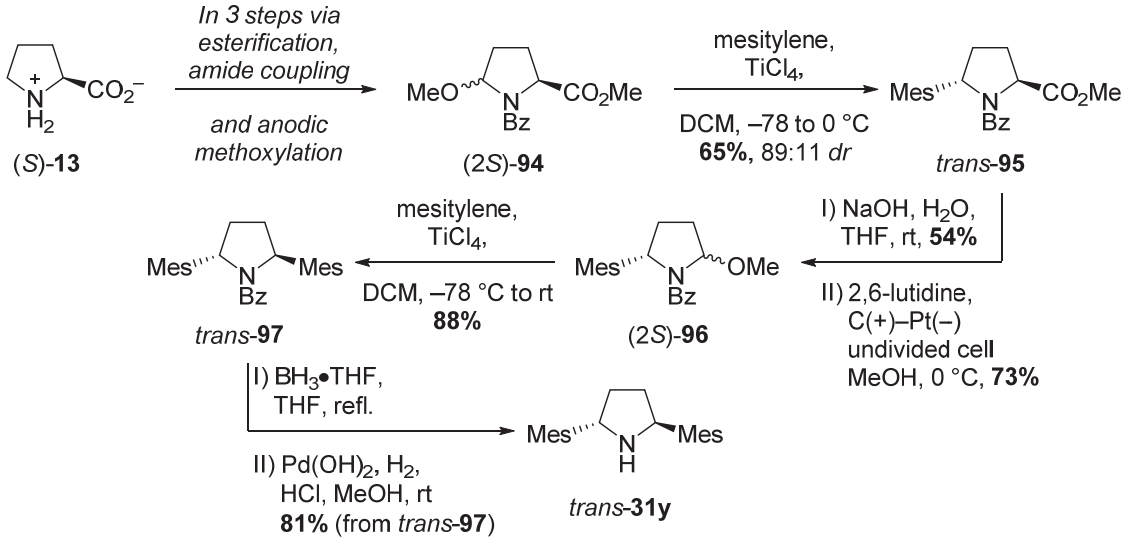
Scheme 9. a) A proposed shortened catalytic cycle of the reaction. b) The final cleavage of the directing group to get 2,5-diarylpyrrolidines.[81]

The arylation reaction was successful with a variety of arylboronic esters (**87** or **88**). Both electron-poor and -rich aryls, as well as some nitrogen-containing heteroaryls, were coupled to (±)-**86** in good to very good yields and with very good diastereoselectivities (Table 3, entries 1–2, 4–8). In addition, the diastereomers were cleanly separable by column chromatography.[81]

A reaction with the acetophenone derivative of **87** was an exception. The yield was poor, and the *dr* could not be reliably detected due to co-eluting impurities along with the *cis*-diastereomer (Table 3, entry 3). It was possible that acetophenone competed in the reduction reaction with *t*-BuCOMe, which was part of the catalytic cycle (Scheme 9a). The authors hypothesised that the reduction step occurred before the transmetalation between the boronic ester (**87** or **88**) and complex **91** to keep the cycle running: without the added ketone (*t*-BuCOMe), the formation of the coupling products (±)-*trans*-**89** was low.[81]

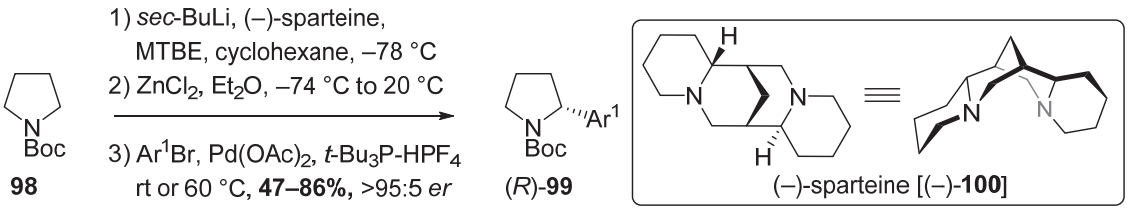
The removal of the directing group was conducted using hydrazine in acidic conditions in a pressure tube. Selected examples, (±)-*trans*-pyrrolidines **31a**, **31b** and **31g**, were deprotected with yields between 66% and 80% (Scheme 9b). Despite the method being concise, the commercial availability of 2-arylpyrrolidines **84**, especially chiral ones, is limited, meaning that some additional synthesis steps are required.[81]

In 2008, Onomura and co-workers disclosed an enantioselective synthesis route to *trans*-(2*S*,5*S*)-2,5-dimesitylpyrrolidine ((*S*,*S*)-**31y**).[82] The route started with a three-step synthesis of benzoyl-protected pyrrolidine (2*S*)-**94** from (*S*)-proline ((*S*)-**13**, Scheme 10).[83,84] (2*S*)-**94** was then arylated with mesitylene in the presence of Lewis acid in a good, 65% yield and with very good *dr* (89:11). The choice of the nitrogen protecting group was essential for the diastereoselectivity of this Friedel–Crafts type reaction; for example, the corresponding *N*-formyl pyrrolidine induced almost no diastereoselectivity (57:43 *dr*), whereas *N*-CO_2Me and *N*-Cbz substituents favoured the formation of *cis*-**95** (0:100 *dr*) exclusively.



Scheme 10: Enantioselective synthesis route to *trans*-(2*S*,5*S*)-2,5-dimesitylpyrrolidine ((*S*,*S*)-**31y**) by Onomura and co-workers.[82]

The mesitylated pyrrolidine *trans*-**95** was then saponified and acidified, giving the corresponding carboxylic acid as diastereomerically pure after recrystallisation in a 54% yield (Scheme 10). The acid was decarboxylated electrochemically in methanol, which gave the methoxylated compound (2*S*)-**96** as a mixture of diastereomers. The earlier arylation reaction was then repeated, giving the benzoyl protected *trans*-pyrrolidine **97** as a single diastereomer in very good yield. The benzoyl group of *trans*-**97** was reduced to a benzyl group, which was cleaved off using Pd-catalysed hydrogenolysis, giving (*S*,*S*)-dimesitylpyrrolidine **31y** in an 81% yield over two steps. It was noteworthy that mainly, the bond between the nitrogen and the protecting group carbon was affected, the other benzylic positions remaining intact. The wider use of the route remained unexplored, though, since only mesitylene was used in the arylations[82].[82]



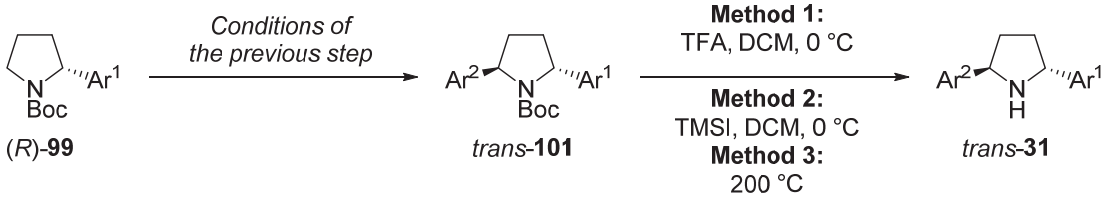
Scheme 11: Enantioselective arylation of Boc-protected pyrrolidine (*R*)-**99**, developed by Campos *et al* and later widely used by Denmark and Trost with their co-workers (see Table 4 for the list of Ar[1]-substituents used in the 2,5-diarylpyrrolidine context).[66,85,86]

One of the most popular ways to construct *trans*-2,5-diarylpyrrolidines was developed by Campos and co-workers at Merck in 2006.[85] They started their synthesis route by deprotonating the C_α-proton of *N*-Boc-pyrrolidine (**98**) enantioselectively with *sec*-BuLi in the presence of a stoichiometric amount of (–)-sparteine (Scheme 11). The lithiated **98** was transmetallated in the same pot with a substoichiometric amount of $ZnCl_2$, forming the corresponding or-

ganozinc-species, which was finally coupled with phenylbromide in a Negishi coupling reaction. No β-elimination was reported to hamper the yields.

Later, both Trost and Denmark, with their co-workers, widened the substrate scope to bulky naphthyls, biphenyls and to aryls with electron-donating groups (Scheme 11, Table 4). Electron-poor aryl and a heteroaryl were also suited. Most of the monoarylated pyrrolidines (*R*)-**99** were obtained in good yields and with excellent enantioselectivities (>95:5 *er*).[66,86]

Table 4: A synthesis route to *trans*-2,5-diarylpyrrolidines **31**, originally developed by Campos and co-workers and later widely used by Denmark and Trost with their co-workers.[66,85,86]



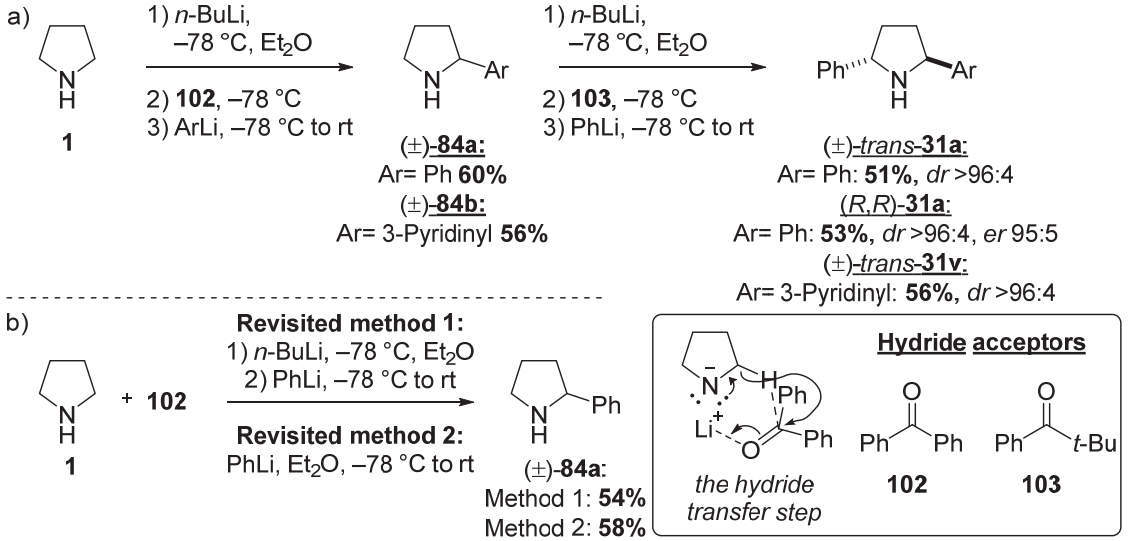
Entry	Ar^1	Ar^2	Yield (%)[a]	*dr*	Yield (%)[b]	Ref
1	Ph	Ph	**a**: 57	96:4[c]	**a**: –	85
2	Ph	2-OMe-Ph	**b**: 44	96:4	**z**: 97[d]	86
3	Ph	2-naphthyl	**c**: 45	>98:2	**aa**: quant.[d]	86
4	1-naphthyl	1-naphthyl	**d**: n.d.	n.d.	**ab**: 10 [d, e]	86
5	2-naphthyl	2-naphthyl	**e**: 50	>98:2	**ac**: 98[d]	86
6	2-naphthyl	1-naphthyl	**f**: 45	>98:2	**ad**: quant.[d]	86
7	2-naphthyl	3,5-*t*-Bu_2-Ph	**g**: 61	>98:2	**ae**: 86[d]	86
8	3-Ph-Ph	3-Ph-Ph	**h**: 49	>98:2	**af**: 97[d]	86
9	4-Ph-Ph	4-Ph-Ph	**i**: 23	>98:2	**ag**: 99[d]	86
10	3,5-Ph_2-Ph	3,5-Ph_2-Ph	**j**: 48	>98:2	**ah**: 92[d]	86
11	2-Me-Ph	2-Me-Ph	**k**: 17	n.d.	**s**: ~97[f]	66
12	3,5-Me_2-Ph	3,5-Me_2-Ph	**l**: 21	n.d.	**q**: 93[d]	66
13	2-OMe-Ph	Ph	**m**: 33	95:5	**z**: *entry 2*	86
14	2-OMe-Ph	2-OMe-Ph	**n**: 37	94:6	**ai**: 71[d]	86
15	4-OMe-Ph	4-OMe-Ph	**o**: 18	n.d.	**aj**: 82[f]	66
16	5-Me-2-thienyl	5-Me-2-thienyl	**p**: 13	n.d.	**ak**: ~64[g]	66
17	3,5-*t*-Bu_2-Ph	3,5-*t*-Bu_2-Ph	**q**: –	n.d.	**al**: –	66
18	3,5-$(CF_3)_2$-Ph	3,5-$(CF_3)_2$-Ph	**r**: –	n.d.	**i**: –	66

a) Yields of Boc-pyrrolidines *trans*-**101**. b) Yields of pyrrolidines *trans*-**31**. c) *er* of *trans*-**31a** was >99:1. d) Method 1 was used. e) Yield over two steps. f) Method 2 was used. g) Method 3 was used.

Campos and co-workers tested first whether *trans*-**101a** could be synthesised diastereoselectively in a substrate-controlled manner by using TMEDA instead

of a stoichiometric amount of (–)-sparteine. Unfortunately, both the yield and *dr* were poor (42%, 66:34 *dr*). The same reaction conditions as in the previous step were then applied, which gave *trans*-**101a** in fair yield, but with excellent *dr* and *er* (Table 4, entry 1).[85]

Later, Trost and Denmark with their co-workers synthesised a variety of both symmetrical and unsymmetrical Boc-protected *trans*-2,5-diarylpyrrolidines **101** with this approach (Table 4). They also noticed that the second arylation was far more challenging to accomplish than the first one. The problems were related to solubility issues and to a competitive deprotonation at C2, which lowered the yields of this transformation. Two compounds (**101q** and **101r**) could not be synthesised at all (Table 4, entries 17–18). The yields were thus mostly under 50%, but the diastereoselectivities still remained outstanding (>94:6 *dr*). Lastly, the pyrrolidines *trans*-**101** were deprotected either under acidic conditions, with TMSI, or by heating at 200 °C, mostly in excellent yields.[66,86]



Scheme 12. a) The synthesis route to *trans*-2,5-diarylpyrrolidines by Seidel and co-workers. In the synthesis of (*R*,*R*)-**31a**, the *er* of the starting material (*R*)-**84a** was 95:5. b) Simplification of the first step of the method.[87]

The last synthesis example, employing a C_α–C_{Aryl} disconnection strategy, was published quite recently in 2018 by Seidel and co-workers, who disclosed a short and protecting-group-free synthesis route to *trans*-2,5-diarylpyrrolidines. In their approach, pyrrolidine (**1**) was first oxidised *in situ* to the corresponding imine, which was then let to react with various nucleophilic aryllithiums (Scheme 12a). The imine formed rapidly, which was a result of a deprotonation of **1** and a hydride transfer from its C_α to the acceptor ketone (**102** or **103**). The sequence worked with aryls having both electron-withdrawing and –donating groups in fair to good yields.[87]

From the wide substrate scope, racemic 2-phenyl pyrrolidine ((±)-**84a**) and 2-(3-pyridynyl) pyrrolidine ((±)-**84b**) were further arylated to the corresponding *trans*-2,5-pyrrolidines **31** in ~50% yields (Scheme 12a). The reactions were highly diastereoselective and favoured the formation of the *trans*-diastereomer al-

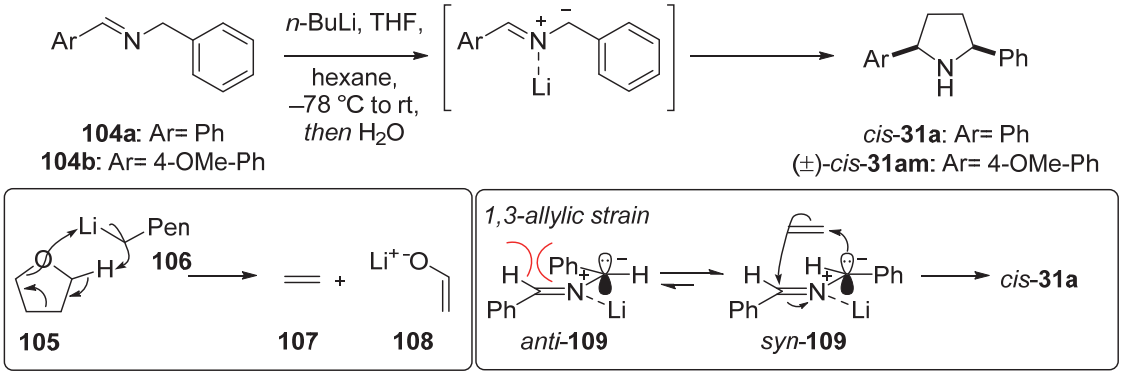
most exclusively. The selectivity was due to the attack of the organolithium reagent from the less hindered face of the imine intermediate. In addition to racemic substrates, enantioenriched (2*R*)-2-phenylpyrrolidine ((*R*)-**84a**) was also arylated. The reaction gave (*R*,*R*)-**31a** in a 53% yield, without epimerisation taking place during the reaction, based on the excellent *dr* and *er*.

Amazingly, the lithiation and pyrrolidine oxidation steps were faster than the attack of the organolithium to the acceptor ketones, leading to a noticeable chemoselectivity in the reaction. The researchers also noticed that the yield of the reaction barely dropped even though a preformed mixture of **1** and **102** reacted with either *n*-BuLi and PhLi or PhLi alone, instead of stepwise addition, as done initially (Scheme 12b).[87]

As short and superb as the Seidel group's method is, there is one drawback. The larger use of the method to produce chiral 2,5-diarylpyrrolidines is dependent on the chiral starting material. Access to these compounds would probably require some additional synthesis efforts since chiral 2-arylpyrrolidines **84** are expensive and not widely available from commercial sources.

2.1.3 C_α–C_β disconnection approach

The C_α–C_β disconnection approach has not been a widely used strategy for making 2,5-diarylpyrrolidines, even though Terashima and Kamata disclosed a short and protecting-group-free synthesis route already in 1980.[88] They found out that a deprotonation of simple imine substrates **104** with *n*-BuLi to make the corresponding aza-allyllithium compounds, followed by 1,3-anionic cycloaddition with ethylene, formed *cis*-2,5-diarylpyrrolidines **31a** and (±)-**31am** exclusively (Scheme 13). The authors did not report yields for these transformations, though, but yields for the corresponding *N*-methyl pyrrolidines, achieved after MeI-quench in place of water, were 61% and 78%, respectively.

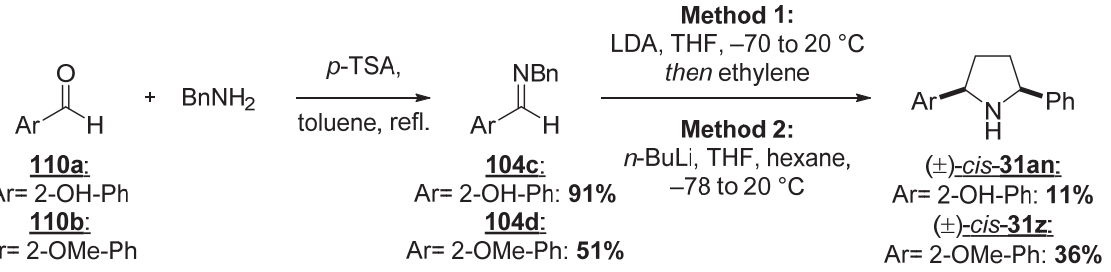


Scheme 13: 1,3-anionic cycloaddition developed by Terashima and Kamata, which was used in *cis*-2,5-diarylpyrrolidine synthesis.[88]

The authors exploited the dissociation of THF into ethylene in the presence of organolithiums in a clever way (Scheme 13). The cycloadducts were absent when the reaction was run in diglyme in place of THF, but were again present when ethylene gas was bubbled into the solution. The reason for the *cis*-

diastereomer preference was probably due to the 1,3-allylic strain that was present in the conformation leading to the *trans*-diastereomer (*anti*-**109**).[88]

A similar approach was later used by researchers in Rhone-Poulenc Rorer S.A in the synthesis of pyrrolidines *cis*-**31an** and *cis*-**31z**. They used both ethylene gas and THF-dissociation methods, but the desired products were obtained in poor yields. Unfortunately, the reasons for the inferior performance of the reactions were not discussed in the patent.[89]



Scheme 14: *cis*-2,5-diarylpyrrolidines synthesised by researchers in Rhone-Poulenc Rorer S.A. using 1,3-cycloaddition. Method 1 was used in the synthesis of (±)-*cis*-**31an** and method 2 was used in the synthesis of (±)-*cis*-**31z**.

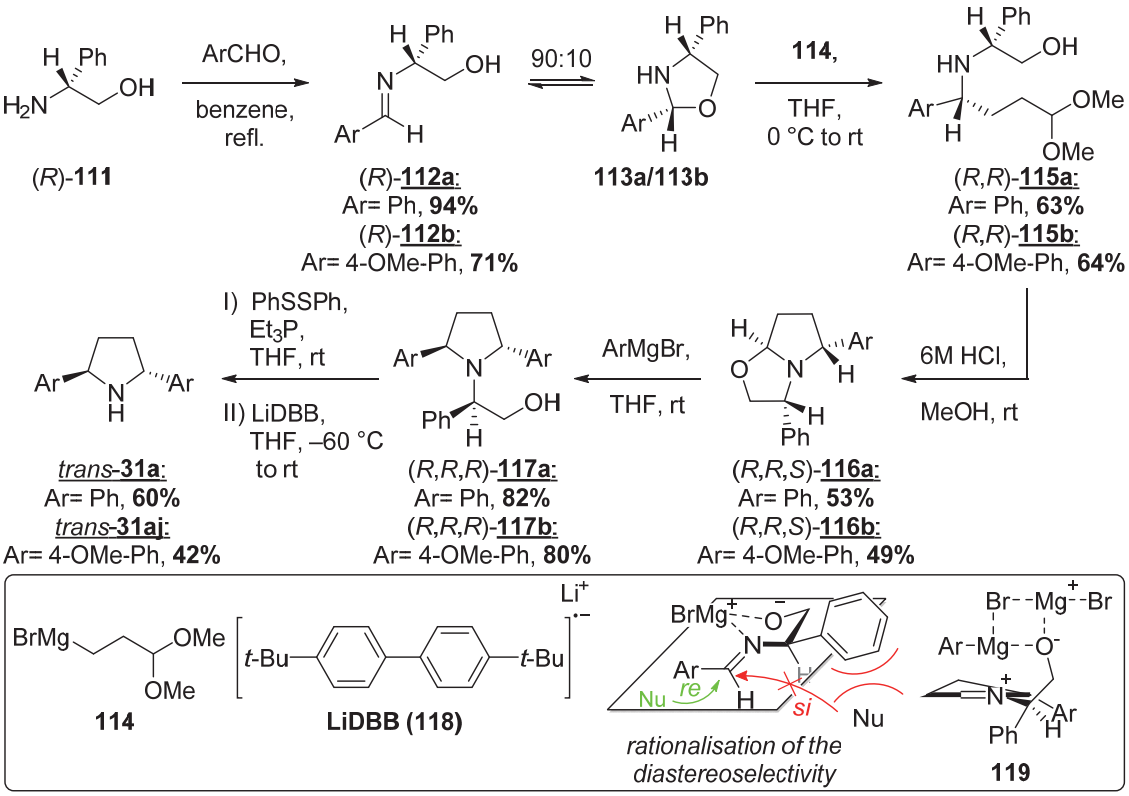
2.1.4 Mixed disconnection approaches

In 1994, Higashiyama and co-workers developed the first chiral approach for the synthesis of enantiopure *trans*-2,5-diphenylpyrrolidine ((*R*,*R*)-**31a**) and *trans*-2,5-bis(4-OMe-Ph)pyrrolidine ((*R*,*R*)-**31aj**) using a mixture of C_α–C_{Aryl}- and C_α–C_β disconnection strategies. They started with the formation of chiral imines (*R*)-**112** with a reaction between (*R*)-2-phenylglycinol and aryl aldehydes (Scheme 15). The imines, which were in an equilibrium with the cyclic oxazolidines **113a**/**113b** in solution, were treated with Grignard reagent **114**, giving acetals (*R*,*R*)-**115a** and (*R*,*R*)-**115b** in good yields. The addition was highly diastereoselective, as (*R*,*R*)-isomers were obtained exclusively. The notable diastereoselectivity was explained to originate from the chelation between the auxiliary's alkoxy and the imine nitrogen, which forced the phenyl ring to shield the *si*-side of the imine from nucleophilic attacks (Scheme 15).[90]

After low-yielding acetal-deprotection–cyclisation reactions, the bicyclic compounds were arylated with aryl Grignard reagents (Scheme 15). The protected pyrrolidines (*R*,*R*,*R*)-**117a** and (*R*,*R*,*R*)-**117b** were obtained in circa 80% yields as single diastereomers. The authors hypothesised that the supreme diastereoselectivities were due to the alkoxy groups that served as directing groups for the Grignard reagents after the oxazolidine rings opened (Scheme 15, complex **119**). In addition, the sterical shielding effect of the two aryl groups on the *si*-side cannot be neglected.[90]

To furnish the targeted *trans*-(2*R*,5*R*)-2,5-diarylpyrrolidines, compounds (*R*,*R*,*R*)-**117a** and (*R*,*R*,*R*)-**117b** were deprotected using the conditions by Meyers and Burgess.[91] The compounds were first converted to the corresponding thiophenyl derivatives, after which, the chiral auxiliary was cleaved off as styrene

under radical conditions. The yields over two steps were good, the average yields per step being 78% for *trans*-**31a** and 65% for *trans*-**31aj**. Interestingly, the route has not gained any wider popularity among the chiral 2,5-diarylpyrrolidine syntheses, even though the possibilities to produce different pyrrolidines are, in principle, limited by the availability of the aryl halides, used in the preparation of different Grignard reagents.[90]

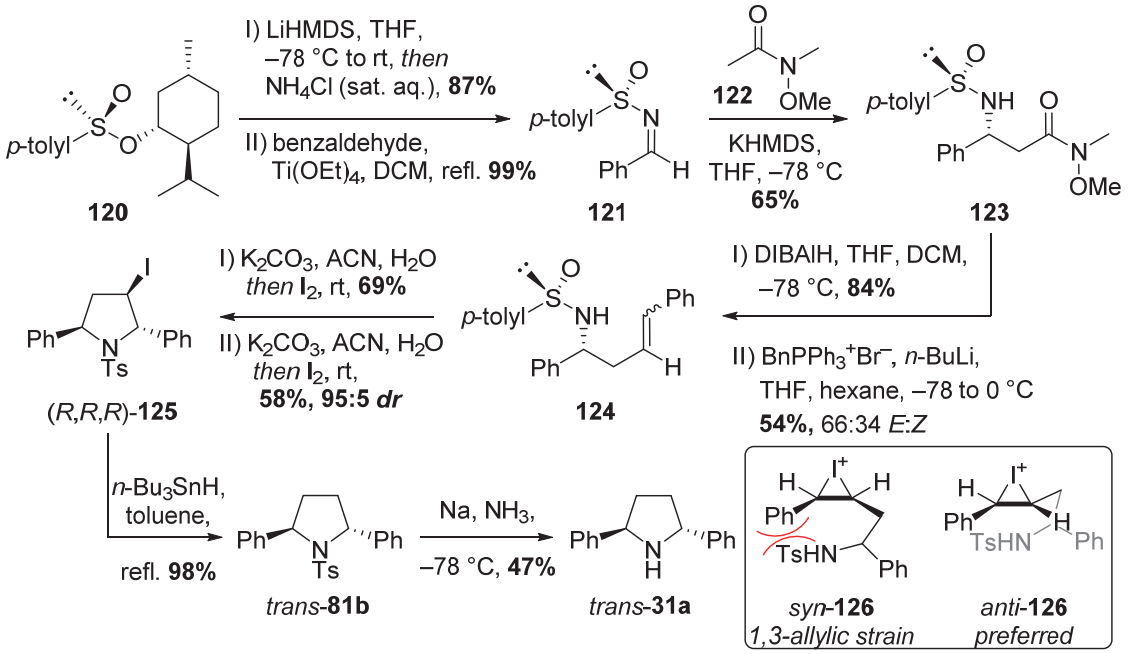


Scheme 15: A synthesis route to chiral *trans*-diarylpyrrolidines **31**, developed by Higashiyama and co-workers.[90]

In 2006, Davis and co-workers published an enantioselective route for (2*R*,5*R*)-2,5-diphenylpyrrolidine, relying also on the mixed disconnection approach (C_α–N, C_α–C_β).[92] They started the work by synthesising chiral sulfinimine **121** from a commercially available (–)-menthyl derivative **120** in excellent yield (Scheme 16).[93] **121** reacted with the enolate formed from Weinreb amide **122** in a Mannich reaction to give β-amino product **123** with very good diastereoselectivity (85:15 *dr*).[94] Diastereomerically pure **123** was achieved after recrystallisation with a 65% yield.[95]

123 was then reduced to the corresponding aldehyde, which was olefinated with Wittig reagent into homoallylic sulfinamide **124** (Scheme 16). The latter transformation proceeded with a fair, 54% yield; the diastereomers were not separable, and the diastereoselectivity was poor (66:34 *E*:*Z*). However, the researchers did not try to enhance the *dr* and proceeded to the next step. Instead of an anticipated iodine-induced cyclisation, the sulfinyl auxiliary part of **124** was oxidised to the corresponding tosyl compound in a 69% yield, without a

change in *dr*. Treating this mixture with the same conditions as previously done eventually provided the desired pyrrolidine (*R*,*R*,*R*)-**125** in a 58% yield and with excellent diastereopurity. This was hypothesised to be because of the allylic strain present in *syn*-**126**, which was absent in the structure leading to the major diastereomer (*anti*-**126**).[92]

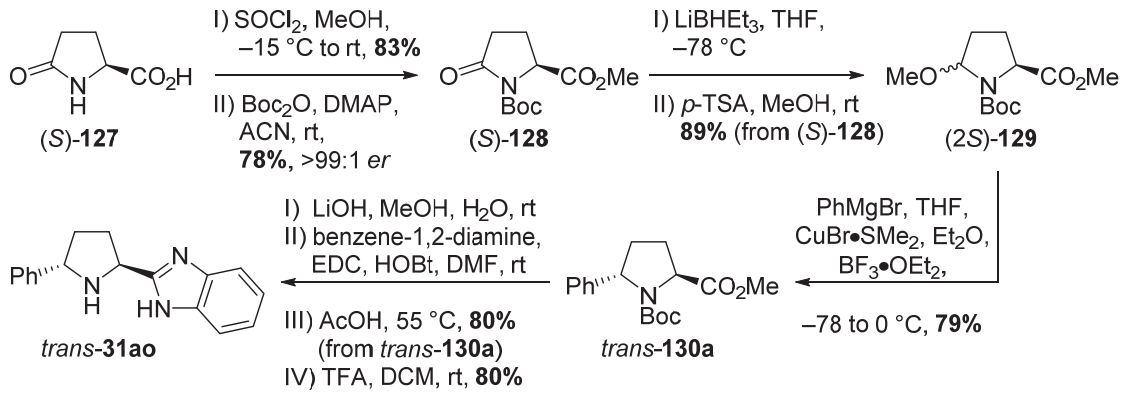


Scheme 16: An asymmetric synthesis route to *trans*-(2*R*,5*R*)-2,5-diphenylpyrrolidine ((*R*,*R*)-**31a**) by Davis and co-workers.[92]

To complete the synthesis route, deiodination was conducted with tributyltin hydride in an almost quantitative yield (Scheme 16). The tosyl protecting group was cleaved off last with sodium in liquid ammonia, affording *trans*-**31a** in a poor, 47% yield. The suitability of the method with other aryls was not tested.[92]

The last example of the mixed disconnection approach was published in 2016 by Pihko and co-workers, who disclosed an enantioselective synthesis for an unsymmetrical pyrrolidine *trans*-**31ao**.[37] One of the aryls was furnished *via* aromatisation, taking the advantage of the pre-set stereocenter and the carbonyl moiety of the chiral pool compound (*S*)-**127**, while the other aryl was disconnected by a C_α–C_{Aryl} approach (Scheme 17).

The route started with the protection of (*S*)-pyroglutamic acid to pyrrolidine (*S*)-**128** in very good yield and without racemisation taking place (Scheme 17).[37] After Super-hydride reduction and *N*,*O*-acetalisation with methanol, (2*S*)-**129** was arylated with a phenyl cuprate, giving *trans*-pyrrolidine **130a** in a 70% yield (three steps). The compound was then saponified, coupled with benzene-1,2-diamine, and cyclised to benzoimidazole under acidic conditions. After Boc deprotection, *trans*-**31ao** was obtained in a 64% yield (four steps). Despite containing many transformations (nine steps), the route was straightforward and gave access to chiral unsymmetrical benzoimidazole-type pyrrolidines.



Scheme 17: A synthesis route for *trans*-pyrrolidine **31ao** by Pihko and co-workers.[37]

2.1.5 Formal and advanced synthesis routes

There are also routes, where the researchers obtained intermediates known to be transformable into 2,5-diarylpyrrolidines. In addition to these "formal 2,5-diarylpyrrolidine syntheses", there are routes where a final, seemingly trivial deprotection of an advanced isolable intermediate was not conducted. We also present these routes to give a more comprehensive picture of the applicable routes.

2.1.5.1 C_α–N disconnection approach

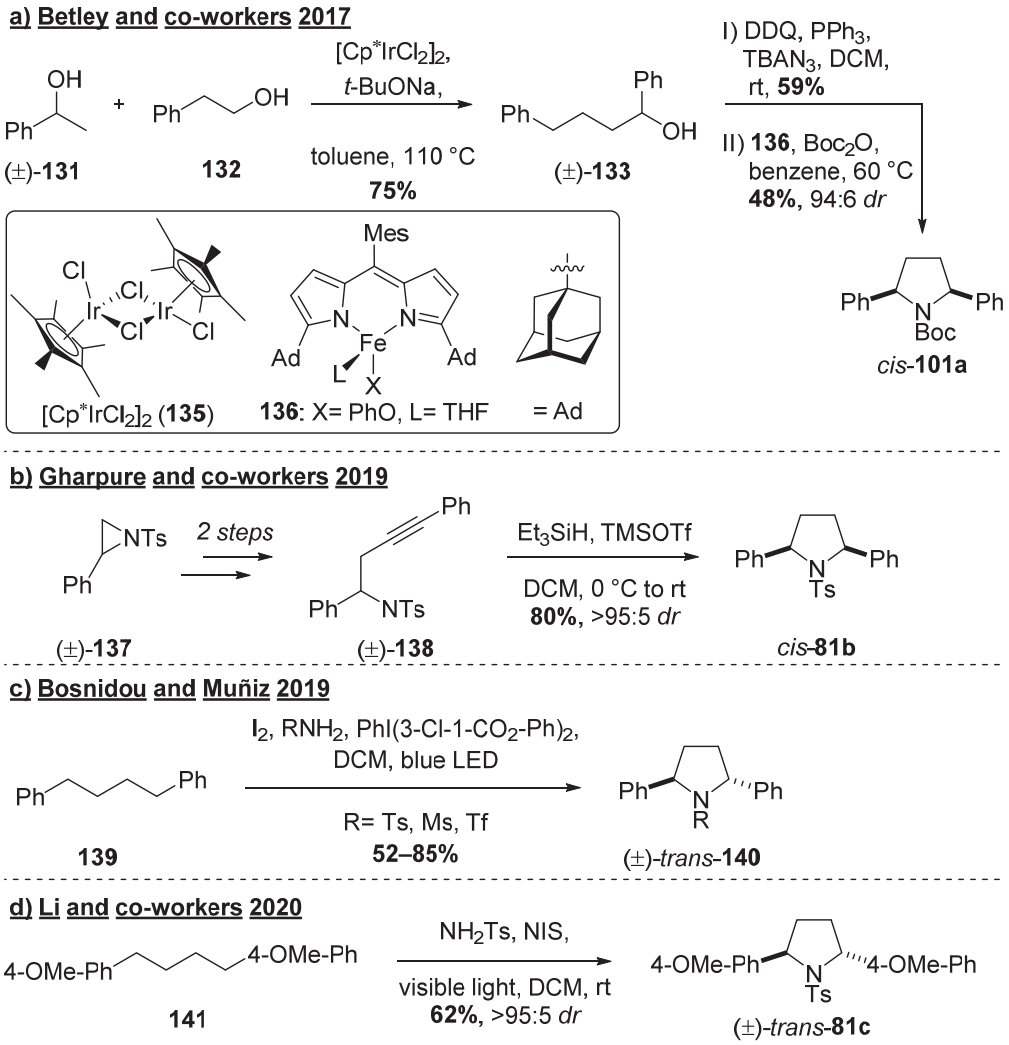
In 2017, Betley and co-workers disclosed a short synthesis route for *cis*-2,5-diphenylpyrrolidine *cis*-**101a** (Scheme 18a).[96] The route started with a β-alkylation of alcohol (±)-**131** with 2-phenylethanol (**132**) under iridium catalysis.[97] Both alcohols were first oxidised *in situ*, which was followed by a cross aldol condensation/reduction sequence. The β-alkylation product (±)-**133** was transformed to the corresponding azide with a Mitsunobu-type[98] reaction, which was intramolecularly C–H aminated under iron catalysis with brilliant diastereoselectivity. *In situ* conducted Boc protection provided *cis*-**101a** with a 48% yield.[96]

In 2019, Gharpure and co-workers developed a Lewis acid catalysed cyclisation–reductive amination method, which was used in the synthesis of *cis*-**81b** (Scheme 18b). When alkynylamine (±)-**138** was mixed with TMSOTf and Et_3SiH, the compound cyclised first in a 5-*endo*-dig manner to an enamine. After tautomerisation to the corresponding imine, it got reduced by the silane from the sterically less demanding side in very good yield and with excellent *dr* (>95:5).[99]

Also in 2019, Muñiz and Bosnidou published a synthesis route for racemic pyrrolidines (±)-*trans*-**140** (Scheme 18**c**). This one-step procedure consisted of a light-induced iodine-catalysed C–H amination reaction, which occurred between 1,4-diphenylbutane **139** and sulphonamides. In this Hofmann–Löffler–Freytag-type reaction[100], an *N*-I intermediate was first formed. It was followed by a sequence of homolytic bond cleavages, which induced a dehydrogenation/iodination sequence at the benzylic carbon. An intramolecular nucleo-

philic attack by the nitrogen atom on the halogenated carbon furnished (±)-*trans*-**140** pyrrolidines as sole diastereomers in an 85% yield at best.[101]

The last example of this approach was published recently by Li and co-workers, who developed another C–H-amination reaction (Scheme 18d). As in the example by Bosnidou and Muñiz, an *N*–I-bond-containing intermediate was needed. This time, it was created *via* halogen bonding activation between NIS and tosylamide and visible light, after which, the reaction proceeded as in the preceding example. The researchers used the method to synthesise (±)-*trans*-**81c** in a 62% yield and with brilliant diastereoselectivity.[102]

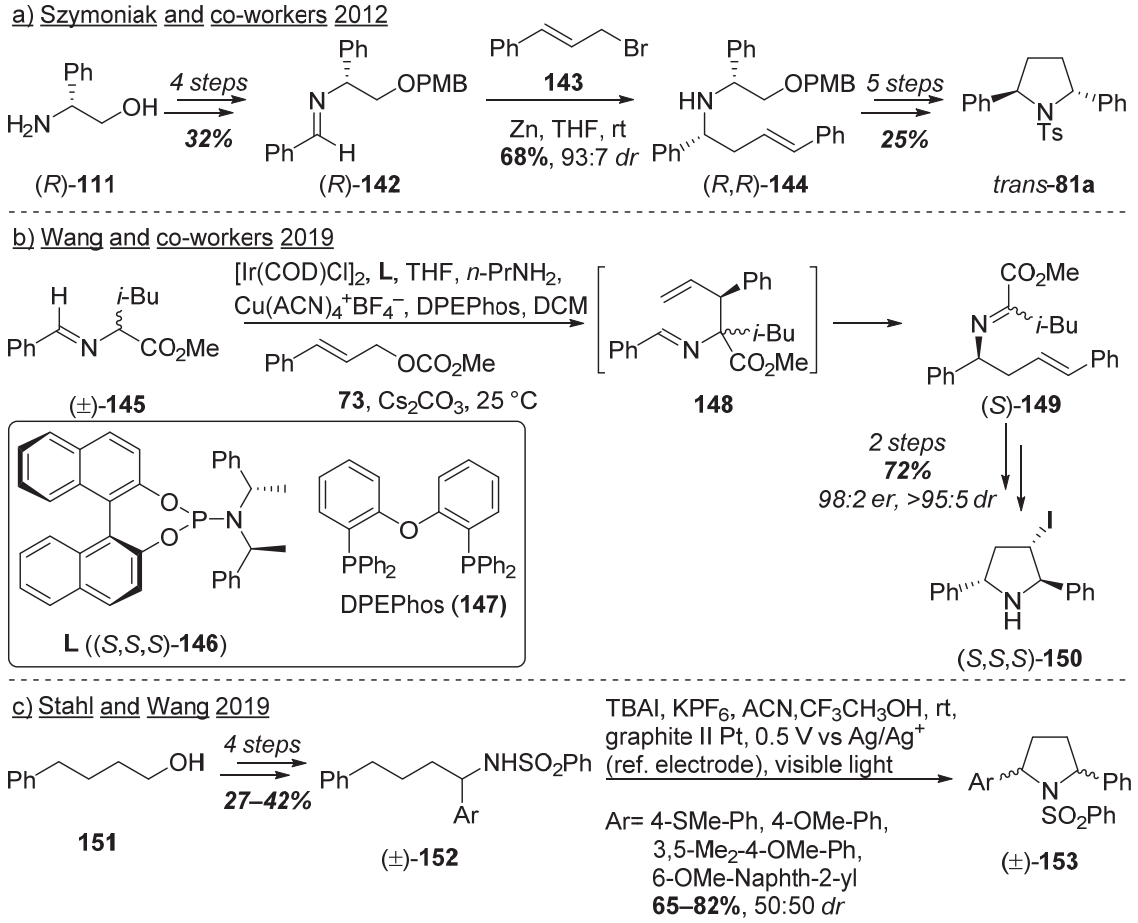


Scheme 18: Synthesis routes for *N*-protected *cis*- and (±)-*trans*-2,5-diphenylpyrrolidines. a) Betley and co-workers.[96] b) Gharpure and co-workers.[99] c) Bosnidou and Muñiz.[101] d) Li and co-workers.[102]

2.1.5.2 Mixed disconnection approaches

In 2012, Szymoniak and co-workers targeted pyrrolidine *trans*-**81a** by using mixed C_α–N and C_α–C_β strategies (Scheme 19a). They started the work by preparing a chiral imine (*R*)-**142** from (*R*)-glycinol, which was then allylated to amine (*R*,*R*)-**144** in good yield and with excellent *dr*. A zinc-chelate between OPMB and amine nitrogen was hypothesised to form during the reaction,

which made the Ph-moiety to block the *si*-face, leading to the observed diastereoselectivity. Amine (*R*,*R*)-**144** was then transformed to *trans*-**81a** in five steps, which included the iodocyclisation reaction used by the Davis group, to reach the known late stage intermediate (Scheme 16).[103]



Scheme 19: a) A synthesis route to 2,5-diarylpyrrolidine *trans*-**81a**, developed by Szymoniak and co-workers.[103] b) Enantioselective dual Cu/Ir-catalysed allylation/aza-Cope-rearrangement sequence used in a route for (*S*,*S*,*S*)-**150** by Wang and co-workers.[104] c) A racemic route to (±)-**153**, where both electro- and photochemistry were used, developed by Stahl and Wang.[105]

Another C_α–N/C_α–C_β example was published in 2019 by Wang and co-workers, who presented a method whereby homoallylic chiral amine (*S*)-**149** was synthesised from a leucine-derived aldimine ester (±)-**145** (Scheme 19b). They used Cu- and Ir-catalysed reactions as the key transformations in the method: first, an *in situ* formed azomethine ylide reacted in a highly enantioselective allylation reaction with **73**, forming an imine **148**. This intermediate reacted further in an aza-Cope rearrangement. After two steps, the authors got pyrrolidine (*S*,*S*,*S*)-**150** in a 72% yield and with excellent stereoselectivities.[104]

The last mixed approach example was published in 2019 by Stahl and Wang. The developed method utilised C_α–N and C_α–C_{Aryl} approaches, and it was suitable for the synthesis of racemic pyrrolidines **153**. One of the cornerstones of the route was the merger of photo- and electrochemistry in a C–H amination reaction (Scheme 19c). The role of electrochemistry was to oxidise a

catalytic amount of I^- to I_2, which was needed to create an *N*–I intermediate. The role of photochemistry was the same as in the example by Bosnidou and Muñiz (see subsubsection 2.1.5.1). The utility of the method was demonstrated by synthesising various pyrrolidines with electron-rich aryls, known to be problematic substituents in electrochemistry due to their tendency to participate in redox reactions. The racemic products were obtained in 65-82% yields, but the reaction did not show any diastereoselectivity, an interesting finding compared with the results by Bosnidou and Muñiz. Probably chiral substrates and/or a chiral *N*-protecting group could have induced some diastereoselectivity, but this possibility was not discussed in the article.[105]

2.1.6 Summary of the 2,5-diarylpyrrolidine synthesis routes

Over the years, 2,5-diarylpyrrolidine synthesis has puzzled researchers throughout the world. After extensive literature searches, we found at least 15 different synthesis routes for the above-mentioned target molecules. We also distinguished seven additional routes, which either could be considered formal syntheses or would lead to a 2,5-diarylpyrrolidine after seemingly trivial deprotection. We identified four disconnection approaches, one of them being a mixture of two main approaches.

The most used strategy has been the C_α-N disconnection, with a total number of ten different synthesis routes (Table 5). Only three of them are asymmetric, and the stereocenters are created by using catalytic methods. The key steps of the most applied route (13 examples) rely on the stereoselective reduction of 1,4-diarylbutane-1,4-diones and a S_N2-cascade reaction with a nitrogen nucleophile. This four-step route is the second most used one in the context of chiral 2,5-diarylpyrrolidine syntheses, tolerating a wide range of different aryls. However, diastereopurity, as well as electron-rich and bulky aryls, have caused problems.

The C_α–C_{Aryl} disconnection approach is the second most used strategy, and five synthesis routes have been released (Table 5). Three of them have been demonstrated to be applicable in the asymmetric synthesis of 2,5-diarylpyrrolidines. The key reactions of the most utilised route (14 examples) include a stereoselective deprotonation, transmetalation and Negishi coupling, all done in one pot. The three-step route is the most used one in the context of chiral unsymmetrical and symmetrical 2,5-diarylpyrrolidine syntheses. It has been demonstrated to tolerate bulky and electron-rich aryl substituents. However, pyrrolidines with electron-poor aryls have not been synthesised with this method, and the use of a stoichiometric amount of chiral (–)-sparteine is required.

The C_α–C_β disconnection strategy has been used in only two instances, both of them producing achiral *cis*-2,5-diarylpyrrolidines (Table 5). The route is short and utilises simple reagents. However, it has not been employed in the synthesis of enantioenriched compounds.

Six mixed disconnection routes have been used in this context, and only one of them has not been applicable in the synthesis of chiral 2,5-diaryl-

pyrrolidines (Table 5). Only a few examples have been presented, even though the route by Higashiyama and co-workers could be usable in a wider sense. One of the asymmetric routes utilised catalytic means to set the stereocenters, while the chiral pool and asymmetric auxiliaries have been the cornerstones of the other routes.

Table 5: Summary of the 2,5-diarylpyrrolidine synthesis routes.

Author(s)	Target(s)[a]	Key step(s)	No. of examples	Longest linear sequence
C_α-N disconnection				
Overberger[40]	symmetrical; (±)-*trans*-**31** and *cis*-**31**	Paal–Knorr pyrrole, nitrosation	2	6
Hashimoto[43]	symmetrical; (±)-*trans*-**31** and *cis*-**31**	S_N2-cascade, Hantzsch's thiazole	2	8 (*cis*-**31b**) 9 (*trans*-**31b**)
Willis[49]	unsymmetrical; (±)-*trans*-**31** and (±)-*cis*-**31**	Rh-catalysed hydroacylation, diastereo-selective reduction	6	4
Chong,[55] Steel,[65] Yamada[59]	mostly symmetrical; enantioenriched *trans*-**31**	Asymmetric reduction, S_N2-cascade	13	4[b]
Feringa[69]	symmetrical; enantioenriched *trans*-**31**	Asymmetric Ir-catalysed double *N*-allylation	1	6
Helmchen[75]	symmetrical; enantioenriched *trans*-**31** and *cis*-**31**	Asymmetric Ir-catalysed *N*-allylation	2	6
Betley[96]	symmetrical; *cis*-**31**	Diastereo-selective Fe-catalysed C–H amination	1	4[c]
Gharpure[99]	symmetrical; *cis*-**31**	Diastereo-selective cyclisation–reductive amination	3	2[c]

table continued from the previous page				
Muñiz[101]	symmetrical; (±)-*trans*-**31**	Diastereo-selective C–H amination	1	2[c]
Li[102]	symmetrical; (±)-*trans*-**31**	Diastereo-selective C–H amination	1	2[c]
C_α–C_{Aryl} disconnection				
Dennstedt & Zimmermann,[77] Potts & Smith,[78] Schulz,[79] Joule[80]	symmetrical; (±)-*trans*-**31** and *cis*-**31**	Diastereo-selective pyrrole trimerisation, diastereo-selective epimer-isation	2	1 (*trans*-**31**) 4 (*cis*-**31**)
Sames[81]	mostly unsymmetrical; (±)-*trans*-**31**	Diastereo-selective Ru-catalysed arylation	3 (8[c])	3
Onomura[82]	symmetrical; enantioenriched *trans*-**31**	Diastereo-selective Friedel–Crafts-type reactions	1	9
Campos[85]	symmetrical and unsymmetrical; enantioenriched *trans*-**31**	Stereoselective deprotonation/ transmetalation/ Negishi cou-pling sequence	14 (15[c])	3
Seidel[87]	symmetrical and unsymmetrical; (enantioenriched) *trans*-**31**	Stereoselective nucleophilic addition	3	2
C_α–C_β disconnection				
Terashima,[88] Rhone-Poulenc Rorer S.A[89]	symmetrical and unsymmetrical; (±)-*cis*-**31**	Diastereo-selective 1,3-dianionic cycloaddition	4	2

table continued from the previous page

Mixed disconnections				
Higashiyama[90]	symmetrical; enantioenriched *trans*-**31**	Diastereo-selective Grignard additions	2	6
Davis[92]	symmetrical; enantioenriched *trans*-**31**	Diastereo-selective Mannich reaction, iodocyclisation	1	9
Pihko[37]	unsymmetrical; enantioenriched *trans*-**31**	Diastereo-selective aryl-cuprate-addition, aromatisation	1	9
Szymoniak[103]	symmetrical; enantioenriched *trans*-**31**	Diastereo-selective imine-allylation	1	11[c]
Wang[104]	symmetrical; enantioenriched *trans*-**31**	Enantio-selective Cu/Ir-catalysed allylation, aza-Cope rear-rangement	1	4[d]
Stahl[105]	unsymmetrical; (±)-*trans*-**31** and (±)-*cis*-**31**	Photo-electrochemical C–H amination	4	6[c]

Colour codes for the sources of asymmetry: catalytic (**blue**), chiral pool (**green**), chiral auxiliary or other stoichiometric strategy (**red**). a) Symmetrical/unsymmetrical refers to the presence of C_2 symmetry in **31**; *trans* and *cis* refer to the relative stereochemistry of the aryls in C2 and C5 of the pyrrolidine. b) Depends on the diketone synthesis. c) If deprotected. d) If deiodinated.

2.2 Use in asymmetric synthesis

In this section, we gathered literature examples where 2,5-diarylpyrrolidines have been used in asymmetric synthesis. We limited the examples to ones where 2,5-diarylpyrrolidines have been the primary targets prior to further utilisation or derivatisation. For instance, we excluded examples from this literature review where the free amine was never formed and the pyrrolidine ring was only part of a bigger structure. We divided the examples into catalytic methods, auxiliary methods and synthesis of biologically active molecules. To

clarify the structure of the section, we divided catalytic methods under separate subsubsections based on the reaction types.

2.2.1 Catalytic methods

2.2.1.1 Iminium ion catalysed Mukaiyama–Michael reactions

Over the years, Pihko and co-workers have developed organocatalysed vinylogous Mukaiyama–Michael reactions between several silyloxyfurans and α,β-(un)substituted enals.[36,56,57] From a range of organocatalysts, C_2-symmetric 2,5-diarylpyrrolidines **31**, which form chiral iminium ions with enals, have proven to be suitable sources of chirality for this reaction type.

The authors tested many catalyst systems, but a salt of 4-nitrobenzoic acid and diphenyl substituted *trans*-**31a** proved to be the most versatile one.[36,56] In the presence of this system, reactions between silyloxyfurans **154** and α-substituted enals **155** or acrolein (**166**) provided furanones **156** with mostly excellent enantioselectivities (Scheme 20a). The diastereoselectivities remained generally poor, though, which was hypothesised to be due to the equilibration process scrambling the α-stereocenter. Despite this, the researchers used the Mukaiyama–Michael reaction as the key transformation in the synthesis of an intermediate (*R*,*R*,*R*)-**157**, applicable in the total synthesis of Pectenotoxin-2.[106]

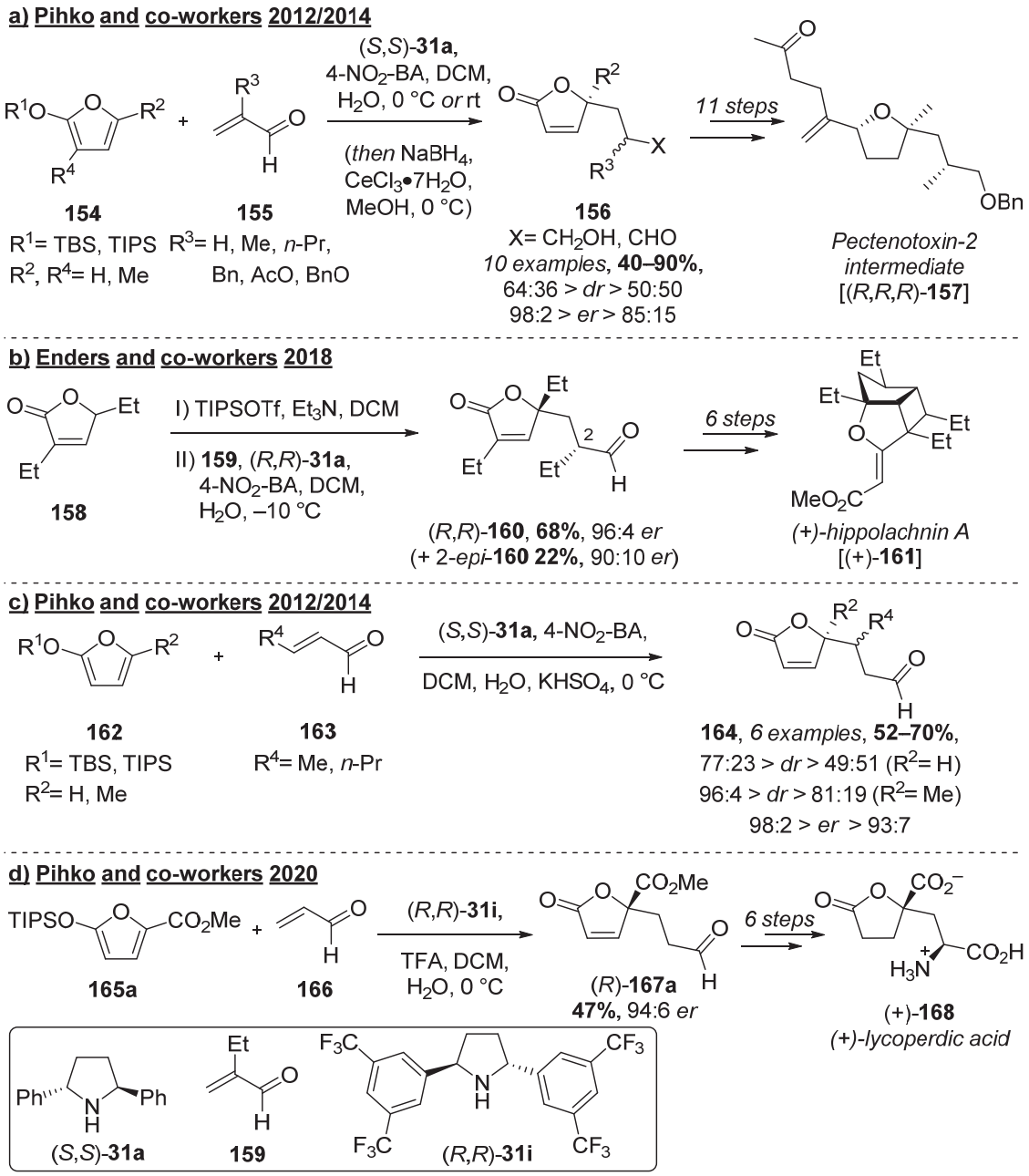
Later, Enders and co-workers demonstrated in the total synthesis of (+)-hippolachnin A ((+)-**161**)[107] that good diastereoselectivities were also achievable (Scheme 20b).[108] They managed to synthesise an intermediate aldehyde (*R*,*R*)-**160** using α-substituted enal **159** with a good diastereoselectivity (76:24 *dr*) and yield (68%), while the *er* was 96:4.

Reactions between silyloxyfurans **162** and β-substituted enals **163** were also possible with the found conditions, and furanones **164** were synthesised in fair to very good yields and with superb enantioselectivity (Scheme 20c).[56] The diastereoselectivity was again an issue, as *dr*'s varied a lot depending on the R^2-substituent of the silyloxyfuran: with H, the *dr*'s were 77:23 at best, whereas, with Me, the *dr*'s reached 96:4. It was proved by DFT-computations that the H substituent was not able to create as much difference between the transition state energies compared with the Me substituent.[56]

Overall, the bulkiness of the organocatalyst was not the only factor that controlled the stereoselectivities of the presented Mukaiyama–Michael reactions. Extensive DFT calculations conducted by Pápai's group showed that attractive noncovalent interactions also played significant roles. The key interactions formed between the iminium ions and silyloxyfuran π-systems and between the silyl protecting groups and iminium ions.[56]

In addition to the non-substituted and alkyl-substituted silyloxyfurans, one silyloxyfuran with electron-withdrawing substituent has also been used.[57] A Mukaiyama–Michael reaction between **165a** and acrolein, catalysed by a salt of TFA and pyrrolidine (*R*,*R*)-**31i** with electron-deficient aryl groups, enabled the synthesis of an aldehyde (*R*)-**167**. The yield of the transformation was 47%, but the enantioselectivity was excellent (94:6 *er*, Scheme 20d). (*R*)-**167** was later

used in the total synthesis of (+)-lycoperdic acid ((+)-**168**),[109] discussed later in Chapter 5 of this dissertation.

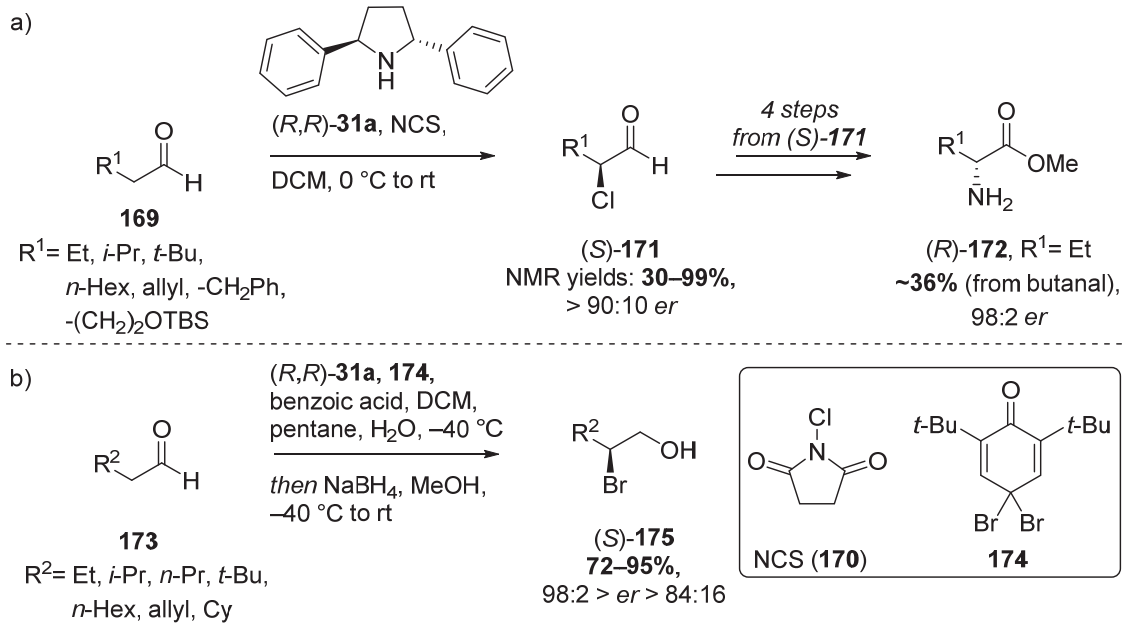


Scheme 20: Examples of 2,5-diarylpyrrolidine-catalysed Mukaiyama–Michael reactions by groups of Pihko and Enders. Reactions between silyloxyfurans and α-substituted (a, b), as well as β-substituted (c), enals have been conducted. Silyloxyfuran with electron-withdrawing substituent (d) is also a suitable substrate.[36,56,57,108]

2.2.1.2 Enamine-catalysed halogenations

One of the earliest literature examples where a 2,5-diarylpyrrolidine was used in organocatalysis came in 2003. In that publication, Melchiorre and Jørgensen studied enantioselective Michael additions between various aldehydes and alkyl vinyl ketones and got promising results with the catalyst (*S*,*S*)-**31a** in the

early screening studies. However, another pyrrolidine-type catalyst performed slightly better than (*S*,*S*)-**31a** and was thus chosen for further studies.[110]



Scheme 21: Organocatalytic α-chlorination (a) and -bromination (b) by Jørgensen and co-workers.[111,112]

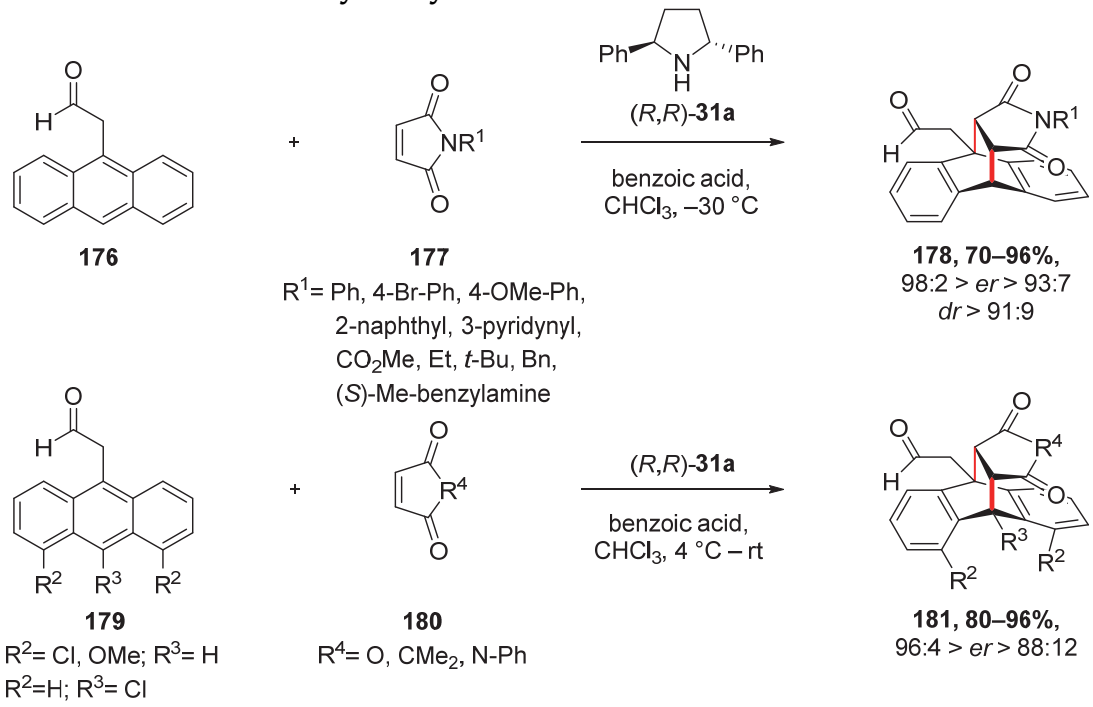
Nevertheless, it did not take long before *trans*-**31a** was finally found to be the optimum catalyst in a catalytic method. In 2004, Jørgensen and co-workers developed enantioselective organocatalytic α-halogenation reactions of aldehydes.[111,112] The reactions were catalysed by (2*R*,5*R*)-diphenylpyrrolidine, which formed the corresponding enamines from the substrate aldehydes. These species reacted well with the Cl^+-source NCS, the reactions giving α-chloroaldehydes (*S*)-**171** mostly in very good to excellent yields (Scheme 21a). The only exception was a *t*-butyl variant, which suffered from a homo-aldol side product formation. The *er*'s were brilliant, and no erosion of optical purity was found to occur in the later transformations, demonstrated in the synthesis of non-proteinogenic amino acid (*R*)-2-aminobutanoic acid methyl ester ((*R*)-**172**).

This methodology was then utilised in the synthesis of chiral terminal aziridines,[113] azetidines[114] and thiomorpholines,[115] as well as in the total synthesis danicalipin A.[116] In addition to the synthetic utility, the detailed mechanism of enamine-catalysed α-chlorination has raised many questions through the years among several researchers.[117–119]

A year after the α-chlorination publication, a more challenging α-bromination reaction was also published by the Jørgensen's group.[112] The successful and optimum reaction conditions included an additional acid co-catalyst, low temperatures and benzoquinone **174** as the Br^+-source (Scheme 21b). The utility of the method was demonstrated with a handful of aldehydes, and after

one-pot reduction, the corresponding bromoalcohols (*R*)-**175** were obtained in very good to excellent yields and with *er*'s between 84:16 and 98:2.

2.2.1.3 Enamine-catalysed cycloadditions



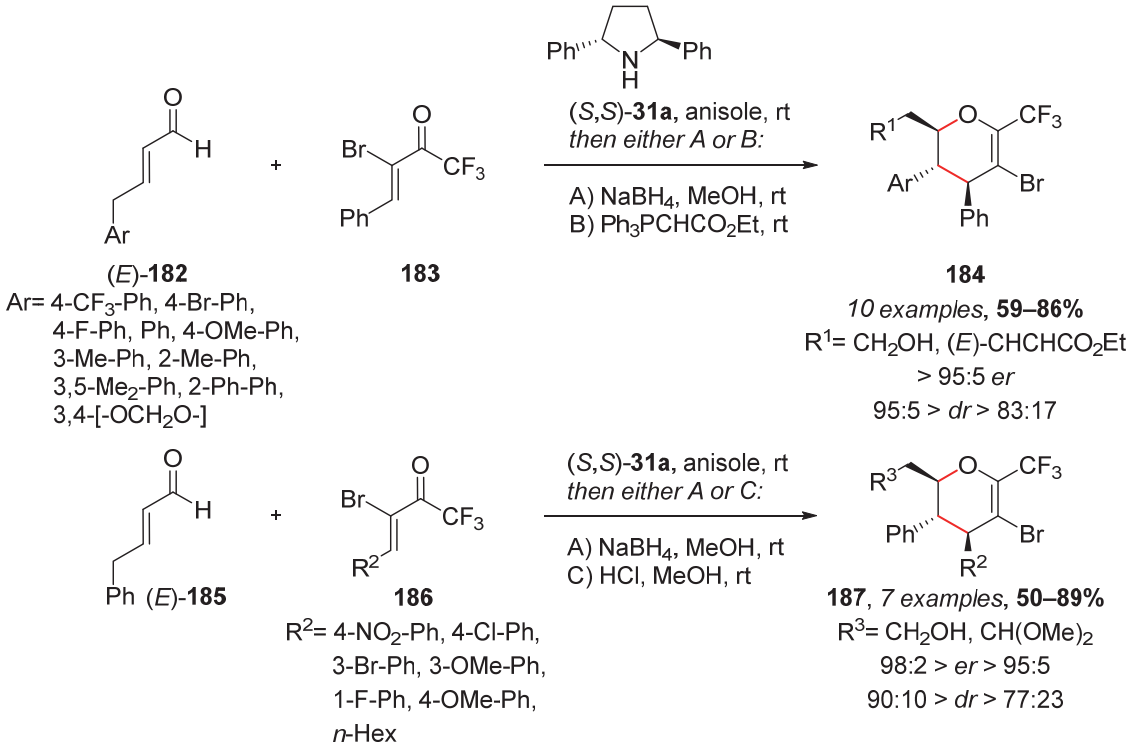
Scheme 22: Asymmetric Diels–Alder-reaction between symmetrical anthracenes, developed by Jørgensen and co-workers.[120]

In 2013, Jørgensen and co-workers developed enantioselective Diels–Alder reactions between anthracenes (**176** and **179**) and maleimides (**177** and **180**), which were catalysed by (2*R*,5*R*)-diphenylpyrrolidine (Scheme 22).[120] The transformation tolerated various *N*-substituted maleimides, such as (hetero)aryl-, alkyl- and benzylic substituents, providing anthracene cycloadducts **178** in high yields and with superb stereoselectivities. In addition, maleic anhydride and dimethylcyclopentenedione were tolerated (**180**, R^4= O, CMe_2), whereas acyclic dienophiles were not. Lastly, the reactions between electron-deficient and -rich anthracenes (**179**) and *N*-Ph-maleimide (**180**, R^4= *N*-Ph) were also successful: only a slight decrease in enantioselectivity was seen when R^3 was substituted with chloride.

Surprisingly, the enantioselectivity of the reaction was not a result of steric shielding by the pyrrolidine aryls. Inspection of the transition state energies by DFT calculations revealed that when the maleimide approached the enamine from a suitable direction, it forced the enamine in conjugation with anthracene moiety, resulting in an increased HOMO-activation. An approach from the opposite direction forced the enamine out of conjugation, the system thus being less activated.[120]

Some years after their previous organocatalysed Diels–Alder reaction, Jørgensen's group published a stereoselective inverse electron-demand hetero-Diels–Alder reaction.[121] Transformations between (*E*)-4-arylbut-2-enals **182** as

the dienophiles and CF_3-substituted enone **183** as the diene gave dihydropyrans **184** in 59-86% yields (Scheme 23). The reaction worked with both electron-poor and -rich aryl aldehydes **182**; aliphatic enals were not tested. The *er*'s were better than 95:5, whereas the *dr*'s were 95:5 at best.



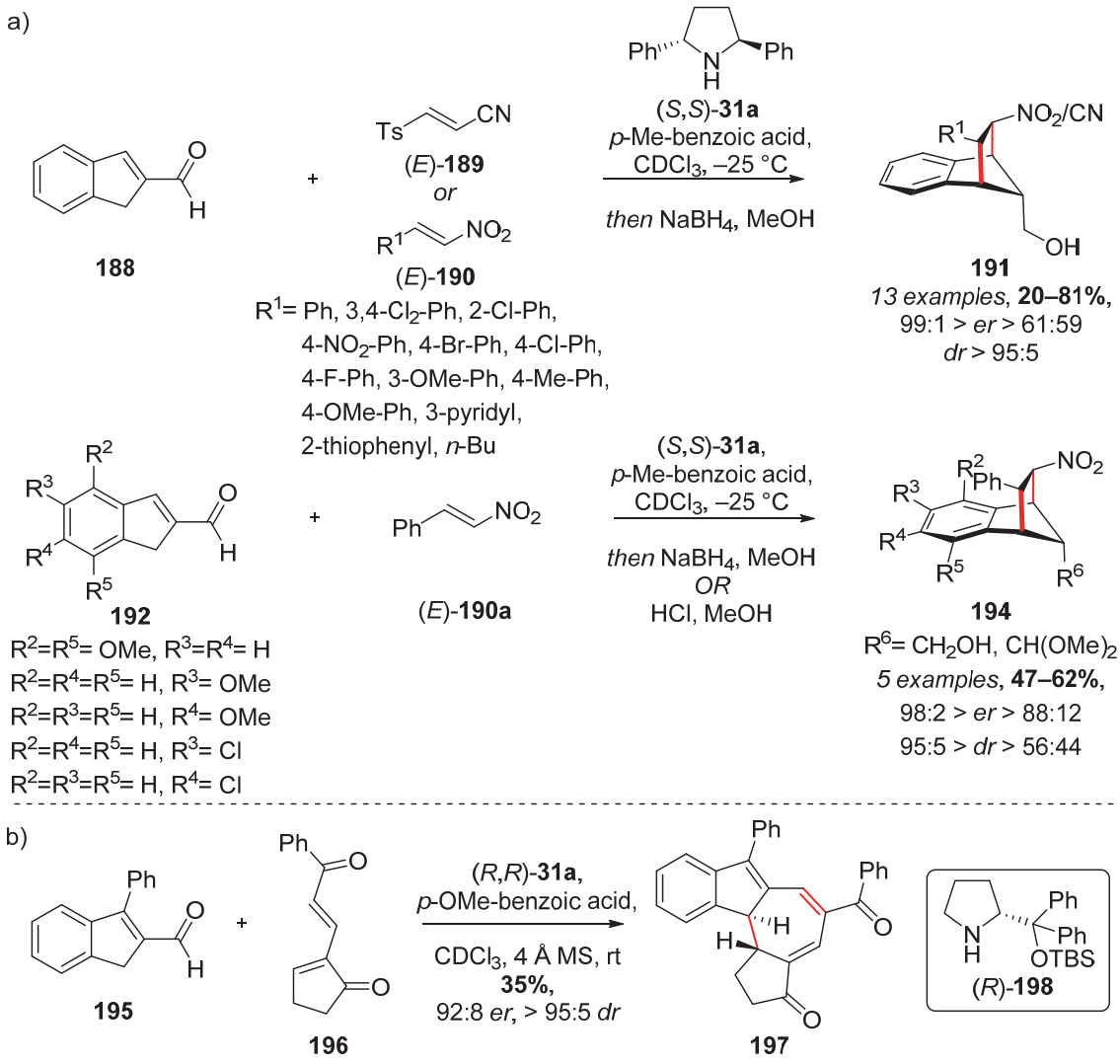
Scheme 23: (2*S*,5*S*)-diphenylpyrrolidine-catalysed stereoselective inverse electron-demand hetero-Diels–Alder reaction, developed by Jørgensen and co-workers.[121]

The researchers expanded the substrate scope to different β-substituted enones **186**.[121] Reactions between these and (*E*)-**185** gave dihydropyrans **187** in 50–89% yields, with excellent *er*'s and mostly with very good *dr*'s (Scheme 23). The synthetical versatility and value of the dihydropyrans were further demonstrated by using them successfully in cross-coupling and nucleophilic addition reactions.

In 2018, Jørgensen and co-workers continued their synthesis efforts in the realm of enamine catalysis by publishing an organocatalysed [8+2]-cycloaddition reaction. The reacting partners were nitro and cyano olefins ((*E*)-**189** and (*E*)-**190**) and isobenzofulvenes, the latter generated *in situ* from indenes (**188** and **192**) and (*S*,*S*)-**31a** (Scheme 24a).[122] With an unsubstituted indene (**188**) and olefins (*E*)-**190**, the transformation gave benzonorbornenes **191** in varying yields, but mostly with excellent *er's* and *dr*'s. The lowest yield (20%) was obtained with an aliphatic olefin (R^1= *n*-Bu), whereas the worst *er* (61:59) was observed with 2-Cl-β-nitrostyrene (R^1= 2-Cl-Ph).

The substitution pattern of the indenes **192** had a great effect on the stereoselectivities (Scheme 24a). A substituent at R^3 lowered the *dr*'s dramatically compared with R^4-substituted indenes. The *er*'s were between 88:12 and 98:2.[122]

The stereoselectivity of the transformation was hypothesised to originate from the steric shielding effect of the catalyst's phenyls. In addition, weak interactions between the terminal substituent of the olefin (NO_2/CN) and the *ipso*-carbon of the catalyst's phenyl were seen as important, based on extensive DFT calculations. These factors limited the substrate scope of olefins to those presented in Scheme 24a.[122]



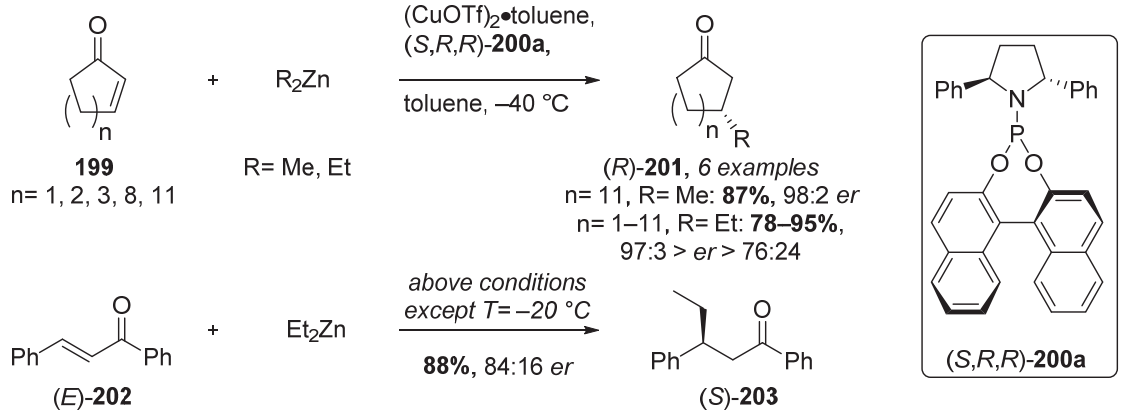
Scheme 24: (2*S*,5*S*)-diphenylpyrrolidine catalysed stereoselective cycloadditions of isobenzofulvenes developed by Jørgensen and co-workers. a) [8+2]-cycloaddition.[122] b) [10+4]-cycloaddition.[123]

The benzonorbornene products were assigned as products of [8+2]-cycloadditions, but the researchers hypothesised that the reactions could also go *via* a [10+4]-mechanism. Later, the group was able to synthesise a [10+4]-cycloadduct **197** with a reaction between indene **195** and diene **196** with a poor yield but with excellent enantio- and diastereoselectivity (Scheme 24b).[123] Despite the stereochemical success, diphenylprolinol-type catalyst (*R*)-**198** was

found to outperform (*R*,*R*)-**31a** and was thus used in the wider studies of the method.

2.2.1.4 2,5-diarylpyrrolidine as a part of a transition metal ligand

2.2.1.4.1 Conjugate additions

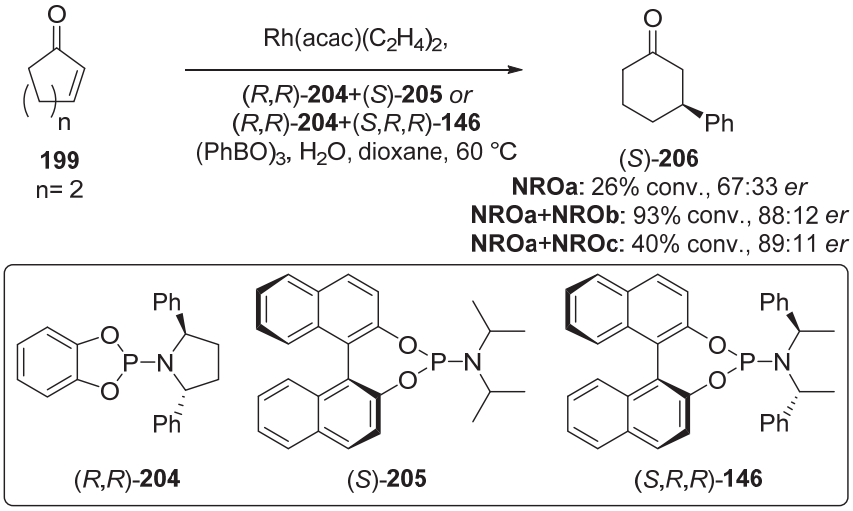


Scheme 25: Copper–phosphoramidite-catalysed conjugate addition of enones, developed by Kim and co-workers.[124]

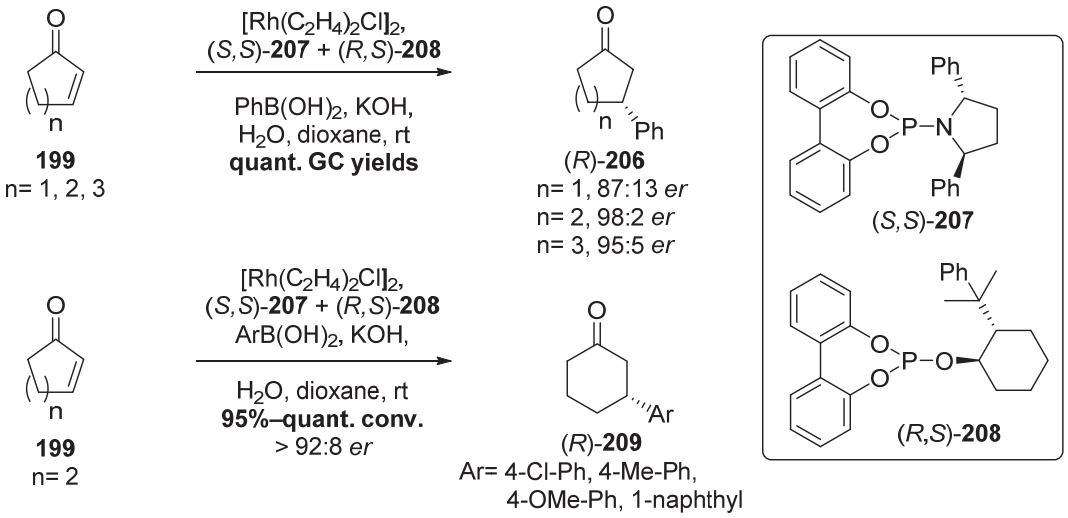
One of the earliest examples where *trans*-2,5-diphenylpyrrolidine was used in a catalytic method was disclosed by Kim and co-workers in 2002. They used the amine as a part of a C_2-symmetric phosphoramidite ligand (*S*,*R*,*R*)-**200a**, derived from (*R*,*R*)-**31a** and (*S*)-binaphthol (Scheme 25).[124] The ligand was used in a copper-catalysed conjugate addition reaction between enones (**199** and (*E*)-**202**) and dialkylzinc compounds.

Only one example with Me_2Zn was given, a reaction with 2-cycloundecenone (**199**, n= 11), which gave the corresponding addition product (–)-muscone[125] in very good yield and with brilliant 98:2 *er*. When the (*S*,*R*,*R*)-diastereomer of the ligand was used, the *er* dropped to 22:78, showing a clear mismatch behaviour. Surprisingly, the reaction with Et_2Zn also lowered the *er* to 87:13. With the other cyclic enones **199**, the *er* varied from 76:24 (cyclopentenone, n= 1) to 97:3 (cyclohexenone, n= 2). The sole acyclic substrate, *E*-chalcone ((*E*)-**202**), gave the addition product (*S*)-**203** in very good yield and enantioselectivity. Overall, the reactions were high-yielding and favoured the 1,4-addition exclusively.

In 2003, Feringa and co-workers noticed that a mixed phosphoramidite ligand combination could also be used to induce enantioselectivity in an asymmetric rhodium-catalysed conjugate addition.[126] They demonstrated the utility of the method by synthesising cyclohexanone (*S*)-**206** with very good enantioselectivity in the reaction between cyclohexenone (**199**, n= 2) and *in situ* generated phenylboronic acid (Scheme 26). The enantioselectivity was high when a hetero combination of either ligands (*R*,*R*)-**204**+(*S*)-**205** or (*R*,*R*)-**204**+(*S*,*R*,*R*)-**146** was used instead of either the homo combinations of (*R*,*R*)-**204** or other ligands. In addition to better selectivity, the hetero combinations were more reactive than the homo combinations because of a sterically less demanding environment.



Scheme 26: Asymmetric conjugate addition, developed by Feringa and co-workers.[126]



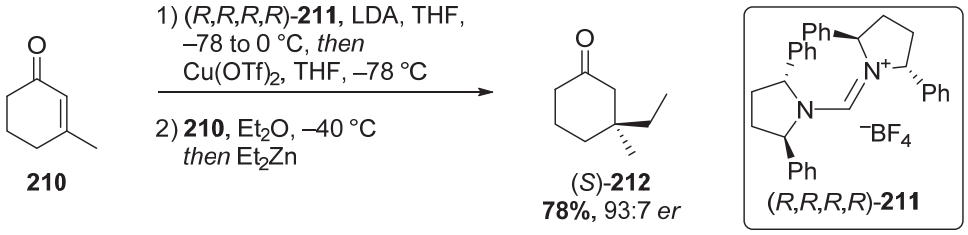
Scheme 27: Modified asymmetric conjugate addition, developed by Piarulli and co-workers.[127,128]

Later, Piarulli and co-workers followed Feringa's approach, with slight modifications.[127,128] The phosphoramidite ligands were biphenol derivatives instead of catechol or binaphthol ones, and a chiral cyclohexanol-derived phosphite-ligand (*R,S*)-**208** was used as the co-ligand (Scheme 27). The authors demonstrated the utility of the method by using cyclic enones **199** of different ring size as substrates. The conjugate additions between phenylboronic acid and cyclohexenone and cycloheptenone gave the addition products with excellent enantioselectivities (>95:5 *er*), whereas the reaction with cyclopentenone (**199**, n= 1) reached merely a very good level of enantioselectivity.

The substrate scope of cyclohexanone substrate (**199**, n= 2) was expanded to aryls with electron-withdrawing and -donating substituents (Scheme 27). In addition, bulky 1-naphthyl was tolerated as well, and the addition products (*R*)-**209** were obtained with excellent *er*'s. However, the limitations of the method

were seen with acyclic enones, and the best *er*'s were achieved with the homo combinations of ligand (*R*,*S*)-**208** instead.[127,128]

The mixing of ligands raised a fundamental question about the active catalytic system since, in principle, three different rhodium–ligand combinations could form during the reaction. In addition, the biphenol unit was not locked to a specific atropisomer, whereas the corresponding binaphthol catalyst would have been, making the catalytic system even more complex. With the help of NMR studies, the authors were able to distinguish the formation of the hetero complexation between rhodium and ligands (*S*,*S*)-**207** and (*R*,*S*)-**208**. In addition, they concluded that, at room temperature, the chiral moieties of the ligands did not induce the biphenols to occupy a certain atropisomer configuration.[127,128]



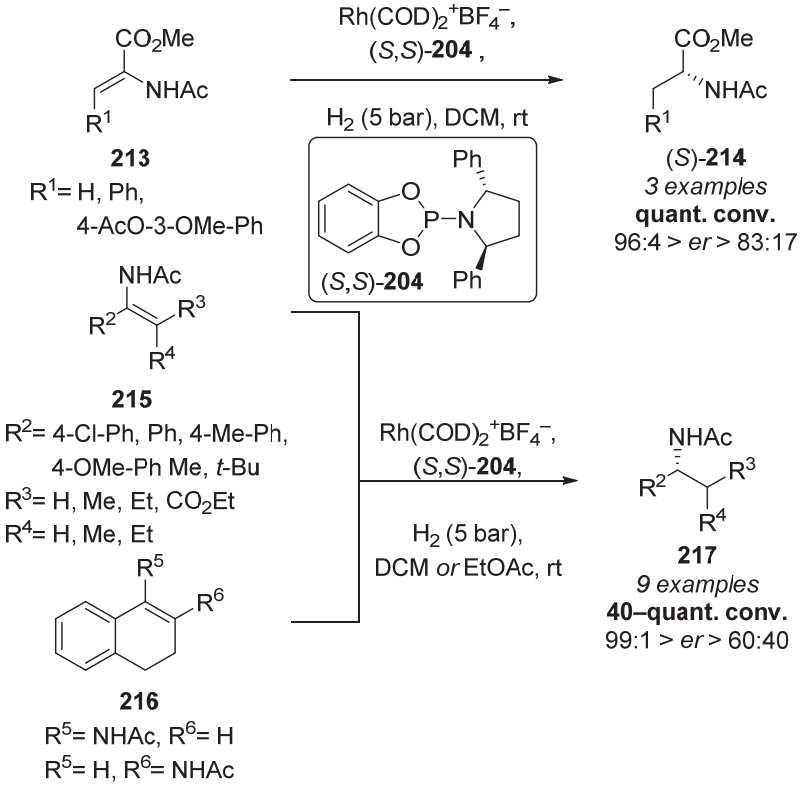
Scheme 28: Enantioselective copper-catalysed conjugate addition, where a chiral carbene-ligand was used.[129]

In 2010, Thadani and co-workers filed a patent, where they formed a copper–carbene complex[130] from (*R*,*R*,*R*,*R*,)-**211** and used it in a catalytic conjugate addition reaction (Scheme 28).[129] The only example the authors gave was a reaction between enone **210** and Et_2Zn. The transformation gave an ethyl-substituted cyclohexanone (*S*)-**212** in good yield and with excellent enantioselectivity.

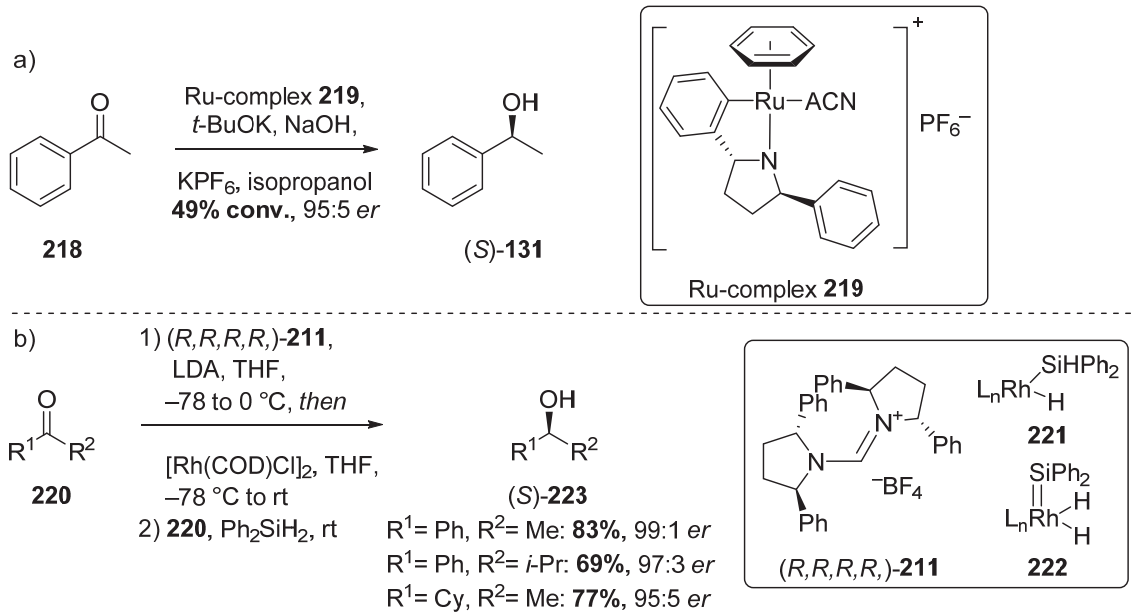
2.2.1.4.2 Asymmetric reductions

Following the 2003 conjugate addition publication,[126] Feringa and co-workers utilised catechol–2,5-diphenylpyrrolidine-phosphoramidite ((*S*,*S*)-**204**) in another method: rhodium-catalysed asymmetric hydrogenation (Scheme 29).[131] The utility of it was demonstrated with dehydroamino acids **213** and enamide **215** substrates. Protected phenylalanine and its oxygenated derivative were obtained with brilliant *er*'s, whereas the hydrogenation of protected dehydroalanine was less enantioselective (83:17 *er*).

With di- and trisubstituted enamides **215**, the enantioselectivities were highest when the R^2 substituent was aromatic regardless of the substituent (Scheme 29).[131] (*Z*)-enamides gave slightly higher *er*'s than the corresponding (*E*)-isomers. Tetrasubstituted and bicyclic enamides, such as dihydronaphthalens **216**, were not ideal substrates: full conversions were not achieved, and the *er*'s were ~70:30 at best. In general, a greater hydrogen pressure did not increase the enantioselectivities, whereas a solvent change to EtOAc was slightly beneficial with some substrates.



Scheme 29: Asymmetric rhodium–(*S*,*S*)-**204** complex-catalysed hydrogenation of enamines by Feringa and co-workers.[131]



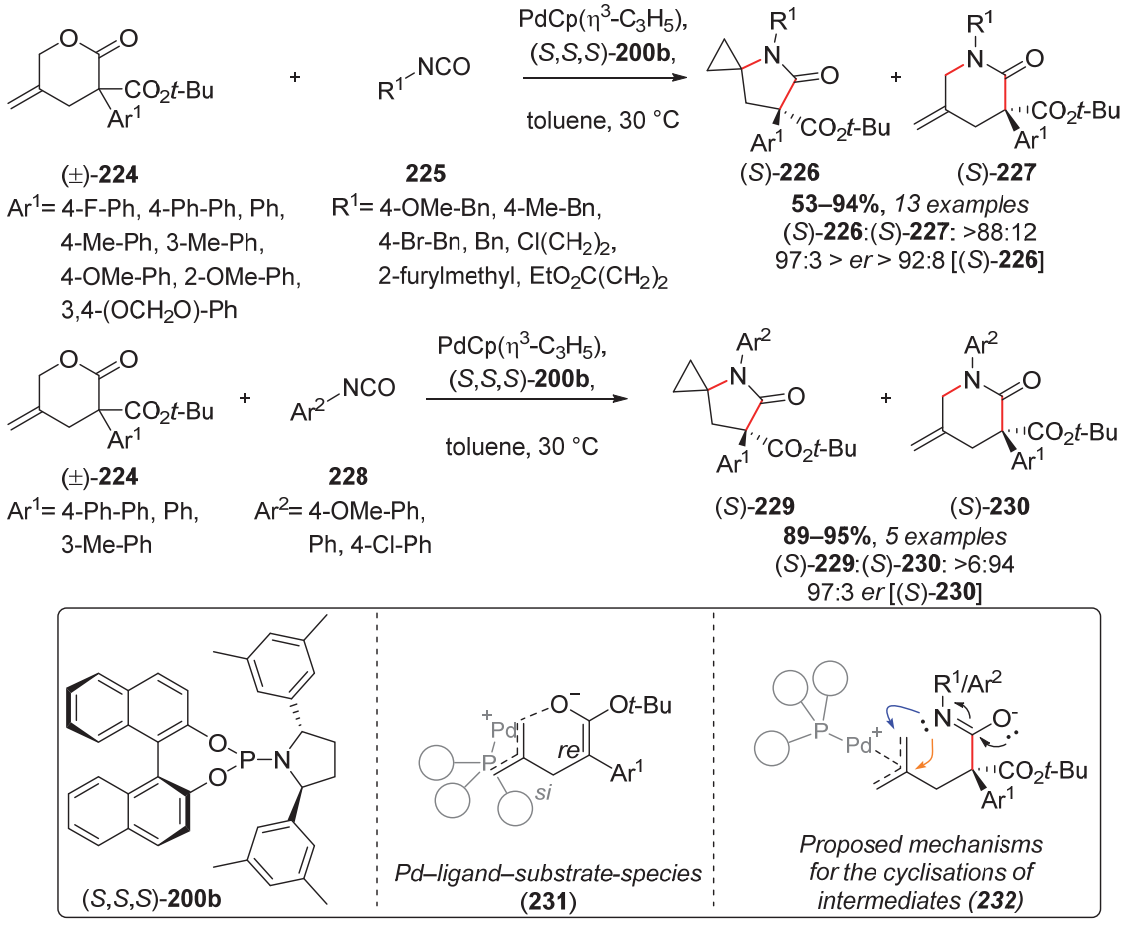
Scheme 30: a) Asymmetric transfer hydrogenation of acetophenone (**218**), catalysed by ruthenium complex **219**.[132] b) Asymmetric hydrosilylation of ketones **220**, catalysed by rhodium–carbene complex.[129]

The versatility of the 2,5-pyrrolidines in the realm of asymmetric synthesis methods was further expanded by De Vries and co-workers, who filed a patent

for a ketone reduction method *via* transfer hydrogenation (Scheme 30a). The Ru-complex **219**, formed between a ruthenium precursor $[Ru(benzene)Cl_2]_2$ and (2*R*,5*R*)-2,5-diphenylpyrrolidine, catalysed the transformation of acetophenone (**218**) to phenylethanol (*S*)-**131** with high enantioselectivity, but with rather poor conversion.[132]

In the same patent, where the copper–carbene-catalysed conjugate addition was described, Thadani and co-workers used (*R*,*R*,*R*,*R*)-**211** in a different method, namely an asymmetric rhodium-catalysed hydrosilylation of ketones (Scheme 30b).[129] The utility of it was demonstrated with three ketones, which, after acidic hydrolysis, gave chiral alcohols (*S*)-**223** in 69–83% yields and with excellent *er*'s (>95:5). Although a straightforward-looking reaction, the mechanistic details of the transformation have been under debate, one of the questions relating to whether the actual reducing agent formed in the reaction is either the complex **221** or **222**.[133]

2.2.1.4.3 Miscellaneous catalytic reactions



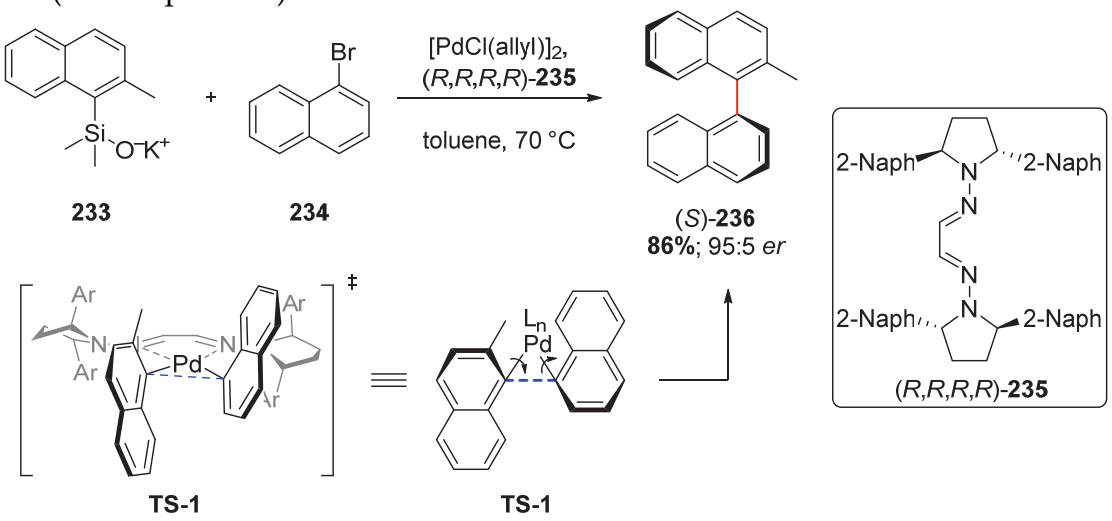
Scheme 31: Palladium-catalysed decarboxylative cyclisation reaction by Hayashi and co-workers.[61,134] The blue arrow describes the attack when aryl isocyanates were used, whereas the orange arrow shows the attack with alkyl and benzyl isocyanates.

In 2012, Hayashi and co-workers published a palladium-catalysed decarboxylative cyclisation reaction, where binaphthol-diarylpyrrolidine (*S*,*S*,*S*)-**200b** was

used as a ligand (Scheme 31).[61] The researchers were able to synthesise chiral pyrrolidinones (*S*)-**226** and piperidinones (*S*)-**230** in a reaction between δ-valerolactones (±)-**224** and isocyanates. The reaction with alkyl and benzyl isocyanates **225** favoured the formation of pyrrolidinones (*S*)-**226**, which were obtained with high enantioselectivity. The yields were mostly very good and 94% at best: the only low-yielding reaction from the studied substrate scope was observed when Ar^1 of (±)-**224** was *o*-OMe-Ph.

The regioselectivity of the cyclisation changed when aryl isocyanates **228** were used, resulting in the selective formation of piperidinones (*S*)-**230** (Scheme 31). The *er*'s of the obtained products were again excellent, as were the yields. However, the method was not suitable for δ-valerolactones (±)-**224** with an α-alkyl substituent in place of Ar^1. This was hypothesised to be because of the poor stabilising ability of the alkyl substituent on the forming negative charge at the α-carbon after the decarboxylation step.[61,134]

Based on the hypotheses by the authors in their preceding work on similar transformations, the high stereoselectivity of the method could be rationalised on the basis of the highly organised Pd–ligand–substrate species (**231**), formed after the decarboxylation and resulting in effective blocking of the species' *si*-face.[135] The reasons for the regioselectivities were also studied, which were dependant on the stabilising effect of the substituent on the anionic amide nitrogen: the more stabilising aryl substituents favoured the attack on the terminal carbon of the π-allyl–palladium complex **232** (thermodynamic product), whereas the less stabilising alkyl substituents preferred the attack on the central carbon (kinetic product).[61,134]

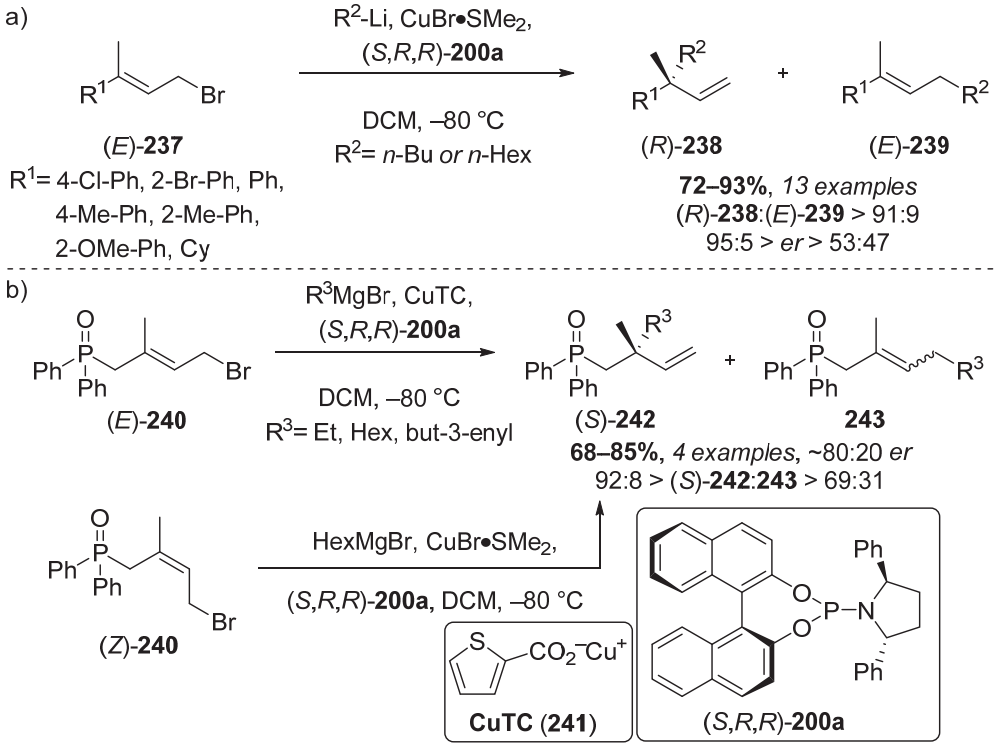


Scheme 32: Enantioselective aryl–aryl-coupling, where a 2,5-diarylpyrrolidine-derived hydrazine-ligand (*R*,*R*,*R*,*R*)-**235** was used. The blue dashed line was used to show the forming bond in the transition state depiction.[66]

In 2015, Denmark and co-workers published a method for the synthesis of axially chiral dinaphthyls (Scheme 32).[66] The key transformation they used was a palladium-catalysed aryl–aryl cross coupling reaction, where a chiral 2,5-diarylpyrrolidine was used as the basis for the bis-hydrazone ligand (*R*,*R*,*R*,*R*)-

235. The utility of the method was demonstrated with a reaction between 2-Me-naphthylsilanolate **233** and 1-bromonaphthalene (**234**), which gave the (*S*)-enantiomer of the coupling product **236** with an excellent 95:5 *er*. The yield was also very good 86%, and only ~1% of a homo-coupled 1,1-binaphthalene was detected.

The authors conducted further studies to get a deeper insight of the reaction mechanism.[66] The stereochemistry-determining step was shown to be the reductive elimination, since the enantioselectivity was not affected, when the methyl substituent was switched from the silanolate **233** to the C2 of 1-bromonaphthalene (**234**). In addition, extensive computational studies revealed that the lowest energy transition state was obtained when steric repulsions between the ligand and the aryl groups, as well as between the coupled naphthyl rings, were minimised (Scheme 32, **TS-1**). When the reaction progressed through this transition state, a clockwise conrotary movement of the naphthyl rings provided the major enantiomer (*S*)-**236**. Another transition state, which afforded the opposite enantiomer, was found to be the second lowest in energy, and the energy difference of these transition states was in unison with the experimentally determined *er*.



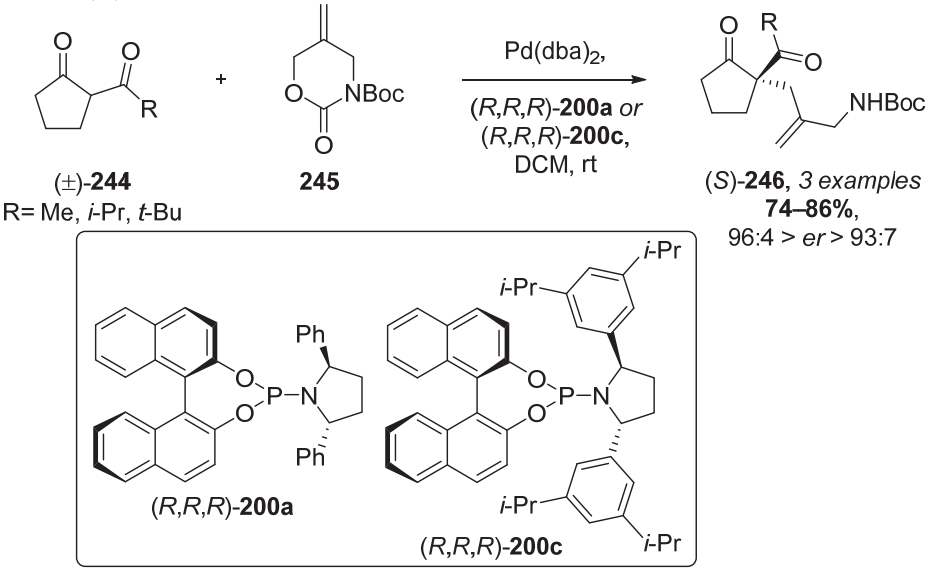
Scheme 33: Asymmetric copper-catalysed alkylations of allylic bromides by Feringa and co-workers.[136,137]

In 2012, Feringa and co-workers published an asymmetric alkylation reaction of allyl bromides (*E*)-**237** (Scheme 33a).[136] The reaction was catalysed by copper, which was complexed with a chiral phosphoramidite ligand (*S*,*R*,*R*)-**200a**. Reactive alkyl lithium reagents *n*-BuLi and *n*-HexLi were used as the alkylating

agents, which, according to the authors, was the first time these reagents were successfully used in an enantioselective all-carbon quaternary stereocenter formation.

The method gave both electron-poor and -rich aryl alkenes (*R*)-**238** in high yields and with excellent *er*'s at best (Scheme 33a). Cyclohexyl-variant, the sole alkyl alkene substrate, was also tolerated, giving the corresponding product with very good yield and *er*. One exception to the triumph was observed when R^1 was 2-Me-Ph: the product alkenes were practically racemic. Despite this, in every case, the S_N2' products were formed almost exclusively, showing the superb regioselectivity of the reaction. Interestingly, halogenated aryls, as well as the halogenated solvent, were tolerated without any evidence of a lithium–halogen exchange hampering the reaction.[136]

A year later, Feringa's group continued their asymmetric alkylation method development efforts.[137] This time, they used allyl bromide phosphine oxides **240** as substrates and alkyl Grignard reagents in a copper–(*S*,*R*,*R*)-**200a**–catalysed reaction, which made it possible to synthesise (*S*)-alkenes **242** with all-carbon quaternary stereocenters (Scheme 33b). The enantioselectivity of the transformation was not excellent this time, the *er*'s being around 80:20. However, the regioselectivity of the reaction was very good, and the S_N2' products **242** were clearly favoured. The stereochemistry of the substrate allyl bromide had a significant effect on the regioselectivity: the *Z*-isomer (*Z*)-**240** gave the lowest regioselectivity, although the enantioselectivity was on the same level as with the *E*-isomer (*E*)-**240**.

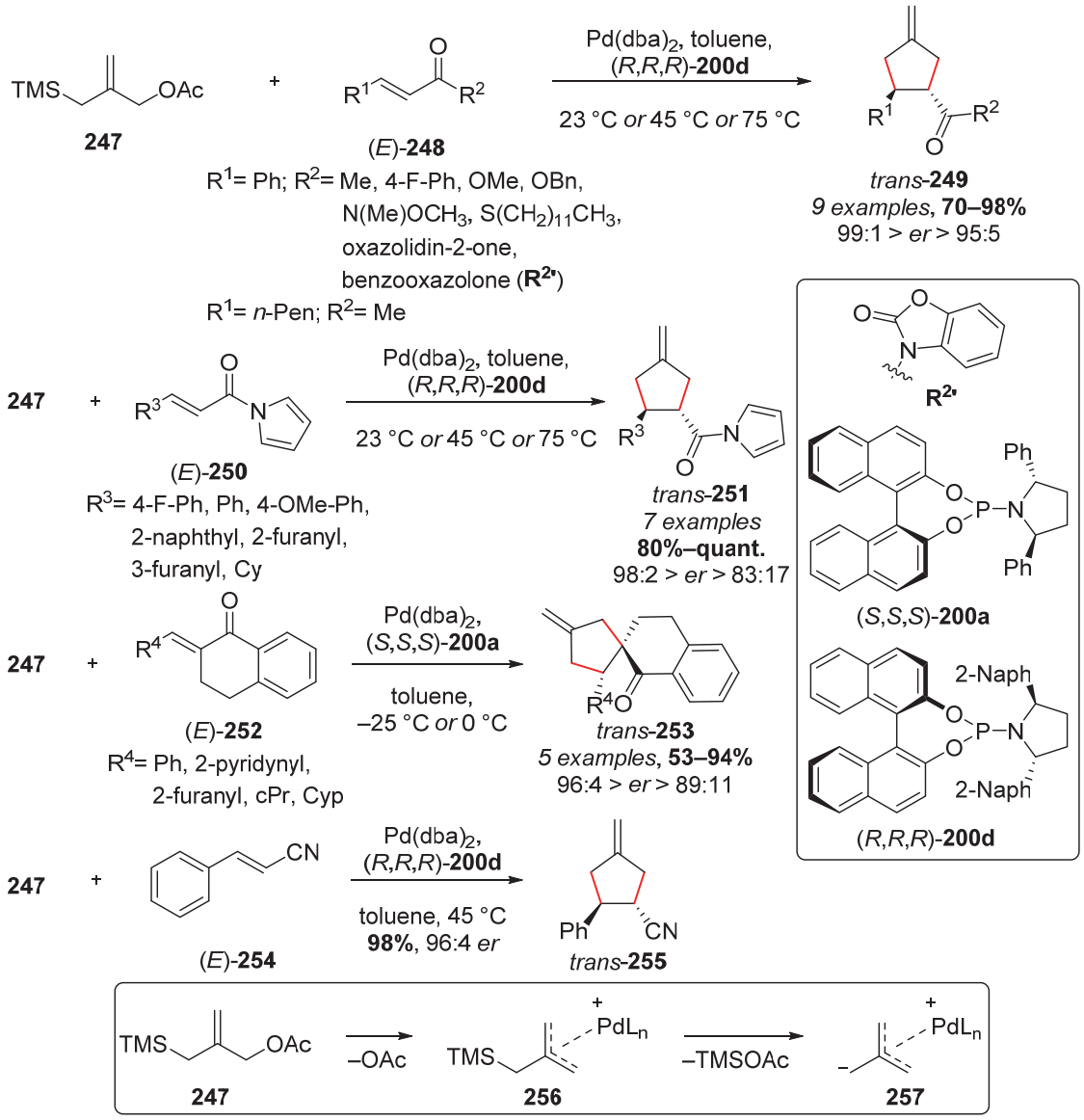


Scheme 34: Asymmetric palladium-catalysed allylation of 1,3-diketones by Harrity and co-workers.[62]

In 2016, Harrity and co-workers published an asymmetric allylation reaction between racemic 1,3-diketones (±)-**244** and carbamate **245** (Scheme 34).[62] The transformation was catalysed by palladium, which created a π-allyl–palladium species *via* carbamate decarboxylation. In the presence of chiral phosphoramidite ligands (*R*,*R*,*R*)-**200a** and (*R*,*R*,*R*)-**200c**, the enols of 1,3-diketones at-

tacked the terminal carbon of the allylic species in a highly enantioselective manner, providing the allylated products (*S*)-**246** in yields between 74% and 86%.

2.2.1.4.4 (3+2) and (6+3) cycloadditions



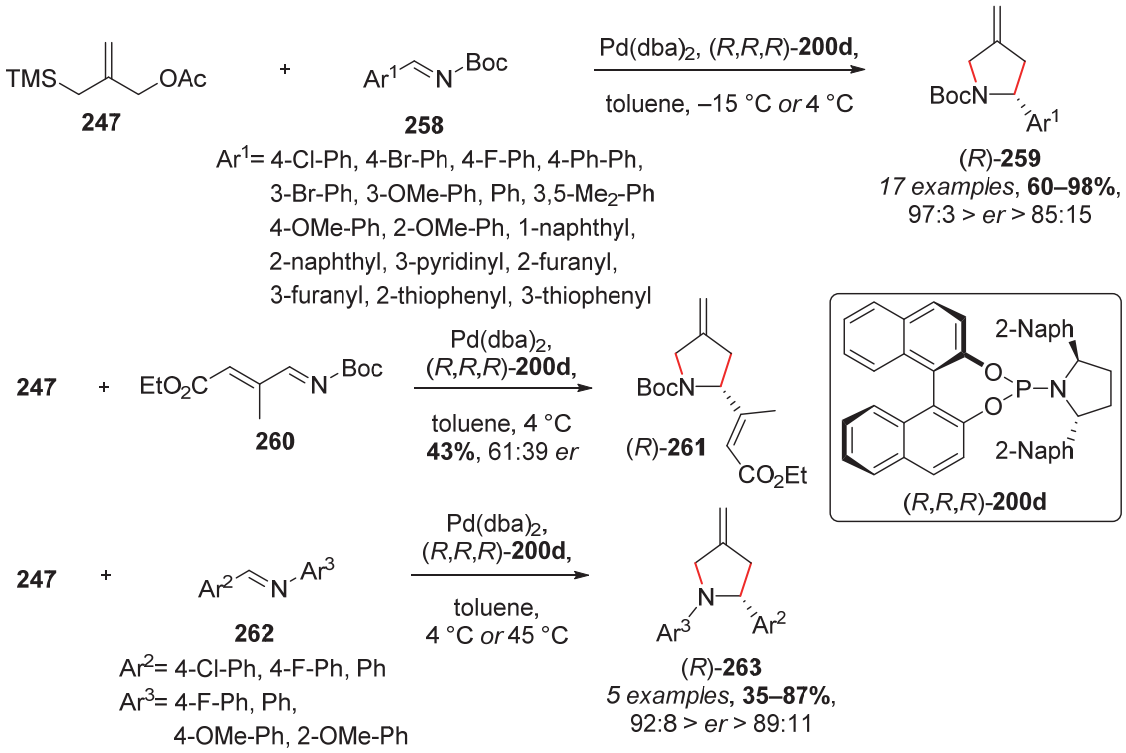
Scheme 35: The seminal studies on asymmetric palladium-catalysed (3+2) trimethylenemethane cycloaddition reactions developed by Trost and co-workers.[86,138]

In 2006, Trost and co-workers started their pioneering work in the realm of asymmetric palladium-catalysed trimethylenemethane (TMM) cycloaddition reactions.[138,139] In the seminal communication, the researchers used chiral phosphosramidite (*S*,*S*,*S*)-**200a** as a ligand (Scheme 35), which was introduced by Kim and co-workers a few years earlier.[124] However, as the group became more experienced with the TMM reactions, they found out that the corresponding 2-naphthyl derivative (*R*,*R*,*R*)-**200d** was usually the optimal catalyst for this type

of reaction due to added steric bulk compared with the preceding phenyl substitution.[86,138]

The Trost group used 2-TMS-methyl allyl acetate (**247**) in the formation of TMM-intermediate **257**, created *in situ* after the elimination of allylic acetate (**256**) and the TMS group (Scheme 35). Once formed, the chiral zwitterionic Pd complex readily reacted with activated alkene compounds. For example, reactions with olefins (*E*)-**248** and (*E*)-**250** furnished chiral *trans*-disubstituted cyclopentanes with *exo*-cyclic double bond in 70–98% yields and mostly with brilliant stereoselectivities (>95:5). The tested substrates consisted of different chalcones, (thio)esters and acyl-*N*-compounds, such as αβ-unsaturated acylpyrroles.[86,138]

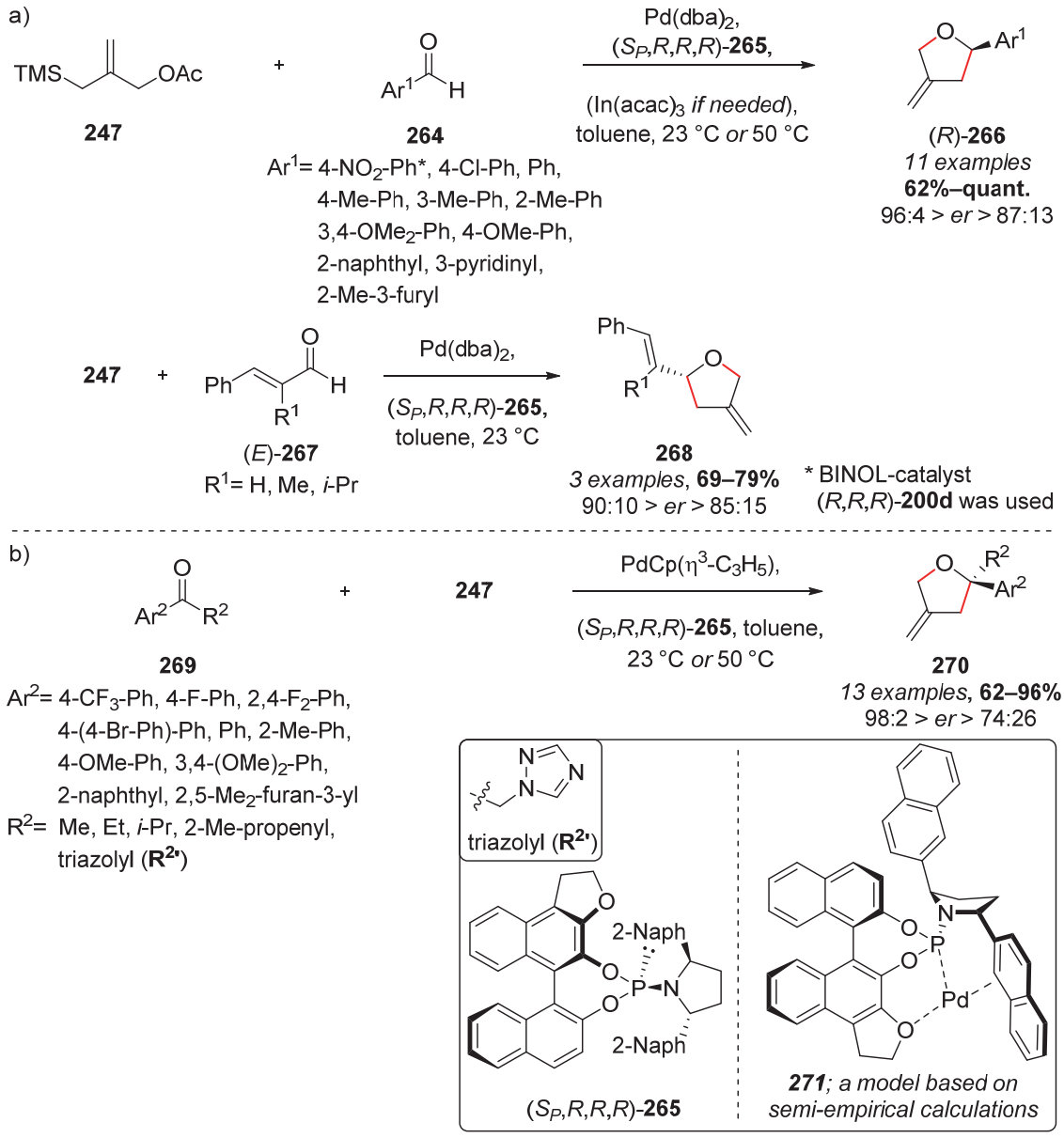
With the optimised conditions, the researchers were able to synthesise spirocyclic tetralone derivatives *trans*-**253** and a nitrile-containing cyclopentane *trans*-**255**. The latter transformation especially was interesting, since it showed the potential of non-carbonyl functional groups as alkene-activating moieties (Scheme 35). Even though the yields varied from 53% to 94%, the stereoselectivities were again mostly very high. In general, most of the examined substrates contained a styryl moiety, but some examples with (cyclo)alkyl substituted alkenes were also tolerated. However, neither cyclohexyl-substituted tetralone (R^4= Cy) nor an (*E*)-olefin-containing compound furan-2(5*H*)-one were suitable substrates.[86,138]



Scheme 36: Asymmetric palladium-catalysed TMM reaction between **247** and imines by Trost and co-workers.[140,141]

In 2007, the Trost group continued its synthesis efforts by developing the first catalytic asymmetric TMM reaction between **247** and imines (Scheme 36).[140,141] With this reaction, the synthesis of monosubstituted pyrrolidines with an *exo*-

cyclic double bond was possible. The largest substrate scope was demonstrated with aromatic Boc-protected imines. Differently substituted aryls with varying electronic properties were well tolerated. Heteroaryls were also suitable, and pyrrolidines (*R*)-**259** were furnished in 60–98% yields and with excellent *er*'s at best. The only tested acyclic substrate **260** gave pyrrolidine (*R*)-**261** with poor yield and 61:39 *er*: the low performance of the reaction was probably due to the activated double bond which caused side reactions. Lastly, a handful of *N*-aryl pyrrolidines (*R*)-**263** could also be synthesised. The yields varied from 35% to 87%, and the *er*'s were on a very good level (~90:10).



Scheme 37: A method using the TMM reaction in the construction of tetrahydrofurans with *exo*-cyclic double bonds by Trost and co-workers. a) Aldehyde substrates.[142] b) Ketone substrates.[143]

The Trost group kept on widening the scope of the TMM reaction by constructing mono- and disubstituted tetrahydrofurans, which could be synthesised with

a reaction between **247** and either aldehydes or ketones. Another piece of novelty came in the form of a new phosphoramidite ligand (S_P,*R*,*R*,*R*)-**265**, needed to achieve the high-performing reactions (Scheme 37)**.**[142,143]

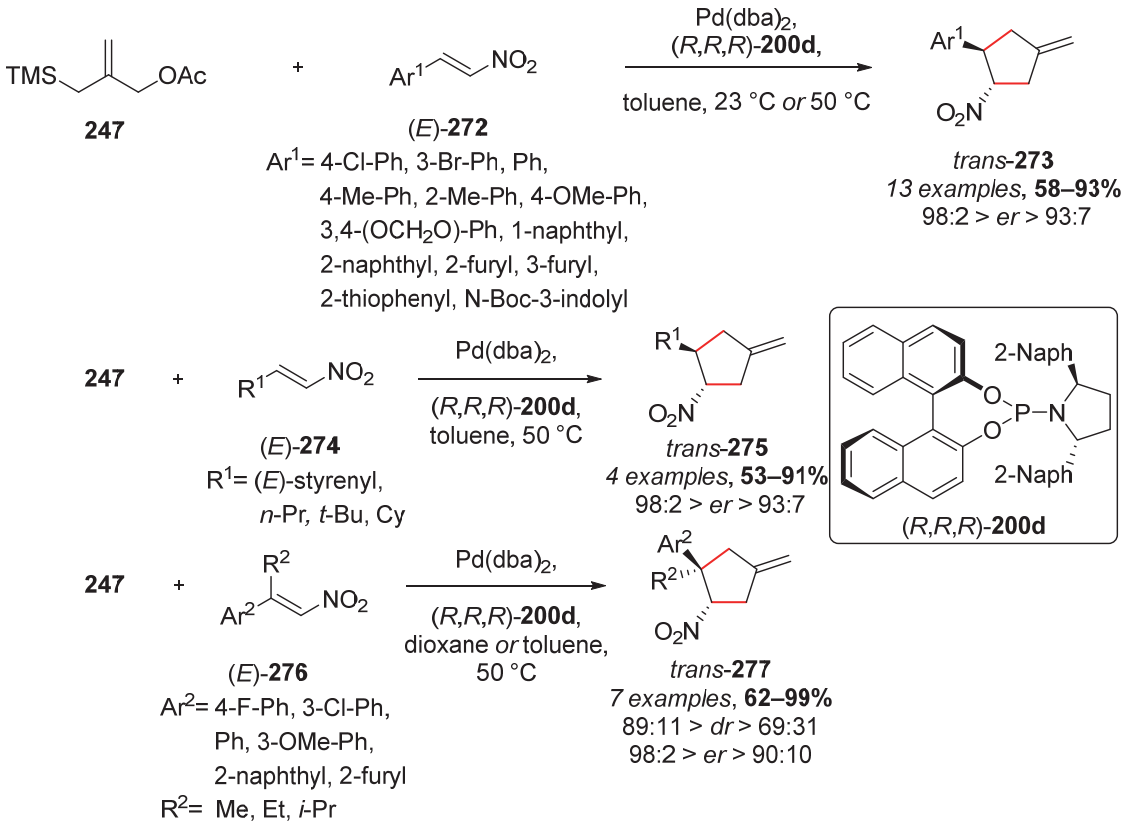
In the case of aldehydes, various electron-rich benzaldehydes, as well as heteroaryl aldehydes, suited well for the method (**264**, Scheme 37a).[142] The yields varied from good to excellent, while the *er*'s were mostly excellent. From electron-poor benzaldehydes, the 4-NO_2-substituted one required the use of 2-naphthyl catalyst (*R*,*R*,*R*)-**200d**, due to plausible interfering coordination between the Pd–**265**-complex and the substituent. Some of the aldehydes required additional Lewis acid activation in order to get satisfactory yields. With α-substituted cinnamaldehydes (*E*)-**267**, the reaction occurred exclusively to the carbonyl, whereas a mixture of aldehyde and olefin cycloadducts were obtained when R^1 of (*E*)-**267** was hydrogen. Aliphatic aldehydes were not tested.

The corresponding reaction with ketones did not require any additional Lewis acid catalysis, resulting in excellent *er*'s mostly (Scheme 37b).[143] The transformation tolerated electron-poor aromatics and, as with aldehydes, both electron-rich aromatics and heteroaryls were also suitable. Great-sized R^2-alkyl substituents gave typically high *er*'s; however, the triazolyl-substituted ketone gave the lowest *er* of the scope (74:26). When enone (R^2= 2-Me-propenyl) was used as a substrate, the reaction favoured the carbonyl over the double bond, which demonstrated that the chemoselectivity of the TMM reaction could possibly be controlled by changing the phosphoramidite ligand (compared with the results in Scheme 35). Fully aliphatic ketones were not tested.

The dihydrofuran moiety in the BINOL part created additional steric bulk to the ligand (S_P,*R*,*R*,*R*)-**265**, but in a more conformationally constrained manner compared with alkyl groups, which were found to be unsuitable in this context. The new catalyst was no longer C_2-symmetric since an additional stereocenter at phosphorus was formed. The researchers noticed that, surprisingly, the *dr* of the catalyst did not affect the enantioselectivities of the reactions since the undesired (R_P,*R*,*R*,*R*)-diastereomer was catalytically inactive. Based on semi-empirical calculations, a hypothesis was made that only the catalytically active diastereomer was able to create stabilizing secondary interactions between palladium and both the pyrrolidine naphthyl group and the dihydrofuran oxygen. These interactions were seen as beneficial factors for both enantioselectivity and yield (Scheme 37).[142,143]

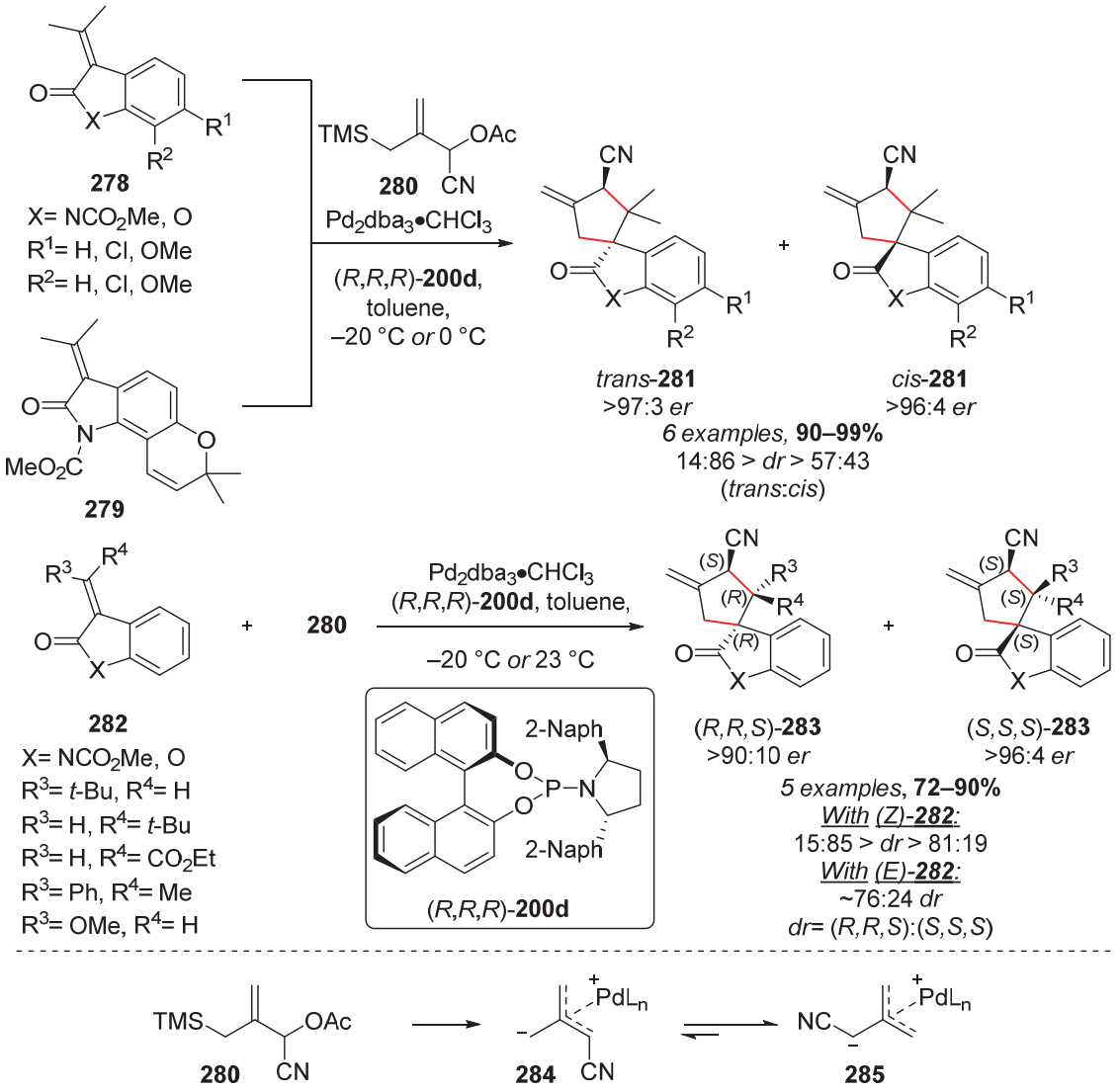
As was seen in the earlier examples, the TMM reaction between **247** and alkenes required the activating group in conjugation to the alkene. It has been almost without an exception a carbonyl group (Scheme 35).[86,138] This prompted the Trost group to study whether another electron-withdrawing group, e.g. nitro, could be used instead. Indeed, they found that both electron-poor and -rich (*E*)-β-nitrostyrenes **272** participated well in the reaction, producing *trans*-disubstituted cyclopentane compounds **273** with excellent *er*'s (Scheme 38).[144] In addition, heteroaryl- and alkyl-substituted (**274**) nitroalkenes were suitable substrates. Interestingly, a 1,4-conjugated diene reacted chemoselectively with the double bond closest to NO_2.

The substrate scope was later extended to β-aryl–alkyl-substituted nitroalkenes, which were used to create cyclopentane compounds *trans*-**277** with all-carbon quaternary stereocenters (Scheme 38).[145] The enantioselectivities were superb (>90:10), while the diastereoselectivities were very good at best (<89:11 *dr*). The diastereoselectivity problem was hypothesised to be a result of high reactivity of the TMM donor formed from **247**, which lowered the stereocontrol of the initial attack on the alkene. The resulting *er*'s of *trans*-**277** were still high, an indication that the chirality of the ligand was controlling the final ring closure step that formed the second stereocenter.



Scheme 38: Asymmetric synthesis of substituted nitrocyclopentanes with *exo*-cyclic double bonds, developed by Trost and co-workers.[144,145]

The seminal asymmetric TMM reaction publication by the Trost[138] group was quickly followed by another one, where a cyano-substituted 2-TMS-methyl allyl acetate (**280**) was used in the TMM-donor **285** formation (Scheme 39).[146] The donor was formed by a quick equilibration reaction after the initial acetate (**284**) and TMS group cleavages. The complex **285** then reacted with the activated *exo*-cyclic double bonds of various oxindoles and benzofuranones. Substrates with Me_2-substituted double bond (**278**, **279**) formed the spiro-compounds **281** with excellent enantioselectivities and yields. Remarkably, the double bond of the aryl dimethylpyran-substituent in substrate **279** did not react, showing the general unreactive nature of the non-activated double bonds in the TMM reactions. The conditions mostly provided the *cis*-**281**, although the selectivity was almost completely lost when both R substituents were methoxies.



Scheme 39: Asymmetric method for creating spirocyclic oxindolic compounds, developed by Trost and co-workers.[146] Yields are of the combined diastereomer mixtures.

An additional stereocenter was generated when the double bond substituents were inequivalent (Scheme 39).[146] The reaction tolerated ethyl ester, Ph and methoxy substituents, as well as a sterically demanding *t*-Bu substituent, and the spiro-compounds **283** were furnished mostly in high yields and with excellent *er*'s (>90:10). The diastereocontrol was not ideal but the *dr*'s were very good, at best. Interestingly, changing the substituent of the ligand (*R*,*R*,*R*)-**200d** from 2-naphthyl to 1-naphthyl had a dramatic effect on the diastereoselectivities: the reactions clearly began to favour the formation of spirocompounds *trans*-**281** and (*R*,*R*,*S*)-**283**, regardless of the *E*,*Z*-geometries of the substrates. However, with this ligand, clear decreases in enantioselectivities were also observed, the lowest *er* being 60:40.

The utility of aryl–alkyl-ketimines in the asymmetric TMM reaction with nitrile-substituted **280** was demonstrated by Trost and Silverman.[141,147] Interestingly, an asymmetric catalytic reaction between 2-TMS-methyl allyl acetate (**247**)

and ketimines was disclosed neither in these publications nor in the accounts prior to them.*,[148] Nevertheless, with a limited substrate scope, the reactions with **286** were shown to tolerate both electron-poor and -rich aromatics, as well as furanyl and bulky naphthyl moieties (Scheme 40a). Methyl and ethyl were found to be suitable aliphatic groups. The presence of a sterically demanding isobutyl group lowered the yield of the reaction to 24%.

The synthesis of spirocyclic pyrrolidines *cis*-**289** was also successful, when the ring size of the cycloalkyl part of **288** was either five or six carbons (Scheme 40a).[147] The reaction with a seven-membered ring variant was low yielding (26%) due to the instability of the substrate itself.[141] The lone example of a fully aliphatic ketimine was demonstrated with cyclopentyl imine, which produced the TMM product in very good yield and with excellent *er*.

Low temperatures were required to avoid the formation of *endo*-tautomer (**292**) (Scheme 40a).[141,147] *N*-tosyl-protection was found to be essential for the reaction, since, with *N*-Boc compounds, isomerisation to the corresponding enamine was observed. The tosyl group was also influencing the stereoselectivity. Its *anti*-preference to the ketimine aryl created sterical hindrance on the alkyl side, causing a severe clash with the Pd–allyl complex and thus disfavouring its approach from the *re*-face of the iminium and the formation of *trans*-cycloadducts. Saccharin-derived ketimine **290** served as proof of this concept: as the aliphatic side was free from the sterical obstacle, the face-selectivity was changed, and *trans*-**291** was formed.

The use of **280** in asymmetric TMM reactions was then extended to *N*-tosyl imines **293** (Scheme 40b).[141] Applying the reaction conditions from the ketimine method, the pyrrolidines *cis*-**294** could be synthesised in very good to excellent yields and with brilliant diastereoselectivities. Interestingly, only electron-rich (hetero)aryls were tolerated, the electron-poor aryls apparently favouring the *endo*-tautomerisation of the double bond. Few aliphatic imines **296** were applicable, although problems with both diastereoselectivity and product selectivity arose, especially with cinnamaldehyde-derived imine (R^2= (*E*)-styrenyl).

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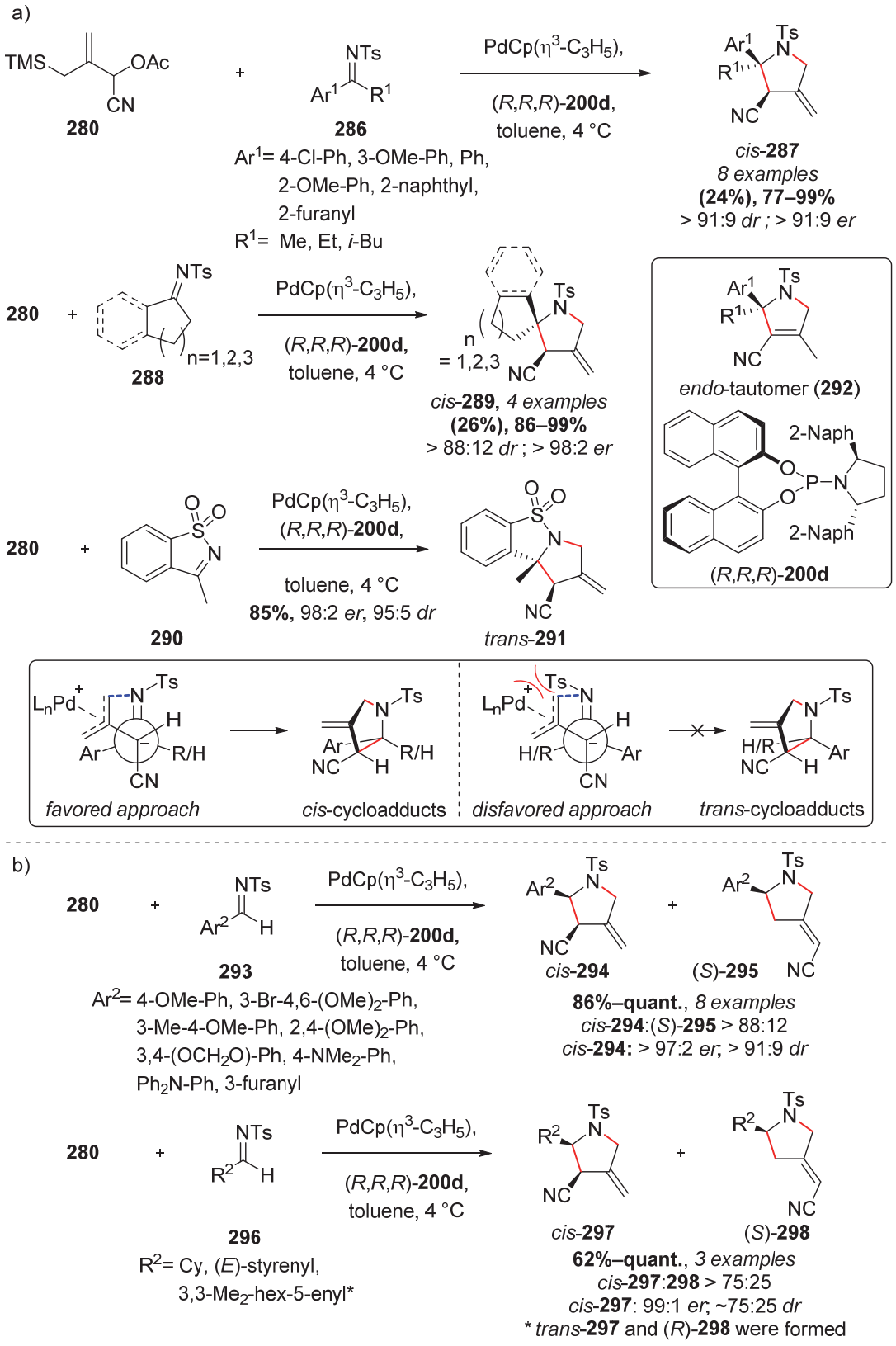
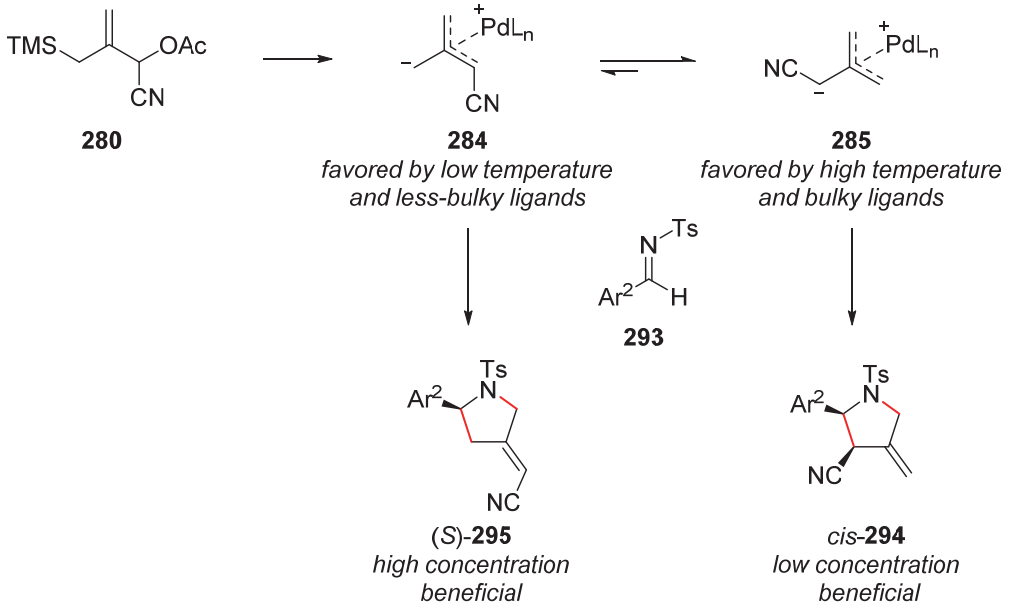
* Later, Stockman and co-workers published a diastereoselective method, where a chiral auxiliary was used.[148]



Scheme 40: Enantioselective TMM reaction for constructing substituted pyrrolidines, developed by Trost and Silverman. a) Reactions with ketimines.[147] b) Reactions with aldimines.[141]

The formation of compounds (*S*)-**295** and **298** was hypothesised to occur due to the high reactivity of the imine and the slow rate of the isomerisation of **284** to the more stable **285** (Scheme 41).[141] The factors affecting the rate of the isomerisation were temperature and the size of the ligand: high temperatures and bulky ligands slowed down the rate of the nucleophilic addition to imine and favoured the isomerisation to **285**. In addition, lowering of the concentration was beneficial for the formation of product *cis*-**294**.



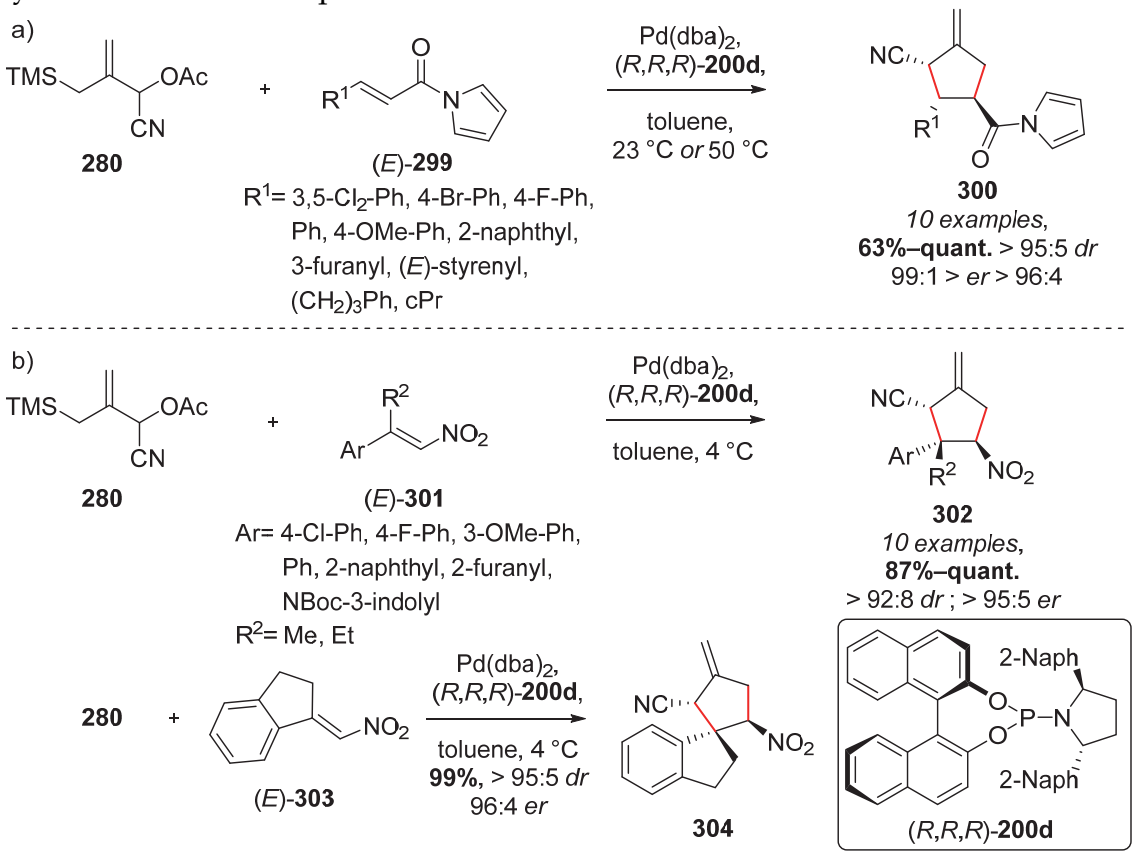
Scheme 41: The factors affecting to the formation of the observed products in the TMM reaction between **280** and imines.[141]

The Trost group showed that CN-substituted TMM-donor **280** could also engage in a reaction with αβ-unsaturated acyl pyrroles (*E*)-**299**[86] (Scheme 42a) and disubstituted nitro olefins (*E*)-**301** (Scheme 42b).[145] Cyclopentanes **300** with three contiguous stereocenters were synthesised mostly in high yields and with brilliant stereoselectivities. The reaction tolerated both electron-poor and -rich aromatics, as well as aliphatic groups, as the β-substituents. Remarkably, only the αβ-double bond of (*E*)-styrenyl-substituted (*E*)-**299** reacted, although the yield of the formed cyclopentane compound was only 63%.

Disubstituted nitro olefins (*E*)-**301** as substrates offered another quick way to obtain cyclopentanes **302** with three contiguous stereocenters (Scheme 42b).[145] The limited scope consisted of aryls with electron-withdrawing substituents and few heteroaryls. With methyl or ethyl as the alkyls, the cyclopentanes **302** were synthesised mostly above 87% yields and with excellent stereoselectivities. A spiro-compound **304** was also synthesised without a problem from indan-derivative (*E*)-**303**.

Interestingly, the sense of enantioinduction was reversed when the CN-substituted TMM-donor **280** was used instead of the unsubstituted one (**247**, Scheme 35 and Scheme 38). The precise explanation for the reverse preference was unclear to the researchers, but they hypothesised that the initial attack of

the donor to the acceptor was more selective with **280** due to the lower reactivity of the CN-derived species.[145]

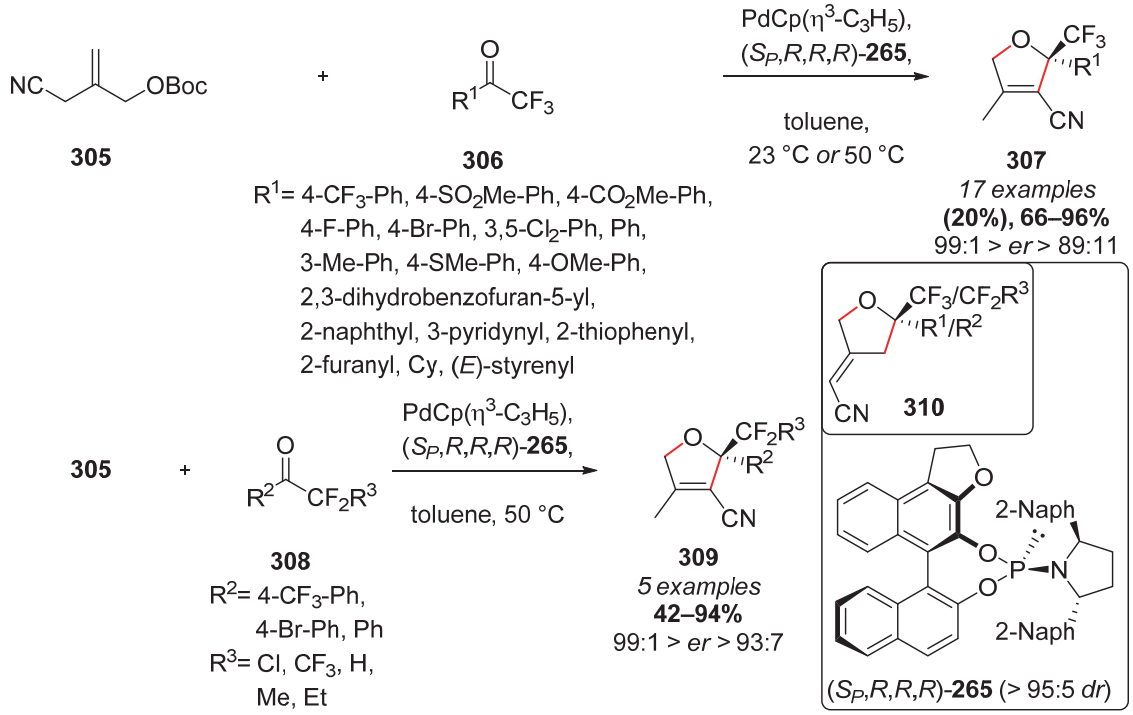


Scheme 42: Stereoselective TMM reactions by Trost and co-workers, where CN-substituted donor **280** was used. a) Reactions with αβ-unsaturated acylpyrroles.[86] b) Reactions with disubstituted nitroalkenes.[145]

Quite recently, Trost and Mata expanded the TMM reaction scope to halogenated ketones and cyanomethyl allyl carbamate **305** (Scheme 43).[74] Catalysed by the Pd–**265** complex, the reactions with both electron-poor and -rich CF_3-arylethanones proceeded mostly in very good yields and with excellent enantioselectivities. Heteroaryls were also tolerated but cyclohexyl and (*E*)-styrenyl substituents were not. The reactions with the latter ones were low-yielding and faced severe chemoselectivity issues, the attack on the double bond being favoured.

The scope of the method was extended to CF_2R^3-ketones, where one fluoride was exchanged with either chloride, (fluoro)alkyl or hydrogen (Scheme 43).[74] This had no effect on the enantioselectivities, which remained high. The lowest yields were gained with substrates, where R^3 was ethyl or hydrogen, the latter probably suffering from side-product formation caused by enolisation.

The regioselectivities were superb, and the amounts of the constitutional isomers **310** with an *exo*-cyclic nitrile-substituted double bond were less than 5% in the presented examples (Scheme 43).[74] This indicated that the unwanted isomerisation of the TMM donor did not occur prior to the addition to the ketone (compare to Scheme 41).



Scheme 43: Asymmetric synthesis of fluorine-substituted dihydrofurans by Trost and Mata.[74]

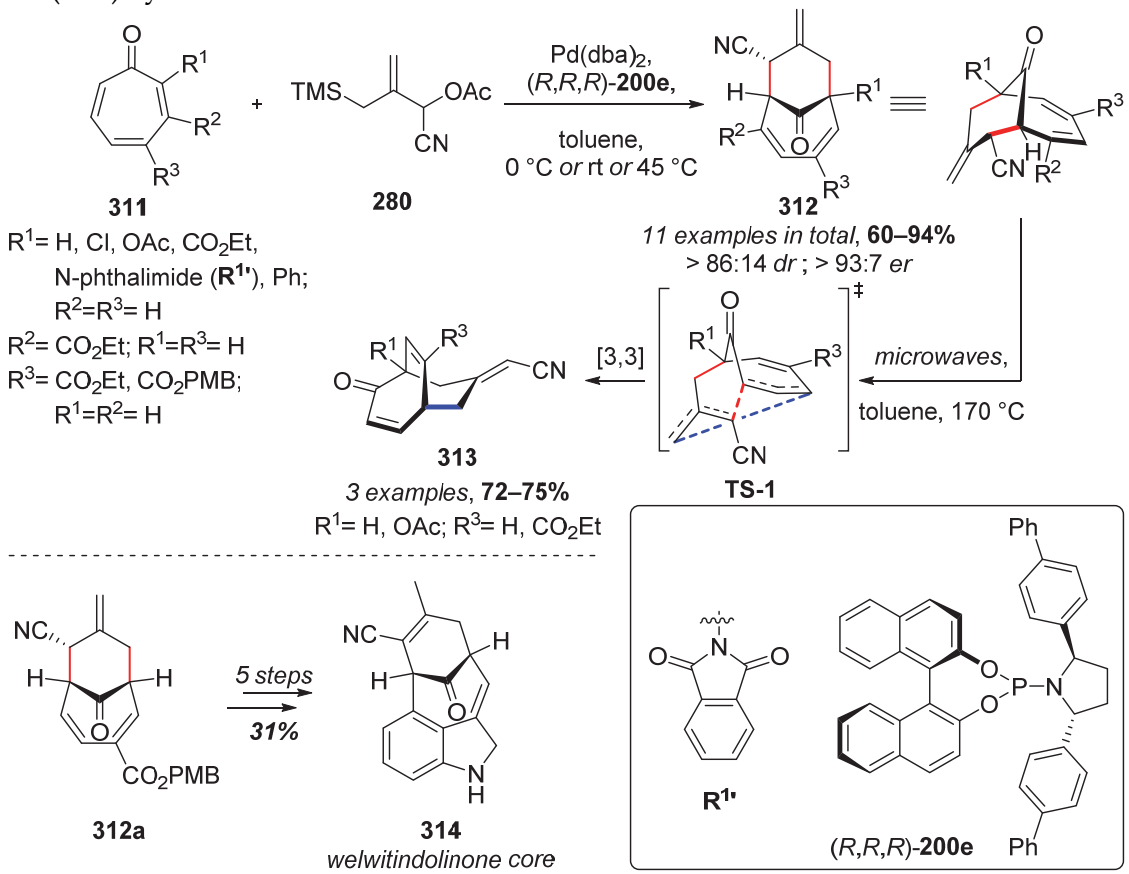
Dihydrofurans **307** and **309** with *endo*-double bonds were obtained as the main isomeric products, indicating that tautomerisation took place readily as the final step.[74] Lowering of the reaction temperature was deadly for the reactivity and could not be applied in order to avoid the isomerisation. This is contrary to the previous examples with ketones as substrates, where tetrahydrofurans with *exo*-cyclic double bonds were formed as main products at 4 °C (Scheme 37).[143]

In addition to extensive studies on (3+2)-TMM-cycloaddition reactions, the Trost group presented their sole example of a (6+3)-cycloaddition reaction, where the 2,5-diarylpyrrolidine-phosphoramidite ligand was used.[149] From the screening studies, biphenyl substitution in the ligand (*R*,*R*,*R*)-**200e** proved to be the ideal one for this reaction (Scheme 44). Remarkably, the reaction conditions favoured the (6+3) cycloaddition over the (3+2) reaction with the ketone functionality and the double bonds.

Various α-substituted tropones **311** were suitable for the reaction, giving the cycloadducts **312** in 60% to 94% yields and with excellent stereoselectivities (Scheme 44).[149,150] Interestingly, chloride was tolerated as an R^1 substituent, but bromide was not, probably due to a more readily occurring oxidative addition reaction. Furthermore, strong electron-donating methoxy- and dimethylamino substituents were not tolerated. β-substituted ester changed the regioselectivity of the attack, placing the nitrile and ester on the same side of the cycloadduct **312**.

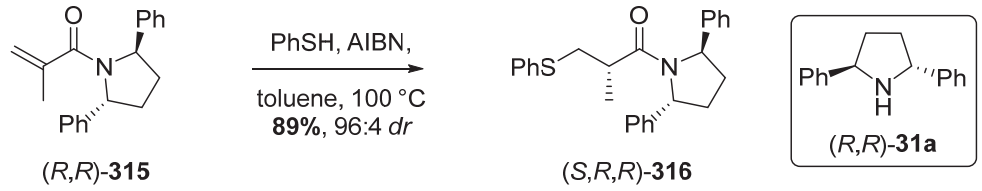
Some of the cycloadducts **312** were demonstrated to undergo a facile Cope rearrangement, giving chiral bridged compounds **313** with various functionalities (Scheme 44).[149] Later, Trost and McDougall utilised the method in a synthe-

sis of welwitindolinone[151] core **314**, which they synthesised in five steps after the (6+3) cycloaddition.[150]



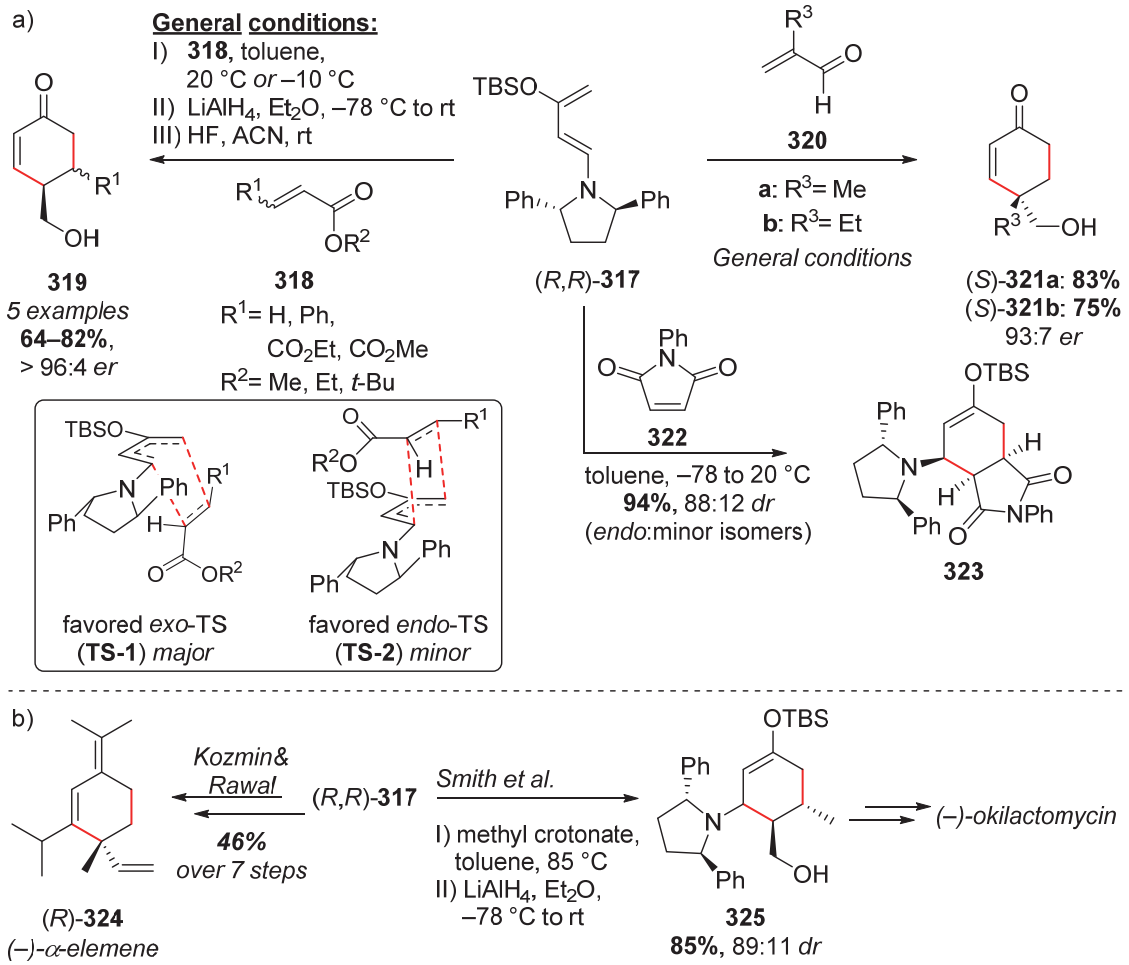
Scheme 44: Trost and co-workers.[149,150] The red dashed bond indicates the breaking bond, and the blue dashed line indicates the forming bond in the Cope rearrangement.

2.2.2 2,5-diarylpyrrolidine as a chiral auxiliary



Scheme 45: One of the first synthesis examples employing chiral *trans*-2,5-diphenylpyrrolidine in asymmetric synthesis, published by Taber and co-workers.[152]

A couple of years after the first chiral syntheses of *trans*-2,5-diphenylpyrrolidine by Higashiyama[90] and Chong,[55] Taber and co-workers used (*R*,*R*)-**31a** as a chiral auxiliary in a diastereoselective radical reaction.[152] They treated methacrylamide (*R*,*R*)-**315** with thiophenol in the presence of radical initiator AIBN, which gave them (*S*,*R*,*R*)-**316** in a very good, 89% yield (Scheme 45). In addition, the *dr* was 96:4, which showed the remarkable sterical steering power of the pyrrolidine phenyls. No attempts to remove the auxiliary were reported.



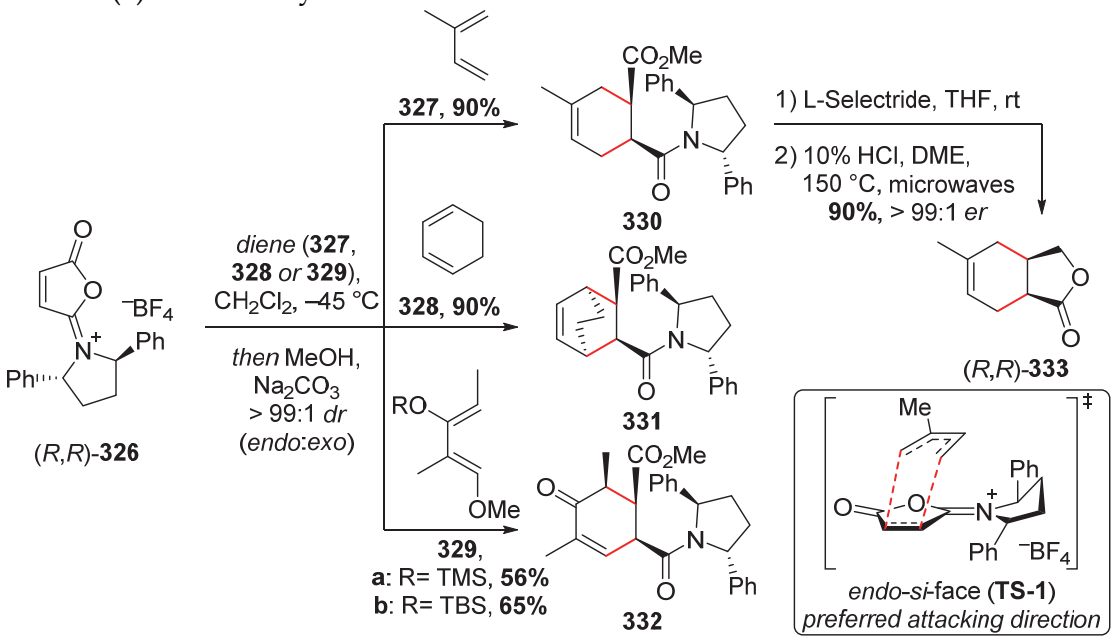
Scheme 46: a) Asymmetric Diels–Alder reaction, developed by Kozmin and Rawal and b) its utilisation in total syntheses.[153–155]

At the same time as Taber and co-workers[152], Kozmin and Rawal used (*R*,*R*)-**31a** in an asymmetric Diels–Alder reaction.[153] They prepared chiral diene (*R*,*R*)-**317** by a two-step process from methoxybutenone and let it react with dienophiles **318** and **320** (Scheme 46a). After reduction and desilylation-induced retro-Michael reaction, cyclohexenones **319** and (*S*)-**321** were obtained in good to very good yields and with greater than 93:7 *er*'s. Also, *N*-phenylmaleimide (**322**) successfully engaged in the transformation, yielding the cycloadduct **323** in 94% yield and with a very good 88:12 *dr*.[154]

The researchers hypothesised that the sterical shielding of the catalyst's phenyls forced the dienophile's electron-withdrawing group to point away from them. This resulted in two favoured transition states, the *exo*-TS (**TS-1**) being the dominant one (Scheme 46a).[154] With α-substituted acroleins (**320**) and maleimide **322**, the situation was the opposite and the *endo*-TS (**TS-2**) was the dominating one. The use of a C_2-symmetrical pyrrolidine was also advantageous since it removed the problem of rotation along the C–N bond, diminishing the effect of different rotamers on stereoselectivity.

Kozmin and Rawal demonstrated the synthetic utility of the method in the total synthesis of (–)-α-elemene[156], which could be completed in seven steps

from diene (*R*,*R*)-**317** (Scheme 46b). Later, Smith and co-workers used the method to synthesise cycloadduct **325**, an early intermediate in the total synthesis route to (–)-okilactomycin.[155,157]

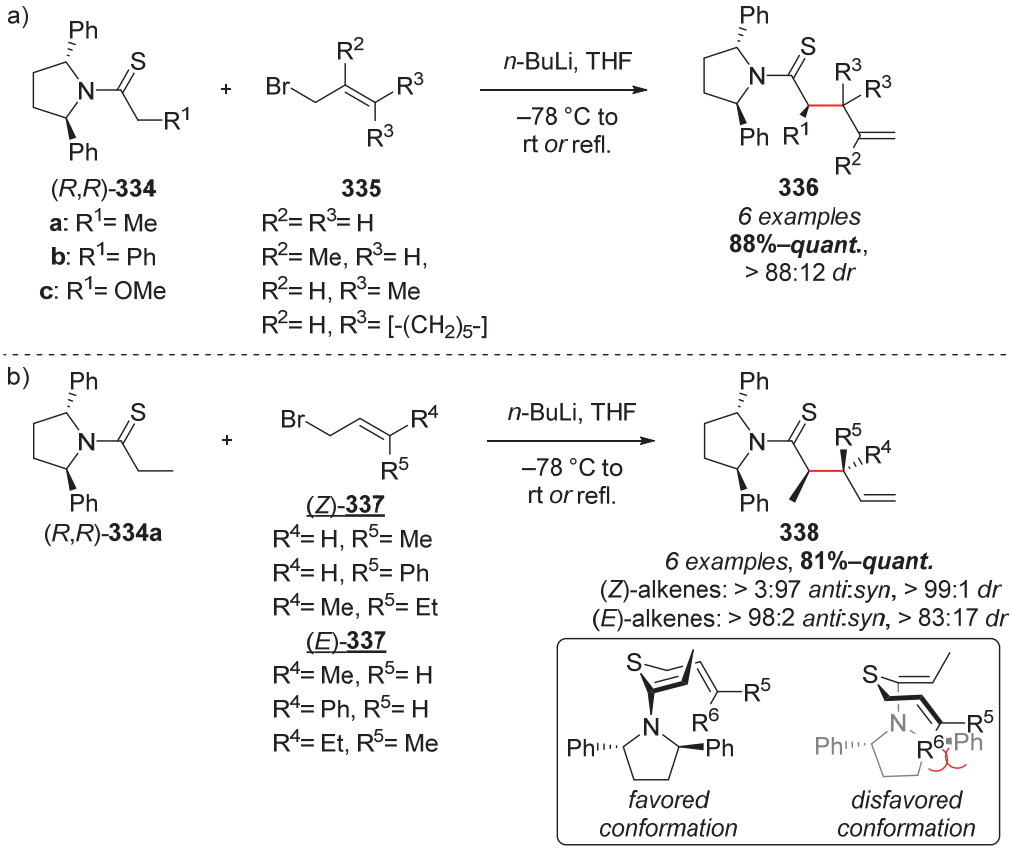


Scheme 47: Stereoselective Diels–Alder reaction of cyclic isoimidium salt (*R*,*R*)-**326**, developed by Boeckman and co-workers.[158,159] The *si*-face refers to the prochirality of (*R*,*R*)-**326** β-carbon.

In 2010, Boeckman and co-workers developed a highly diastereoselective Diels–Alder reaction for isoimidium salt (*R*,*R*)-**326**, derived from maleic anhydride and (*R*,*R*)-**31a** in two steps.[158] The highly reactive salt created cycloadducts **330–332** with brilliant diastereoselectivity, forming the *endo*-products exclusively (>99:1 *dr*, Scheme 47). The yields for **330** and **331** were high, while the yields from the reactions with more reactive Danishefsky's dienes **329** were significantly lower.

The cleavage of the chiral auxiliary was a challenging one due to the hindered nature of the amide: mildly acidic, basic and oxidative reaction conditions failed to remove the pyrrolidine. However, when the ester groups of the compounds **330–332** were reduced to alcohols and then heated up to 150 °C under acidic conditions, the auxiliaries were successfully removed and the corresponding lactones were formed due to an intramolecular attack of the alcohol. For example, lactone (*R*,*R*)-**333** was successfully synthesised in a 90% yield without any loss of stereopurity.[158]

Later, the reasoning for the high *endo*-selectivity of the reaction was thoroughly examined computationally by Bakalova and Santos.[159] They came to the conclusion that the sterics of the pyrrolidine phenyls forced the diene to approach the dienophile exclusively from its *si*-face (**TS-1**, Scheme 47). This was confirmed by the calculated transition state energies. These were significantly higher for both attacks from the *endo*-*re*-face and from the lowest energy *exo*-direction compared with the *endo*-*si*-face attack.



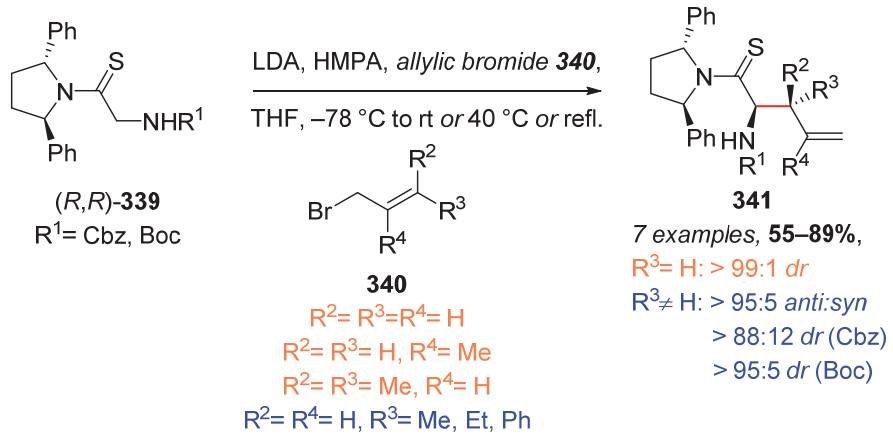
Scheme 48: Diastereoselective asymmetric thio-Claisen rearrangement, developed by Rawal and co-workers.[160]

Along the asymmetric Diels–Alder reaction, Rawal's group used 2,5-diphenylpyrrolidine in a diastereoselective asymmetric thio-Claisen rearrangement.[160] Thioamides **334**, prepared in two steps by acylation and thionation, reacted with allylic bromides **335** in 88% yield at best and mostly with brilliant diastereoselectivity (Scheme 48). The reaction also worked with (*E*)- and (*Z*)-allylic bromides **337**, which created an additional stereocenter in the β-position of thioamides **338**. The transformations had very high *anti*–*syn*-selectivities: (*Z*)-**337** favoured the formation of the *anti*-diastereomers, whereas (*E*)-isomers favoured the *syn*-diastereomers.

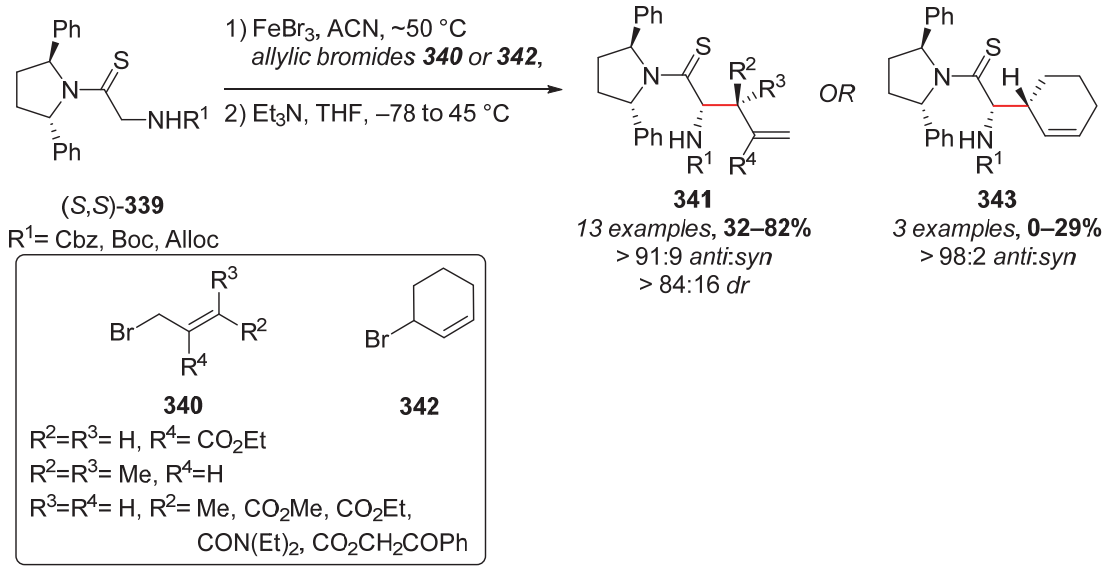
The stereochemical outcome was based on an exclusive formation of (*Z*)-thioenolate, which rearranged *via* chair-like transition state (Scheme 48b). Also, steric interactions between pyrrolidine phenyls and the olefinic part of the allyl chain played a critical role. The sterical factors influenced more on compounds **337** with (*Z*)-configuration than with (*E*)-configuration, thus leading to a higher observed diastereoselectivity in the former cases. Lastly, the removal of the auxiliary was demonstrated to occur after the S-methylation/reduction/hydrolysis sequence.[160]

Around a decade later, Hruby and co-workers extended the utility of the thio-Claisen method to glycine-derived thioamides (*R*,*R*)-**339** (Scheme 49).[161,162] The yields of the reactions with allylic bromides **340** varied from 55% to 89%, but the transformations were highly diastereoselective, and the stereochemical

results were consistent with the model proposed by Rawal *et al.* (Scheme 48b). Some deviation from the excellent diastereoselectivities occurred with bigger olefin substituents (R^3= Et, Ph; Scheme 49). The reason for this was a hypothetical sterical clash between the Cbz group and R^3. Changing the nitrogen protecting group from Cbz to Boc increased the diastereoselectivity of the reaction to a very high level, which was demonstrated with a phenyl substituted allylic bromide.



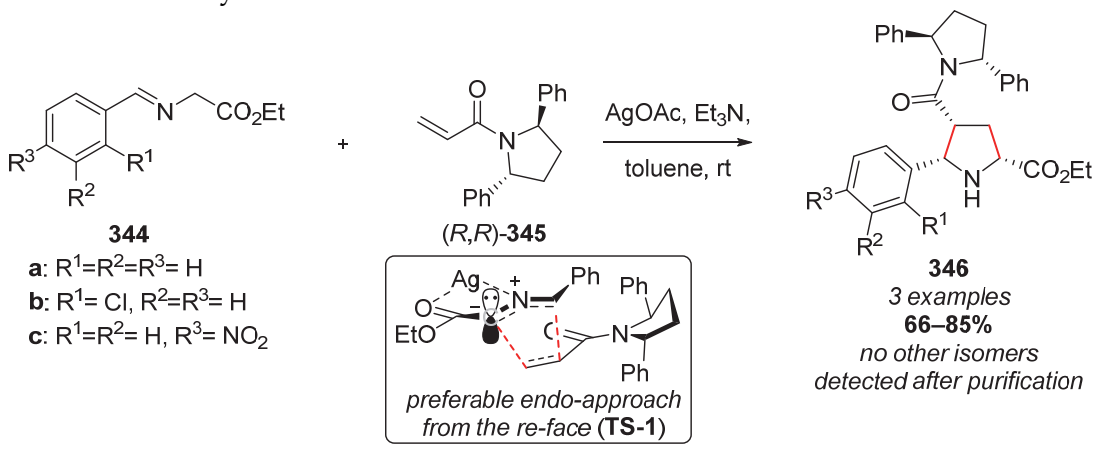
Scheme 49: Asymmetric thio-Claisen rearrangement by Hruby and co-workers.[161,162]



Scheme 50: Alternative enolisation method for asymmetric thio-Claisen rearrangement by Hruby and co-workers.[162]

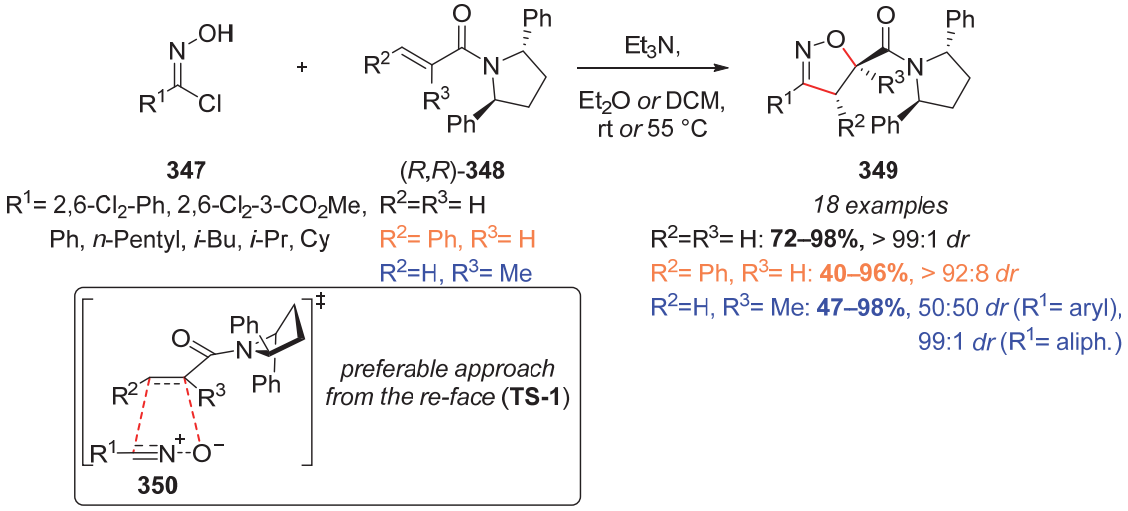
In addition to the LDA-promoted S-allylation and enolisation sequence, Hruby and co-workers used a milder $FeBr_3$-mediated thio-Claisen rearrangement (Scheme 50).[162] The transformation worked mostly with excellent diastereoselectivity and with several nitrogen protecting groups. The yields varied from zero to 82%, depending on the allylic moiety and the protecting group. However, no clear correlation between the size of the protecting group and the yields could be generalised. Lastly, the researchers demonstrated that the auxiliary

could be removed either by an S-alkylation/reduction/oxidation sequence[161] or by an oxidation/iodolactonisation/reduction sequence,[162] both of them giving access to a variety of substituted amino acids.



Scheme 51: 1,3-dipolar cycloaddition reaction of azomethine ylides, developed by Nyerges and co-workers.[163] The *re*-face refers to the prochirality of the (*R*,*R*)-**345** α-carbon.

In 2005, Nyerges and co-workers generated an asymmetric 1,3-dipolar cycloaddition reaction between *N*-metallated azomethine ylides and chiral acrylamide (*R*,*R*)-**345** (Scheme 51).[163] Glycine-derived imines **344** were used in a silver acetate-catalysed reaction to create the desired ylides, which then reacted with (*R*,*R*)-**345**, creating all-*syn*-cycloadducts **346** exclusively in 85% yield at best. The authors did not offer any explanations for the great face selectivity of the reaction. Probably the *re*-face of the chiral dipolarophile was sterically less demanding, and thus, an *endo*-approach to the ylide furnished the all-*cis*-stereochemistry of adducts **346**. Finally, the auxiliary was removed by refluxing the cycloadduct in ethanolic HCl.



Scheme 52: Asymmetric 1,3-dipolar cycloaddition between nitrile oxides formed from hydroximoyl chlorides **347** and chiral acrylamides (*R*,*R*)-**348** by Lassaletta and co-workers.[164] The *re*-face refers to the prochirality of the (*R*,*R*)-**348** α-carbon.

Later in the same year, Lassaletta and co-workers published an asymmetric 1,3-dipolar cycloaddition reaction between chiral acrylamides (*R*,*R*)-**348** and various nitrile oxides, prepared *in situ* from hydroximoyl chlorides **347** (Scheme 52).[164] The reaction was demonstrated to be suitable with aromatic nitrile oxides with electron-withdrawing substituents, while electron-donating ones were absent from the tested scope. In addition, both acyclic and cyclic alkyls were tolerated and the cycloadducts **349** were obtained with very high diastereoselectivities. It was thought that the sterical factors created a stereochemical bias where the approach of the nitrile oxide from the *re*-face of the acrylamide was favoured over the *si*-face approach.

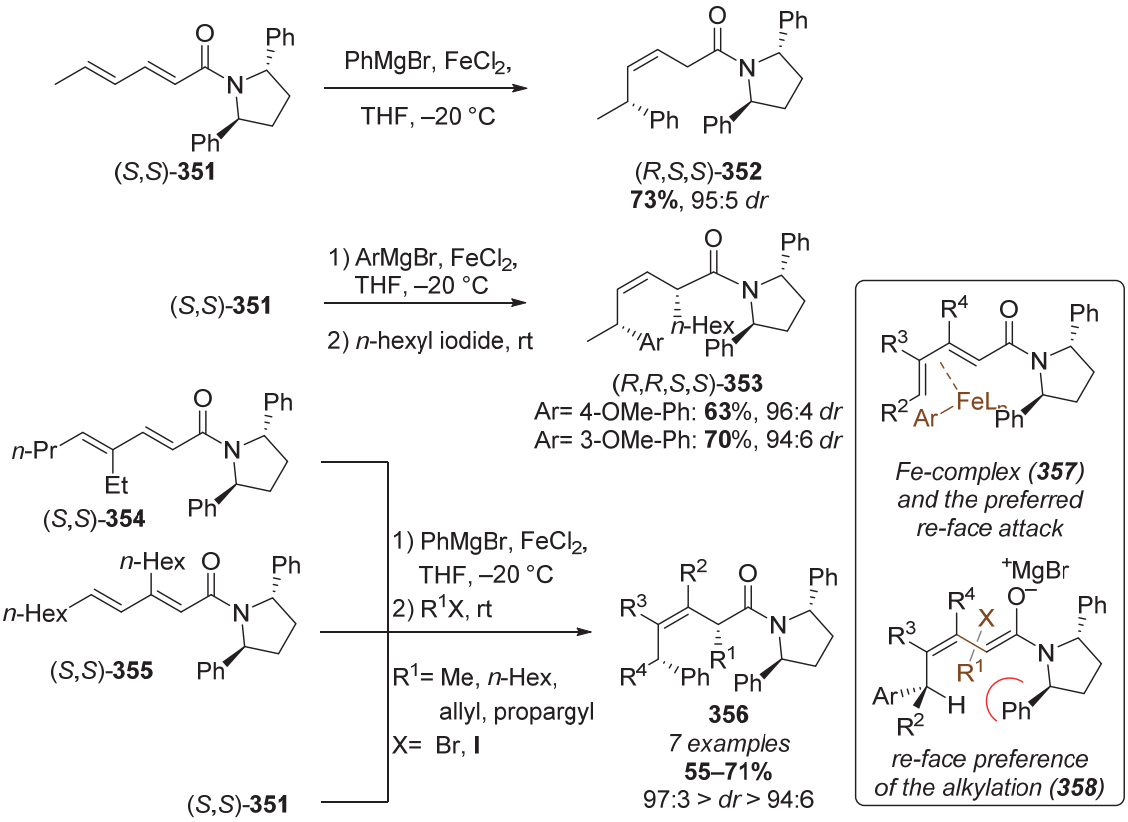
The only exceptions to the great diastereoselectivities were obtained with reactions between aryl nitrile oxides and methacrylamide (R^3= Me), which showed no diastereomeric preference. This was probably due to a lack of bias between s-*cis* and s-*trans* conformations of the acrylamide. The yields varied greatly: the lowest yields were observed when aliphatic nitrile oxides were reacting either with phenyl-substituted acrylamide or methacrylamide derivative, a sign of a sterical clash between the substituents R^1 and R^2/R^3.[164]

Finally, the removal of the auxiliary was demonstrated with a couple of examples. Hydrolysis with AcOH-HCl was successful, whereas reductive cleavage attempts were fruitless.[164]

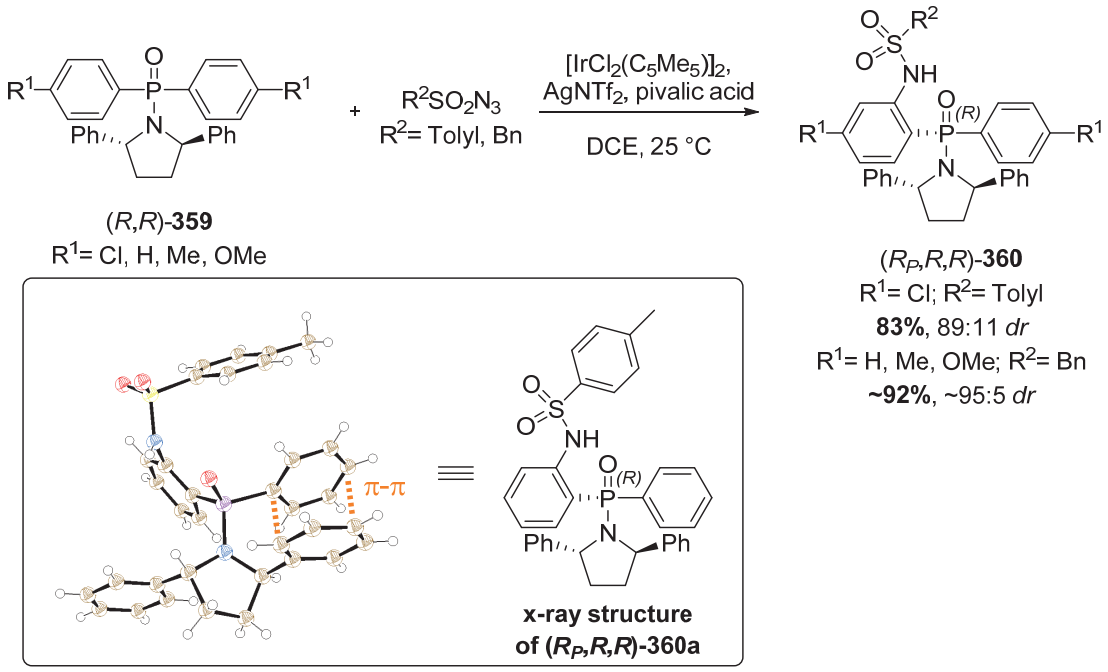
In 2008, Urabe and co-workers developed an asymmetric $FeCl_2$-catalysed 1,6-conjugate addition reaction between chiral α,β,γ,δ-unsaturated (*S*,*S*)-amides (**351**, **354**, **355**) and aryl Grignards (Scheme 53).[165] The utility of the method was mainly demonstrated with PhMgBr, but two examples with 4-OMe-PhMgBr and 3-OMe-PhMgBr were also given. When quenched with acid, the reaction provided the addition product (*R*,*S*,*S*)-**352** in good 73% yield and with a 95:5 *dr*. Quenching the reactions with alkyl halides expanded the scope to α-alkylated compounds, furnishing the final products **353** and **356** with excellent *dr*'s and ~70% yields at best. No attempts to remove the pyrrolidine auxiliary were reported.

The regioselectivity of the 1,6-addition was hypothesised to rise from the formed s-*cis*–Fe-complex **357**, which forced the reaction to occur at the δ-carbon (Scheme 53).[165] This also induced the final geometry of the product's olefin to (*Z*)-configuration. The attack from the *re*-face was justified based on the sterical shielding that the auxiliary's phenyls effected on the *si*-side. It also controlled the stereochemistry of the α-alkylations (**358**).

The latest synthesis method described in the literature so far, where 2,5-diarylpyrrolidine was used as a chiral auxiliary, dates back to 2014 (Scheme 54).[166] This publication was released by Chang and co-workers, who described a way to access chiral arylphosphorus compounds (*R*,*R*,*R*)-**359** with a *P*-stereogenic center *via* diastereoselective iridium-catalysed amidation.



Scheme 53: Iron-catalysed 1,6-conjugate addition reaction, developed by Urabe and co-workers.[165]



Scheme 54: Diastereoselective iridium-catalysed amidation of arylphosphoryl compounds (*R*,*R*)-**359**, developed by Chang *et al.*[166] X-ray structure of (*R*$_P$,*R*,*R*)-**360a** (CSD-KUCKIE).[167]

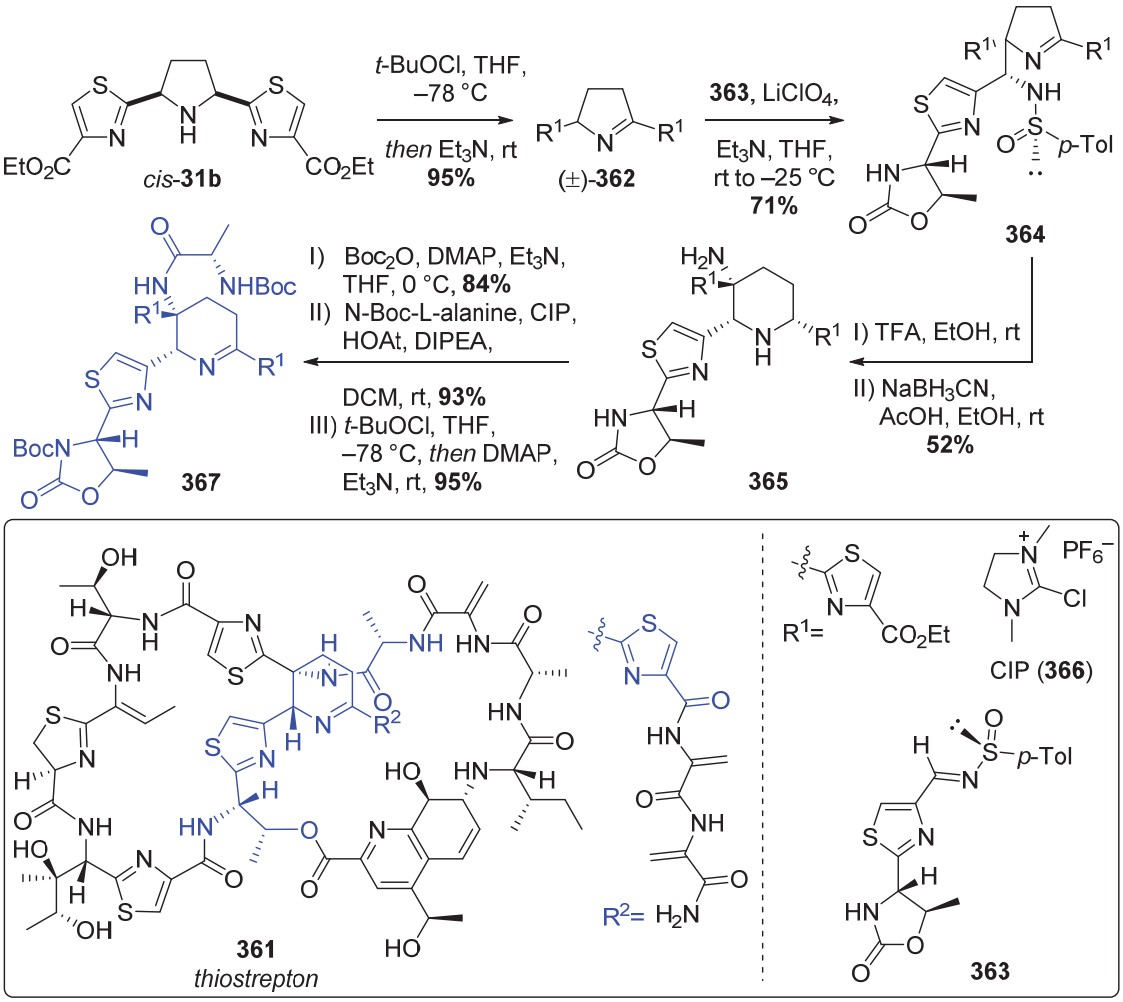
The utility of the method was demonstrated with reactions between phosphinic amides (*R*,*R*)-**359** and sulfonyl azides (Scheme 54).[166] The amidated products (R_P,*R*,*R*)-**360** were synthesised with excellent *dr*'s and high yields when tosylazide (R^2= tolyl) was used. However, when the amine source was changed to benzylsulfonyl azide, both the yields and diastereoselectivities got even higher. Even though the substrate scope was limited, the authors noted that the substituent of the azide had a bigger influence on the overall performance of the reaction than the electronic nature of the phosphine aryl substituents.[166]

The origin of the diastereoselectivity was hypothesised to stem from π-π-interactions between the auxiliary's phenyl rings and the unamidated P-aryl ring, supported by a DFT study and an x-ray structure of (R_P,*R*,*R*)-**360a** (Scheme 54). The π-π-interactions induced pseudo-chirality to the P-atom, which affected to the direction of the phosphine oxide in the C–H activation step. In addition, the unamidated aryl was closer to the auxiliary's phenyl than the amidated aryl, making the latter occupy a sterically less-hindered environment. No attempts to remove the auxiliary were reported.[166]

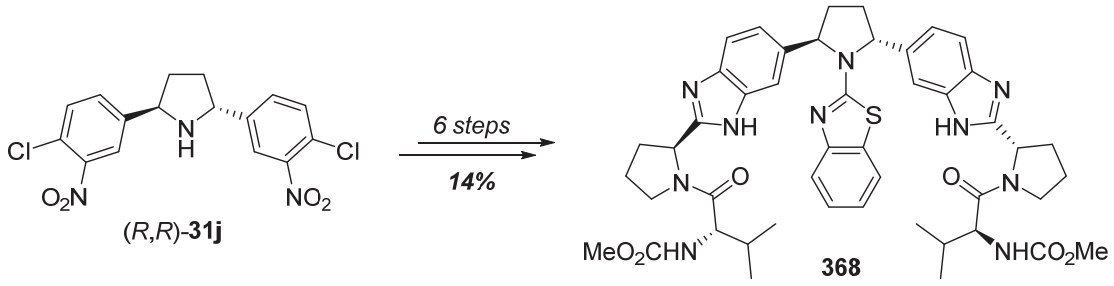
2.2.3 Use in the synthesis of biologically active molecules

The sole example found from the literature, where 2,5-diarylpyrrolidine was used as a part of a natural product total synthesis route, was published by Hashimoto and co-workers in 2002 (Scheme 55).[43] They used thiazole-substituted pyrrolidine *cis*-**31b** in an enantioselective synthesis of the pentasubstituted dehydropiperidine moiety **367**, which connects the two macrocycles of a thiostrepton antibiotic **361**.

The convergent route began with an oxidation of *cis*-**31b** to the corresponding imine (±)-**362** in a 95% yield.[43] It was followed by a diastereoselective 1,3-dipolar addition reaction with a chiral sulfinimine **363**, synthesised in four steps from L-threonine.[168] The addition product **364** was desulfinylated under acidic conditions, which also created an equilibrium situation between a five-membered dihydropyrrole and six-membered tetrahydropyridine imines. The mixture was reduced with $NaBH_3CN$, which gave the desired piperidine **365** in a 52% yield. To finish the route, the oxazilidinone nitrogen of **365** was selectively Boc-protected, which was followed by a coupling of Boc-protected L-alanine. Finally, the piperidine ring was oxidised to dehydropiperidine **367** in a 95% yield.



Scheme 55: Convergent enantioselective synthesis route to a pentasubstituted dehydropiperidine moiety **367**, developed by Hashimoto and co-workers.[43]



Scheme 56: Synthesis of a drug candidate **368** against Hepatitis C virus, patented by AbbVie.[60]

The last example of the use of 2,5-diarylpyrrolidines in asymmetric synthesis was disclosed by the researchers of an American pharmaceutical company, AbbVie. They patented a synthesis route for potential anti-viral compounds, which could act as Hepatitis C virus replication inhibitors.[60] One of the candidates, pyrrolidine **368**, was synthesised from 2,5-diarylpyrrolidine (*R*,*R*)-**31j** in six steps (Scheme 56). The synthesis route included two Pd-catalysed Buch-

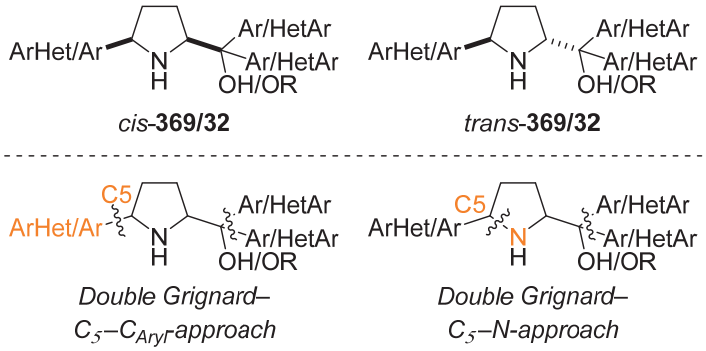
wald-Hartwig cross coupling reactions and a reduction of the nitro-group to amine. Cyclisation of an amide to benzoimidazole, Boc-deprotection, and amide coupling of a valine derivative gave the drug candidate in a 14% yield over six steps. The compound was tested against HCV replication and was found to have a sub-nanomolar EC_{50}-value.

2.3 Summary of the asymmetric syntheses

2,5-diarylpyrrolidines are versatile compounds, both as chiral auxiliaries and asymmetric catalysts. Their synthetic utility was quickly realised after the first enantioselective synthesis routes for them were developed. Since then, they have mostly been used as auxiliaries in conjugate additions, cycloadditions and rearrangement reactions. After the "organocatalysis boom" started in the early 2000s, the potential of 2,5-diarylpyrrolidines in this field was noticed. The applications have been enamine- and iminium-ion-catalysed transformations, which have enabled asymmetric (conjugate)addition and α-halogenation reactions.

The largest use of the pyrrolidines of interest, though, has been in the realm of transition metal catalysis. A suitable pyrrolidine has been a part of a large ligand, which has dominantly been of a phosphoramidite type. These type of ligands have been used in various reactions, such as reductions, alkylations, and different kinds of additions. The use of 2,5-diarylpyrrolidines in the synthesis of biologically active molecules has not been popular thus far.

3 PYROGLUTAMIC-ACID-DERIVED 2-DIARYLMETHYL-5-ARYL-PYRROLIDINES



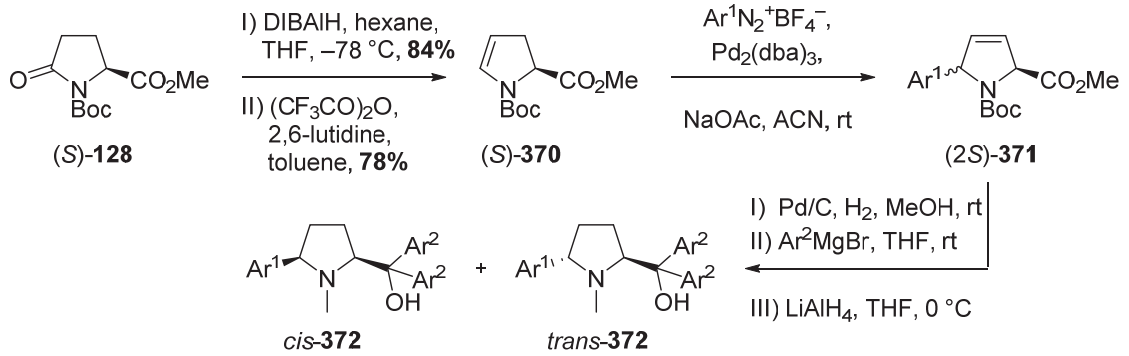
Scheme 57: Structure search in Reaxys.

2-diarylmethyl-5-aryl-pyrrolidines, which are also known as pyroglutamic-acid-derived pyrrolidines, are novel secondary amines. They can be seen as bulkier versions of Hayashi–Jørgensen-type pyrrolidines due to the added aryl group in C5. As in the case of 2,5-diarylpyrrolidines, we made the Reaxys searches with several different structures, including aryl, heteroaryl and their mixed variants (**32** and **369**). As these types of pyrrolidines are still quite novel, the number of related publications also stayed rather low. Actually, heteroaryl-containing structures did not provide any hits, as can be seen from the upcoming review part. This fact also reflects the number of strategies. There are only two types of approaches, and a double Grignard reaction is the common feature between them. The differentiating characteristic has been the C5-aryl incorporation, C_5–C_{Aryl}- and C_5–N disconnections being the used approaches. We included both the *cis*- and *trans*-diastereomer synthesis routes to give a more comprehensive picture.

3.1 The synthesis routes

Correia and co-workers developed the first synthesis route for pyroglutamic-acid-derived 2-diarylmethyl-5-aryl-pyrrolidines in 2010.[169] The route made use of a C_5–C_{Aryl} disconnection approach, and it started with a reduction of a protected L-pyroglutamic acid ((*S*)-**128**) to the corresponding hemiaminal (Scheme 58). This was transformed to enecarbamate (*S*)-**370** in very good yield over two steps.[170] (*S*)-**370** was then substituted with different aryl diazonium tetrafluoroborates using Heck–Matsuda coupling.[171] The reactions gave dihydropyrroles (2*S*)-**371** in excellent 90% yield at best. Unfortunately, only 4-OMe-derivative (2*S*)-**371b** was obtained with a good diastereoselectivity (85:15 *dr*) in favour of the *trans*-isomer, whereas the other dihydropyrroles ((2*S*)-**371a,c,d**) were achieved practically without any selectivity (Table 6).

The dihydropyrroles **371** were then hydrogenated, followed by a double Grignard reaction to the ester with PhMgBr or 2-Me-PhMgBr (Scheme 58). Unfortunately, the Boc-protected aminoalcohol diastereomers were not separable chromatographically. The separation was possible after the reduction of the Boc-groups to methyl with $LiAlH_4$, giving the chiral pyrrolidines **372** in very good yields over three steps.[169]

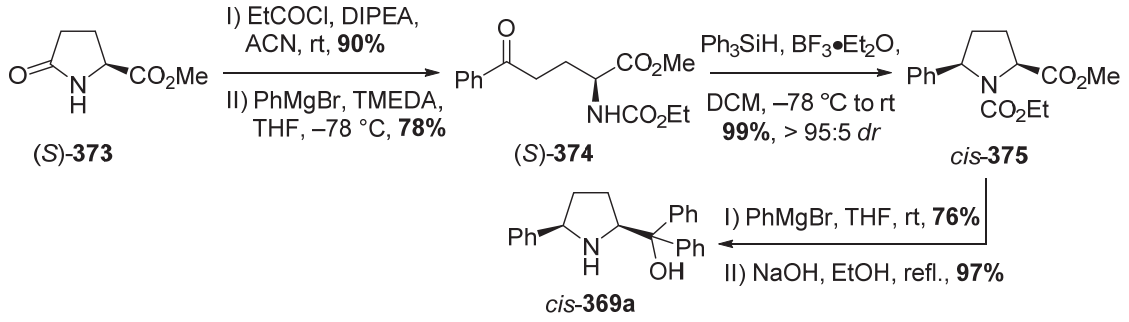


Scheme 58: Synthesis route for pyrrolidines **372** by Correia and co-workers.[169]

Table 6: Yields for the arylations to dihydropyrroles **371** and transformations of them to pyrrolidines **372**, by Correia and co-workers.[169]

Entry	Ar^1	(2*S*)-371 yield (%)	*dr*[a]	Ar^2	*cis*-372 yield (%)	*trans*-372 yield (%)
1	Ph	**a**: 85	45:55	Ph	**a**: 33	**a**: 27
2	Ph			2-Me-Ph	**b**: 22	**b**: 18
3	4-OMe-Ph	**b**: 90	85:15	Ph	**c**: 9	**c**: 49
4	4-F-Ph	**c**: 82	44:56	Ph	**d**: 26	**d**: 21
5	2-naphthyl	**d**: 70	42:58	Ph	**e**: 32	**e**: 23

a) *dr* corresponds to the *trans*:*cis* ratio of compounds **371**.



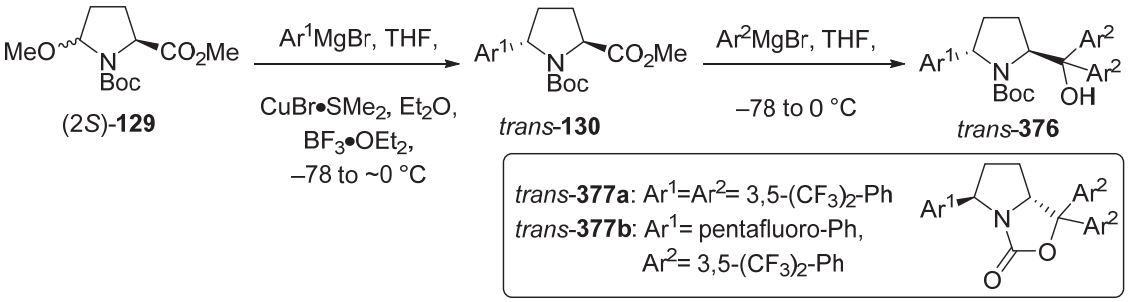
Scheme 59: Synthesis route to pyroglutamic-acid-derived *cis*-pyrrolidine **369a**, by Trost and Miege.[172]

In 2014, Trost and Miege developed another synthesis route for pyroglutamic-acid-derived pyrrolidine *cis*-**369a**, solving the diastereoselectivity issue present in Correia's route.[169,172] They started the synthesis by making a carbamate from a chiral pool molecule L-pyroglutamic acid methyl ester ((*S*)-**373**),[173] which was reacted with PhMgBr in the presence of TMEDA to provide acyclic amino acid derivative (*S*)-**374** (Scheme 59). This was cyclised back to make an iminium ion, which was reduced with a bulky silane to pyrrolidine *cis*-**375** with excellent 99% yield and diastereoselectivity (>95:5 *dr*). The second Grignard reaction with PhMgBr, followed by a carbamate deprotection, provided the desired *cis*-**369a** in very good yield.

In the same publication, Trost and Miege presented a synthesis route to pyroglutamic-acid-derived *trans*-pyrrolidines **369**, later used by Pihko and co-workers.[37,57,172] The route began with an addition reaction between different aryl cuprates and an iminium ion, formed from hemiaminal ether (2*S*)-**129** (see the synthesis in subsection 2.1.4, Scheme 17). The transformation provided *trans*-2,5-substituted pyrrolidines **130** exclusively (Table 7). The reaction worked with a range of different aryls: it tolerated bulky naphthyls as well as aryls with strongly electron-withdrawing and -donating groups. Only a few of the arylated pyrrolidines **130** were obtained in poor yields (Table 7, entries 7, 10, 13).

The cuprate addition was followed by a double Grignard reaction to the methyl ester carbonyl (Table 7). Again, a range of aryls with varying electronical properties were suitable, and pyrrolidines *trans*-**376** were synthesised mostly in very good yields. Interestingly, pyrrolidines *trans*-**376i** and *trans*-**376j**, with strongly electron-withdrawing aryls on both side of the pyrrolidine, favoured the formation of carbamates *trans*-**377a** and *trans*-**377b** (see also Section 4.4).[37,57,172]

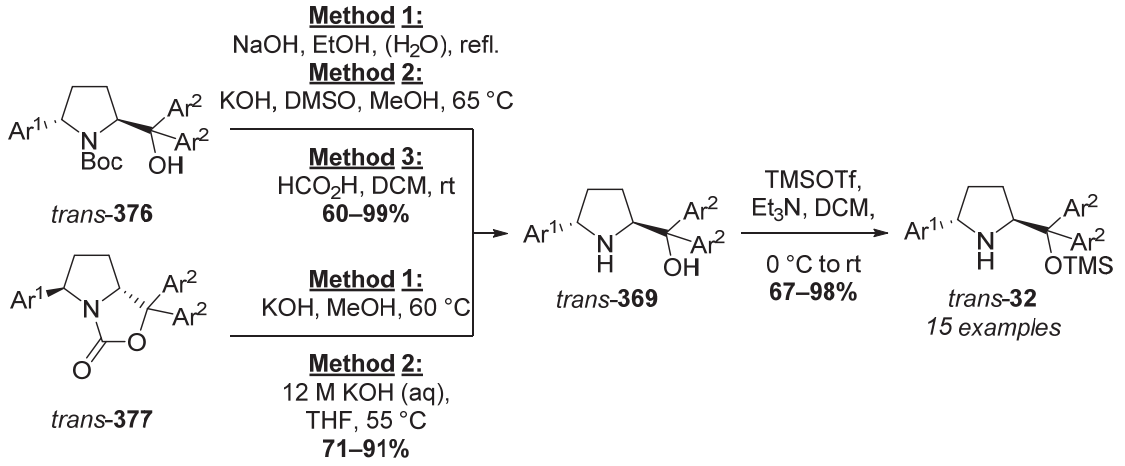
Table 7: Synthesis of Boc-protected 2,5-substituted pyrrolidines *trans*-**376** from hemiaminal ether **129**.



Entry	Ar^1	Yield (%)[a]	Ar^2	Yield (%)[b]	Ref
1	Ph	**a:** 99	Ph	**a:** 92	172
2	Ph		3,5-$(CF_3)_2$-Ph	**b:** 55	37
3	Ph		3,5-Me_2-Ph	**c:** 87	37
4	Ph		4-OMe-Ph	**d:** 86	37
5	1-naphthyl	**b:** 90	Ph	**e:** 94	172
6	2-naphthyl	**c:** 61	Ph	**f:** 41	172
7	4-Ph-Ph	**d:** 20	Ph	**g:** 95	172
8	3,5-$(CF_3)_2$-Ph	**e:** 73 (79[c])	Ph	**h:** 64	37,57
9	3,5-$(CF_3)_2$-Ph		3,5-$(CF_3)_2$-Ph	**i:** 11 (49)[d]	57
10	pentafluoro-Ph	**f:** 40[e]	3,5-$(CF_3)_2$-Ph	**j:** 26 (39)[f]	57
11	3,5-Me_2-Ph	**g:** 89	Ph	**k:** 80	37
12	4-OMe-3,5-*t*-Bu_2-Ph	**h:** 58	Ph	**l:** 83	37
13	4-OMe-Ph	**i:** 43	Ph	**m:** 73	37
14	4-OMe-3,5-Me_2-Ph	**j:** ~99	Ph	**n:** 75	37
15	4-OMe-3,5-Me_2-Ph		4-OMe-Ph	**o:** ~89	37

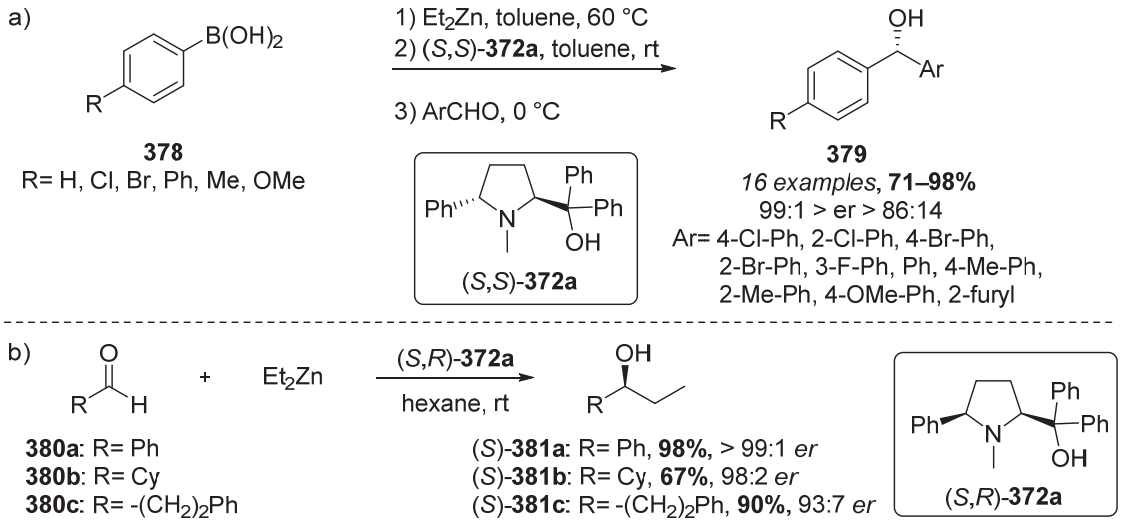
a) Yield of pyrrolidines *trans*-**130**. b) Yield of pyrrolidines *trans*-**376**. c) Yield of (*R*,*R*)-**130e**. d) Yield of (*R*,*R*)-**377a** in parentheses. e) Yield of (*R*,*R*)-**130f**. f) Yield of (*R*,*R*)-**377a** in parentheses.

Pyrrolidines *trans*-**376** and *trans*-**377** were then deprotected under various conditions, which provided amino alcohols *trans*-**369** in good to excellent yields (Scheme 60). A final silylation of the free hydroxyl group with TMSOTf created pyrrolidines *trans*-**32** with yields ranging from 67% to 98%.[37,57,172]



Scheme 60: Deprotection of pyrrolidines *trans*-**376** and *trans*-**377** to amino alcohols *trans*-**369**, which could be silylated to pyrrolidines *trans*-**32**.[37,57,172] See Table 7 for the list of Ar^1 and Ar^2.

3.2 Use in asymmetric synthesis

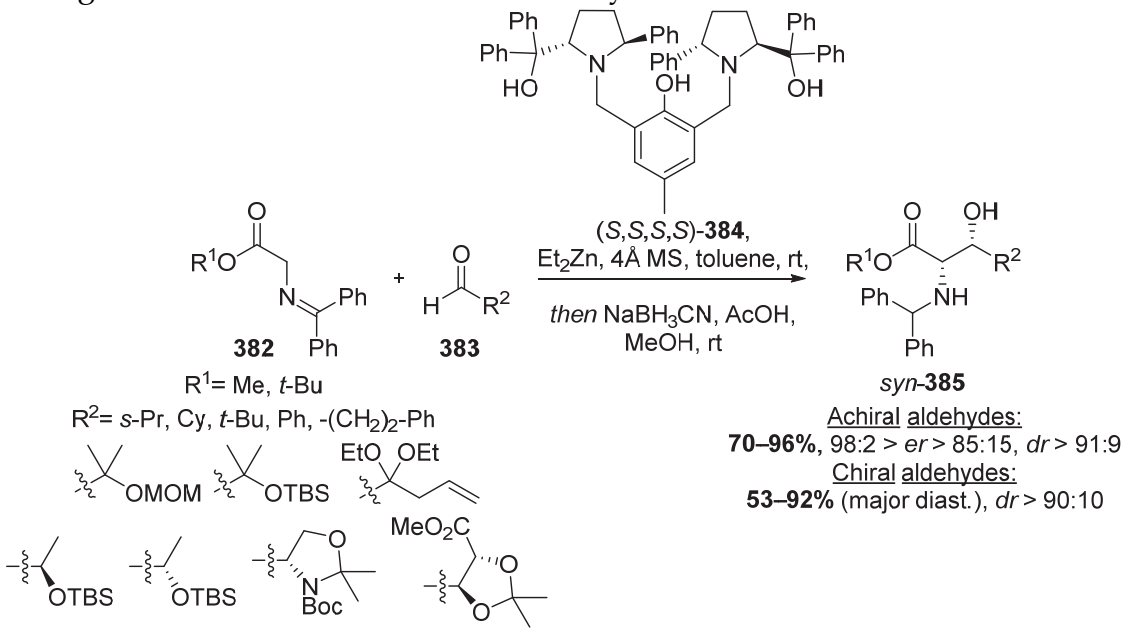


Scheme 61: a) Asymmetric arylation method of aldehydes, developed by Correia and co-workers.[169] b) Asymmetric ethyl addition to aldehydes developed by Breuning and co-workers.[174]

Correia and co-workers made use of their synthesised pyrrolidines in an asymmetric aldehyde arylation method, which was catalysed by a chiral *N*-methyl pyrrolidine (*S*,*S*)-**372a**.[169] They used aryl-zinc compounds as nucleophiles, which formed in an exchange reaction between Et_2Zn and boronic acids **378** (Scheme 61a). The reaction worked with *para*-substituted aryl boronic acids with both electron-withdrawing and -donating substituents. In the case of aryl aldehydes, both electron-poor and -rich aryls were suitable. The yields of the obtained chiral secondary alcohols **379** were excellent (98%) at best, which also

held true for the *er*'s. A probable coordination of the aldehyde to a zinc complex, which formed between the catalyst and the zinc species, enabled the arylation to proceed in an asymmetric manner.[175]

Later, Breuning and co-workers used the *cis*-diastereomer (*S*,*R*)-**372a** in an asymmetric ethyl addition to aldehydes, a reaction also known as the Soai reaction.[174,176] The utility of the reaction was tested with benzaldehyde (**380a**), cyclohexanecarboxaldehyde (**380b**) and hydrocinnamaldehyde (**380c**) as the substrates (Scheme 61b). With a limited substrate scope, the method was deemed highly enantioselective. The yields of the alcohols (*S*)-**381a** and (*S*)-**381c** were very high, (*S*)-**381b** being an exception. As with Correia's example, the authors hypothesised that a chiral catalyst–zinc chelate steered the enantioselectivity of the reaction by complexing the aldehyde and Et_2Zn to the catalyst and thus directing the attack on the *si*-face of the aldehyde.

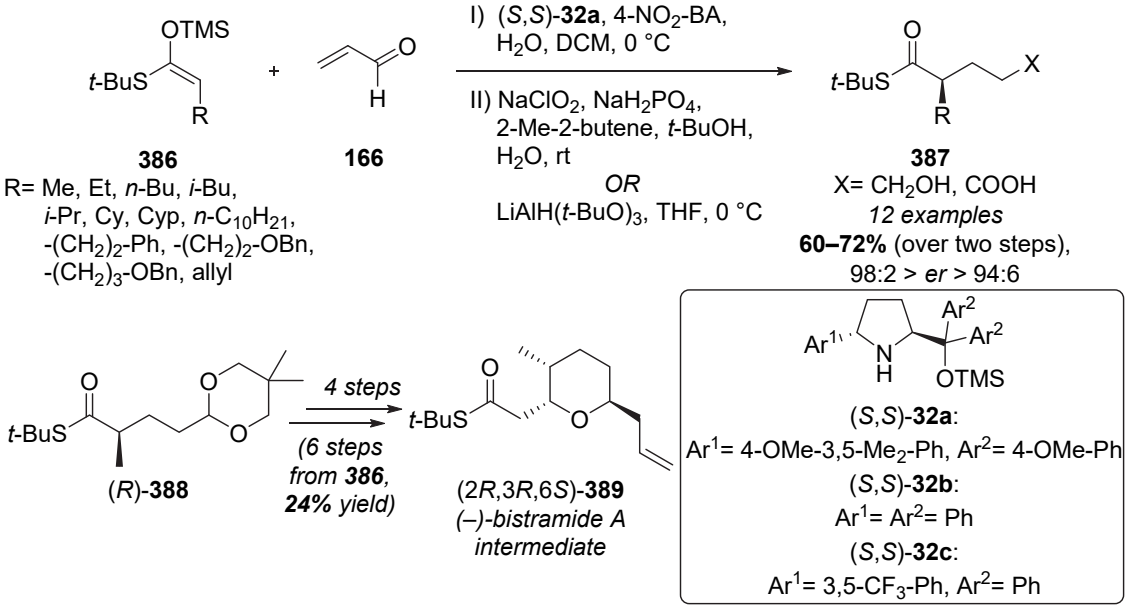


Scheme 62: Asymmetric aldol reaction between glycine-derived imines and aldehydes, developed by Trost and Miege.[172]

In 2014, Trost and Miege disclosed an asymmetric aldol reaction between glycine-derived imines **382** and aldehydes **383**, which provided chiral β-hydroxy-α-amino esters **385**.[172] The reaction was catalysed by an organometallic complex that formed between zinc cations and the ProPhenol catalyst (*S*,*S*,*S*,*S*)-**384** (Scheme 62). The authors hypothesised that this dinuclear zinc complex further coordinated with the glycine derivatives **382**, forming the corresponding (*Z*)-enolates, which then attacked on the *si*-faces of the aldehydes **383**. After the completion of the reaction, the imines were reduced in the same pot, producing *syn*-1,2-aminoalcohols **385**.

With achiral aldehyde substrates, both the yields and stereoselectivities of the aldol products **385** ranged from 70% to 96%. With chiral aldehyde substrates, the yields were 53–92% and the diastereomeric ratios were better than 90:10. It was noteworthy that only minimal mismatch effect was seen with aldehydes

bearing an (*S*)-α-stereocenter. The authors also screened several ProPhenol catalyst variants, where the C5-Ph of the pyrrolidine part was a bulky naphthyl or biphenyl substituent. However, (*S*,*S*,*S*,*S*)-**384** proved to be the ideal one in terms of stereoselectivity and yield. It also outperformed its *cis*-diastereomer, as well as less bulky Hayashi–Jørgensen-type catalysts.[172]



Scheme 63: Indirect asymmetric α-alkylation of thioesters **387**, developed by Pihko and co-workers.[37]

The last example of the asymmetric synthesis methodologies was published by Pihko and co-workers in 2016; they developed an indirect way to α-alkylate thioesters enantioselectively with a Mukaiyama–Michael reaction.[37] The transformation was conducted between α-substituted enolsilanes **386** and an iminium ion, formed from acrolein (**166**) and a secondary amine (Scheme 63). After persevering catalyst development and screening research, (*S*,*S*)-**32a** with electron-rich aryl groups proved to be the best amine for the studied reaction. The transformation tolerated a wide range of straight chain alkyls, cycloalkyls and alkylbenzylethers in the α-position, giving thioesters **387** in very good 60–72% yields and with excellent *er*'s. The utility of the method was further demonstrated in the synthesis of tetrahydropyran (2*R*,3*R*,6*S*)-**389**, an intermediate available in four steps from a suitable enolsilane **386** and usable in the total synthesis of a natural product (–)-bistramide A.[177]

Extensive DFT studies were conducted by Pápai's group to find explanations for the stereoselectivity. They found out that, in the lowest energy transition state, non-covalent attractive interactions between the enolsilane and iminium ion were readily present, whereas repulsive steric interactions were found in the other diastereomeric transition state, leading to the opposite enantiomer. The calculated transition state energy differences, however, were not in full unison with the experimental results. Based on computations, catalysts (*S*,*S*)-**32b** and (*S*,*S*)-**32c** should have outperformed (*S*,*S*)-**32a** in terms of enantioselectivity since the energy differences between the diastereomeric transitions states

were found to be larger with the former ones compared to the latter one. The fundamental reason explaining the effect of the electron-rich aryls on the enantioselectivity thus remained a mystery.[37]

3.3 Summary of the synthesis routes and uses in asymmetric synthesis

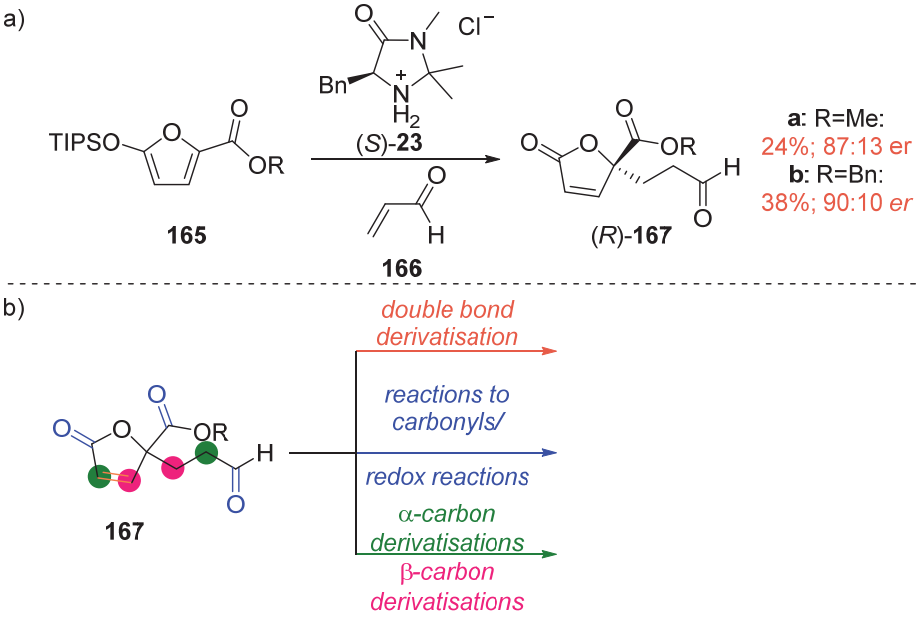
2-diarylmethyl-5-aryl-pyrrolidines are secondary amines that structurally resemble Hayashi–Jørgensen catalysts. Currently, the number of synthesis routes for these types of compounds is three. They all rely on the same chiral pool molecule (*S*)-pyroglutamic acid, hence the epithet pyroglutamic-acid-derived pyrrolidines. The routes make use of two strategies: a double Grignard reaction, combined with either a C_5–C_{Aryl} or C_5–N disconnection. The C_5–N approach has been used in selective *cis*-diastereomer synthesis, whereas the C_5–C_{Aryl} approach can be used in selective *trans*-diastereomer formation. In the case of *trans*-compounds, a cuprate addition to an *in situ* prepared iminium ion has been the most practical and selective choice over a Heck–Matsuda coupling between aryl diazonium tetrafluoroborates and enecarbamates. The key reactions in the selective *cis*-diastereomer formation have been a nucleophilic addition to a lactam, followed by the reduction of an *in situ* generated iminium ion.

The use of these pyrrolidines in asymmetric synthesis is still in its infancy since only four groups have published an asymmetric application for them. All of the methods are catalytic addition reactions, and as in the case of 2,5-diarylpyrrolidines, these pyrrolidines have also been used both as secondary amines and as tertiary amines. With the added steric and electronic properties, they could probably be used e.g. in reactions, which have been out of the reach of Hayashi–Jørgensen catalysts. Time will tell whether the scientific community finds a wider use for these pyrrolidines.

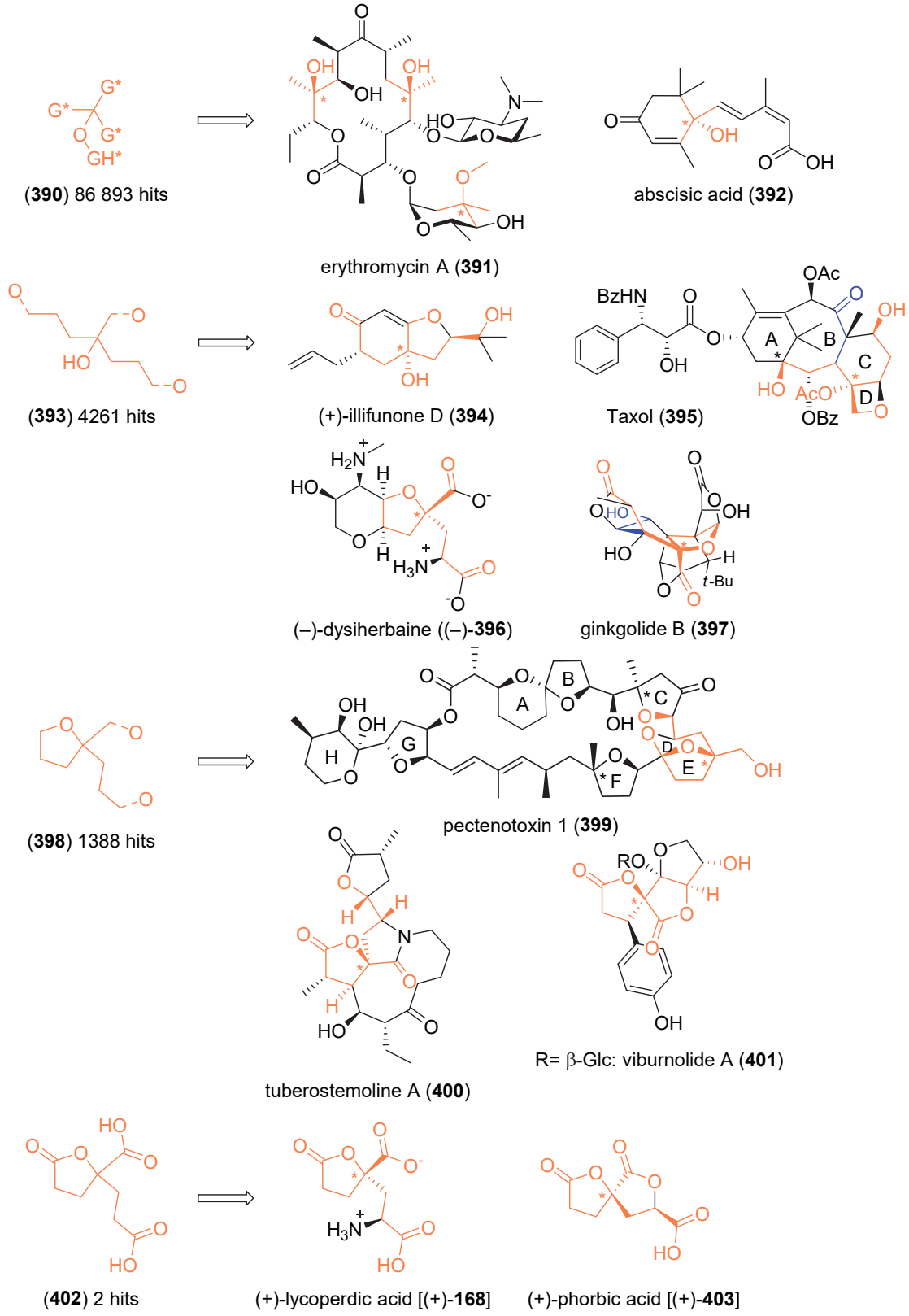
4 CATALYST AND METHOD DEVELOPMENT FOR A MUKAIYAMA-MICHAEL REACTION

4.1 Introduction

The literature examples in the previous chapters revealed our research group's interests toward organocatalytic enantioselective transformations, especially the Mukaiyama–Michael reactions between silyloxyfurans and enals.[36,56] After the development of these successful methods, we were again ready to challenge ourselves to widen our Mukaiyama–Michael reaction repertoire even further. We saw quickly from the literature that there was plenty of room for improvement in the construction of seemingly simple aldehydes **167** (Scheme 64). These were synthesised by Pansare and co-workers in 2010 with an iminium ion catalysed reaction between a suitable silyloxyfuran **165** and acrolein (**166**).[178]



Scheme 64: a) A Mukaiyama–Michael reaction, developed by the Pansare group.[178] b) Modularity of the core structure **167**.



Scheme 65: Natural product search with different core substructures. A tertiary oxygen-containing stereocenter is marked with an asterisk (*). The orange colour shows the match between the core and the natural product. The alternative core match is marked with blue. A dashed line between oxygen and carbon illustrates a freely varying oxidation state. G* and GH* represent Reaxys Generic Groups.

As can be seen, the aldehydes **167** consist of an oxygen-containing tertiary stereocenter (Scheme 64). They possess a modular core: a furanone ring and carbonyl groups one and three bonds away from the stereocenter, which make the derivatisation options of this core diverse and increase its synthetic utility. To our delight, quaternary-substituted oxygen-containing tertiary stereocenters are widely present in the structures of natural products and pharmaceuticals (Scheme 65). Developing a wide variety of synthetical tools that gives access to these types of compounds is thus reasonable and of great importance.

Substructure searches in Reaxys* with a general core **390** reveal that there are almost 87000 natural products, such as erythromycin[18] and abscisic acid,[179] which contain the above-mentioned stereocenter (Scheme 65). Adding three oxygen atoms, all present in the Mukaiyama–Michael product **167**, and letting the saturated carbon chain be acyclic (**393**), reduce the amount of hits to around 4000, but still leave some interesting molecules, such as (+)-illifunone D[180] and Taxol.[181]

Substructure searches with a cyclic core **398** cut down the number of suitable natural products to around 1400, revealing potential total synthesis targets **399–401** (Scheme 65).[106,182–186] Finally, the strictest substructure searches with a lactone core **402** reveal that this moiety is present only in two natural products: (+)-lycoperdic acid ((+)-**168**)[109] and (+)-phorbic acid ((+)-**403**).[187]

Before we chose any total synthesis target and started the route scouting studies, we wanted to enhance the conditions of the Mukaiyama–Michael reaction found by Pansare *et al.* (Scheme 64).[178] As they demonstrated in their publication, they managed to synthesise aldehydes (*R*)-**167a** and (*R*)-**167b** with good enantioselectivities, but rather poor yields. MacMillan's trimethyl imidazolidinone (*S*)-**23** was the optimum catalyst, based on brief iminium catalyst screening studies.

From the other precedents, we were aware that the MacMillan group had successfully made the first enantioselective Mukaiyama–Michael reactions between various silyloxyfurans and β-substituted acroleins (Scheme 66). One of them, a reaction between **165a** and crotonaldehyde ((*E*)-**405**), was quite close to the transformation of our interest. The reaction was catalysed by a triflate salt of imidazolidinone (*S*,*S*)-**404** and it gave the aldehyde (*R*,*R*)-**406** with excellent stereoselectivities and yield.[188]

It seemed that the difficulty of the reaction of interest was partly in its simplicity. Acrolein is a small electrophile and lacks even the smallest sterical bias, which, for example, crotonaldehyde gets from its β-Me-substituent. Fortunately, our group had studied iminium-catalysed Mukaiyama–Michael reactions with acrolein (Scheme 66, also subsubsection 2.2.1.1 and Section 3.2). The experience gathered from these projects with 2,5-diarylpyrrolidine catalysts (*trans*-**31**) and pyroglutamic-acid-derived pyrrolidines (*trans*-**32**), suggested that persevering and systematic optimisation of the catalyst could offer better results in the Mukayiama–Michael reaction of interest.[36,37,56]

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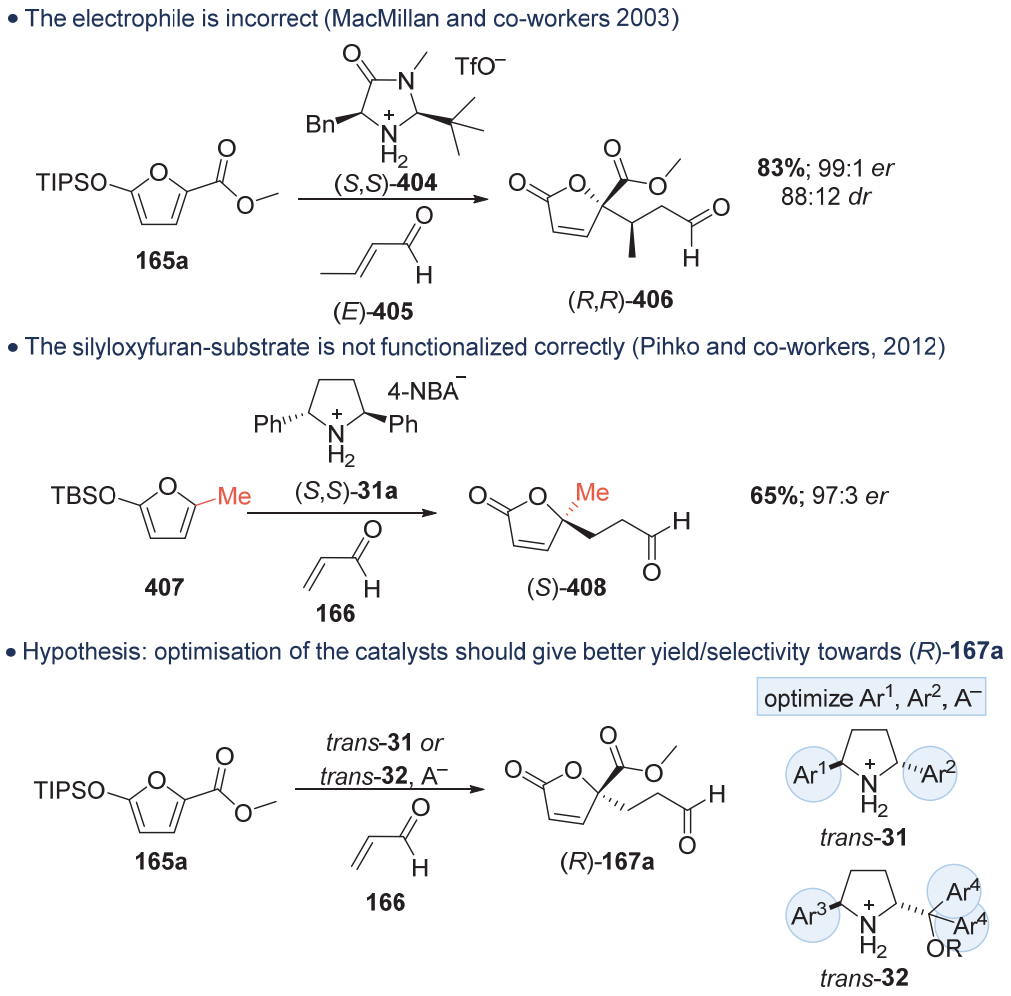
* The substructure searches were conducted in March–April 2020.



Scheme 66: The preceding relevant Mukaiyama–Michael reactions and our hypothesis.[36,188]

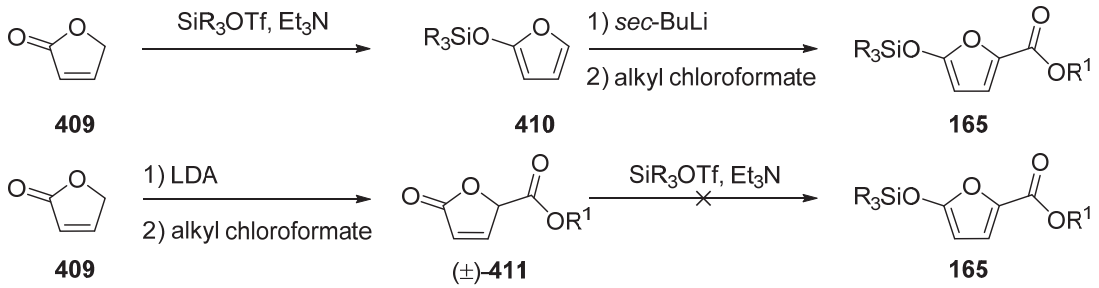
Contrary to the Pansare example, we wanted to develop a catalytic method where the bulkiness of the substrate had a minimum effect on the enantioselectivity. We wanted to avoid the use of any bulky ester groups, or even benzyl esters (Scheme 66). In addition, with this approach, we would avoid some conflicts with later operations along a chosen (total) synthesis route. For example, benzyl esters were deemed unsuitable, as they might require special precautions in the projected hydrogenation of the butenolide C=C bond. We thus selected the methyl ester **165a** as the starting point for the method development.

The synthesis of silyloxyfurans is known in the literature (Scheme 67). They can be made from a commercially available furanone **409*** in two steps by first silylating it with a suitable silyltriflate and then alkoxycarbonylating with an alkyl chloroformate after a lithiation. The order of the reactions is essential since the silylation of (±)-**411** is not possible.[189] Additionally, the furanone needs to be silylated with a TIPS group because the regioselectivity of the lithiation

* In addition, furanone **409** can be easily made from furfural by Näsman's hydrogen peroxide oxidation.[191]

and thus the methoxycarbonylation are known to be better with large silyl groups than with silyl groups smaller than TIPS.[56,189–191]

Acrolein used to be commercially available before the year 2018. However, at least within the European Union, regular chemical vendors, such as Merck (Sigma Aldrich), have not sold it anymore since 2018. Its dimethyl and diethyl acetals are still available, though. Luckily, we had ample supplies of acrolein in storage and, thus, were able to begin finding the conditions for the desired Mukaiyama–Michael reaction.



Scheme 67: The general synthesis of silyloxyfurans.[189,190]

4.2 The first Mukaiyama–Michael screening studies

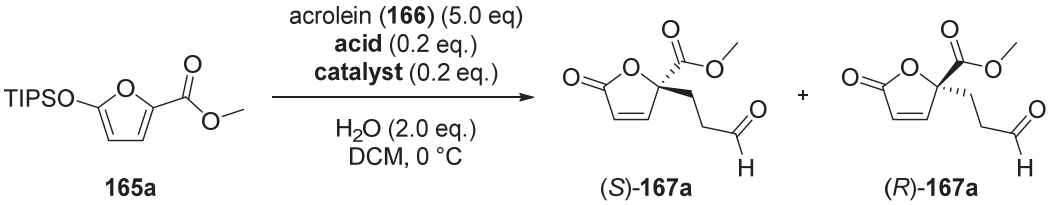
The initial Mukaiyama–Michael tests were conducted by the author in his master thesis project, and the related work was later continued in this dissertation. The early results were later used in the related publication by us, and for the sake of completeness, selected results from the early studies are presented here as well, along with a fresh analysis and discussion.[57,192]

We started the first reactivity studies with similar conditions that were used earlier by Pihko and co-workers, with an exception that the catalyst system was achiral, i.e. a salt of dibenzylamine and 4-nitrobenzoic acid.[36] Fortunately, we saw the disappearance of the starting material and new promising-looking doublets in the double bond region in the ^{1}H NMR of the samples taken from the reaction mixtures. The reaction was sluggish, though, and the starting material was still visible after 41 hours (Table 8, entry 1). Another reaction with a stronger counter acid, TFA, increased the rate of the reaction, and it was finished almost within 65 hours (Table 8, entry 2). Switching to even stronger acid, namely TfOH, did not enhance the performance of the reaction, making it very sluggish (Table 8, entry 3). Finally, we were able to isolate the aldehyde (±)-**167a** with a good, 59% yield, when we used TFA as the counter acid.

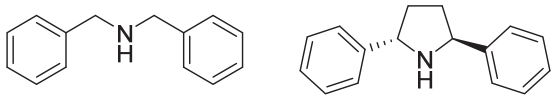
We then changed to the enantioselective conditions and chose (*S*,*S*)-2,5-diphenylpyrrolidine ((*S*,*S*)-**31a**) as the secondary amine. Again, we saw the same phenomenon as previously noted: triflic acid and 4-NBA as counter acids gave slower reactions than TFA (Table 8, entries 4–6). To our disappointment, these initial reactions were hardly enantioselective, the *er*'s being 62:38 at the best. Interestingly, the salt of (*S*,*S*)-**31a** and triflic acid gave a completely racemic mixture of **167a**, suggesting that the reaction was solely acid catalysed. The

change in the enantioselectivity was dramatic compared with the literature precedent,[36] which just showed that this secondary amine was not suitable for catalysing a reaction between acrolein and an electron-poor silyloxyfuran like **165a**. We were thus forced to start a screening of other iminium catalysts in a search for better enantioselectivity and reactivity.

Table 8: The first reactivity tests of the Mukaiyama–Michael reaction.



catalysts



412 (*S*,*S*)-**31a**

Entry	Catalyst	Acid	Time (h)	SM:product[a]	*er*[b]
1	**412**	4-NBA	41	59:41	–
2	**412**	TFA	65	8:92 (59%)[c]	–
3	**412**	TfOH	88	74:26	–
4	(*S*,*S*)-**31a**	4-NBA	92 (213)	31:69 (7:93)	53:47
5	(*S*,*S*)-**31a**	TFA	92 (213)	14:86 (0:100)	62:38
6	(*S*,*S*)-**31a**	TfOH	213	63:37	51:49

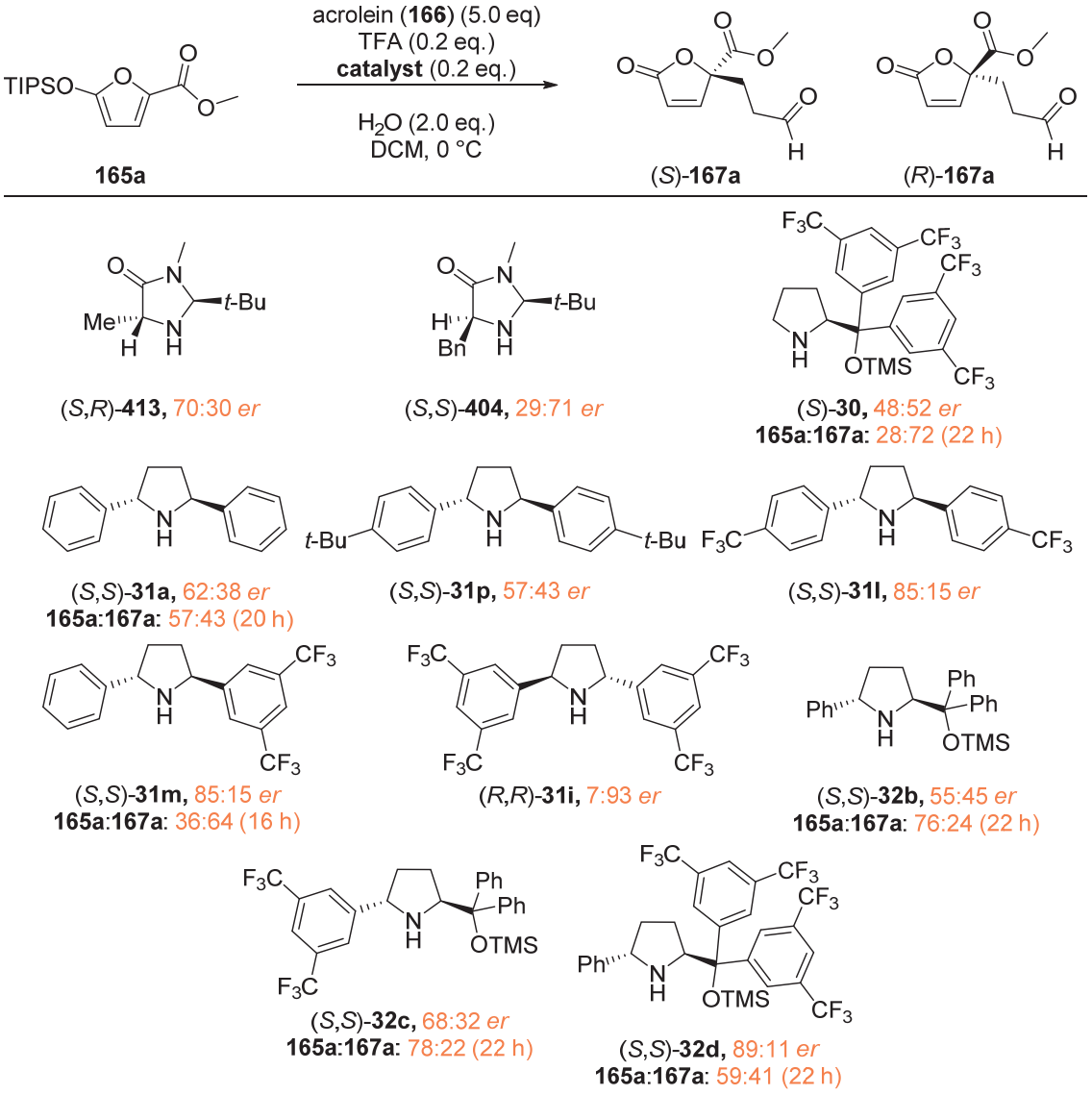
a) Determined from a reaction mixture ^{1}H NMR. b) *er* corresponds to a ratio [(*S*)-**167a**:(*R*)-**167a**] and was determined by chiral GC from the reaction mixture. c) Isolated yield after column chromatography.

We chose TFA as the counter acid in the following screens since it gave the most promising results thus far. From the "traditional" iminium catalysts, MacMillan's imidazolidinones (*S*,*R*)-**413** and (*S*,*S*)-**404** were only moderately enantioselective, whereas the Hayashi–Jørgensen catalyst (*S*)-**30** gave practically a racemic mixture of **167a** (Scheme 68)**.** From the 2,5-diarylpyrrolidine catalysts,[56] an electron-donating *para*-*t*-butyl-substituted catalyst (*S*,*S*)-**31p** lowered the *er* to 57:43 compared with (*S*,*S*)-**31a**, but electron-withdrawing *para*-CF_3 substitution pumped up the *er* to 85:15 ((*S*,*S*)-**31l**). The same *er* was achieved with unsymmetrical CF_3-catalyst (*S*,*S*)-**31m**. Increasing the number of CF_3-groups to four was beneficial for the enantioselectivity, giving the best *er* thus far (7:93, (*R*,*R*)-**31i**).[57,192]

Having access to novel pyroglutamic-acid-derived catalysts **32**, we also tested their performance in the reaction (Scheme 68).[37] The "undecorated" triple-phenyl catalyst (*S*,*S*)-**32b** gave almost a racemic mixture of **167a**, but again, the addition of electron-withdrawing CF_3 groups pumped up the enantioselectivity. Two *meta*-CF_3-groups on the left-side aryl group gave a 68:32 *er* ((*S*,*S*)-

32c), and four *meta*-CF_3 groups on the right side increased the *er* all the way to 89:11 ((*S*,*S*)-**32d**).[57,192]

We also noticed that the reactions catalysed by pyrrolidine (*S*,*S*)-**31m** and the Jørgensen–Hayashi catalyst (*S*)-**30** were progressing a lot faster than a reaction with (*S*,*S*)-**31a** (Scheme 68). A reaction with catalyst (*S*,*S*)-**32d** showed a similar rate to (*S*,*S*)-**31a**. From the pyroglutamic-acid-derived catalysts, (*S*,*S*)-**32d** gave the fastest reaction, whereas catalysts (*S*,*S*)-**32b** and (*S*,*S*)-**32c** offered the slowest ones. Even though we did not monitor the progress of reactions more thoroughly, these results were enough to reveal that electron-withdrawing CF_3 groups enhanced not only the enantioselectivity, but also the rate of the Mukaiyama–Michael reaction.

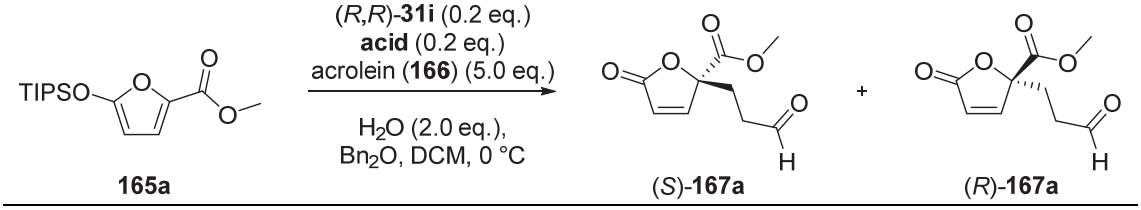


Scheme 68: Mukaiyama–Michael reaction catalyst screening studies. *er* corresponds to a ratio [(*S*)-**167a**:(*R*)-**167a**]. The ratio **165a**:**167a** was determined from the reaction mixture ^{1}H NMR spectra after the specified time.

We continued the screening studies with the best pyrrolidine catalyst (*R*,*R*)-**31i** by varying the counter acid. The tests revealed that TFA was the best one from

the studied acids **(**Table 9, entry 7). It outperformed weaker acids, such as several nitrobenzoic acids (Table 9, entries 1–3) and chlorinated acetic acids (Table 9, entries 4–6), when both conversion and enantioselectivity were considered. Also, stronger acids, HCl and triflic acid, were tested, but these did not give better results than TFA (Table 9, entries 8–9). Interestingly, triflic acid produced again a racemic mixture of **167a**, suggesting that this reaction was also solely acid catalysed. We speculate that the weaker acids were not strong enough to keep the amount of required iminium ion high, resulting in low conversions.[57,192,193]

Table 9: Screening of acids, and other optimisation experiments of the Mukaiyama–Michael reaction.



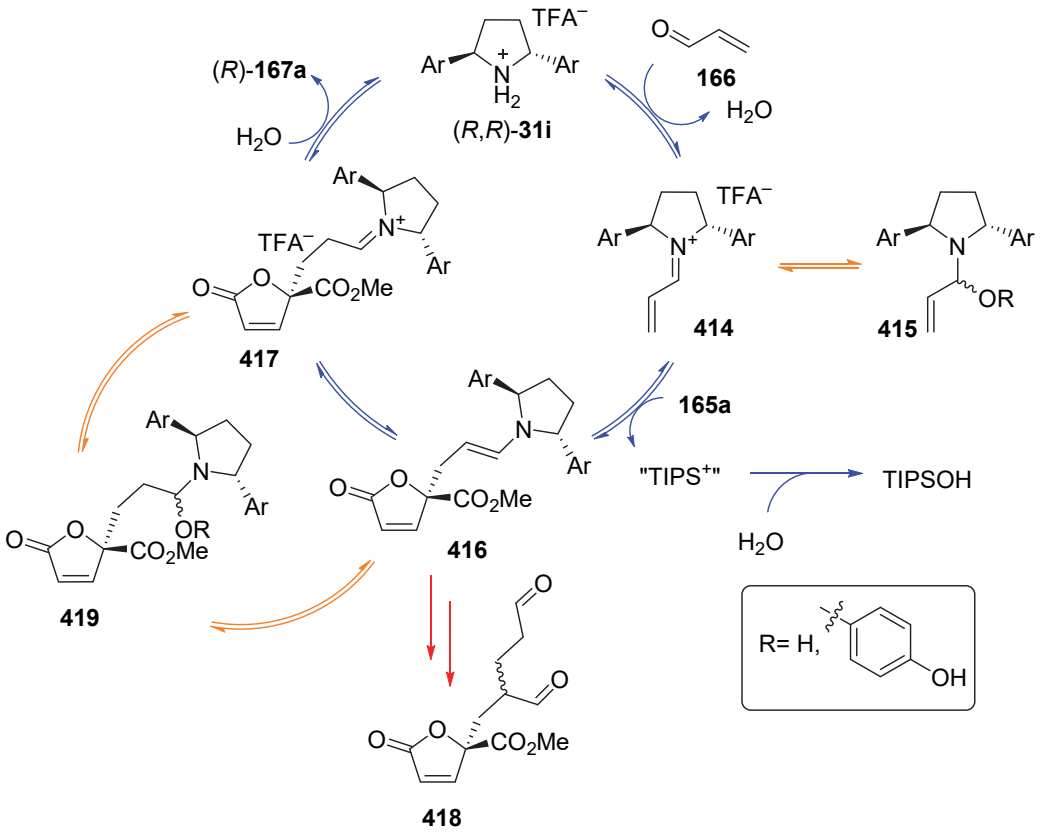
165a (*S*)-**167a** (*R*)-**167a**

Entry	Acid[a]	Time (h)	Conversion[b] (%)	*er*[c]	pK_a[d,194,195]
1	4-NO_2-BA	67	4	16:84	3.43
2	2-NO_2-BA	67	2	20:80	2.17
3	2,4-diNO_2-BA	67	36	7:93	1.43
4	MCA	67	14	9:91	2.87
5	DCA	46	43	7:93	1.35
6	TCA	24	48	8:92	0.66
7	TFA	23	54 (50)[e]	7:93	0.52
8	HCl	46	31	8:92	–8.0
9	TfOH	23	41	50:50	–14.0
10	TFA[f]	45	23	7:93	0.52
11	TFA[f, g]	45	17	5:95	0.52
12[h]	4-NO_2-BA	144	0	–	3.43

a) BA= benzoic acid, MCA= monochloroacetic acid, DCA= dichloroacetic acid, TCA= trichloroacetic acid. b) Conversion from starting material to product calculated by using Bn_2O as the internal standard. c) *er* corresponds to a ratio [(*S*)-**167a**:(*R*)-**167a**]. d) pK_a's in water. e) Isolated yield after chromatographic purification in a 0.3 mmol scale reaction in parentheses. f) Reaction at –30 °C. g) Without H_2O. h) The reaction was run without the catalyst (*R*,*R*)-**31i** and Bn_2O.

The differences in the reaction rates between pyrrolidine (*R*,*R*)-**31i** and the other catalysts were also notable, as the starting material was readily consumed within 23 hours, with TFA as the counter acid. The rate of the reaction increased to a good level, but the conversion was rather low (54%, Table 9, entry 7). We tested the reaction in a 0.3 mmol scale with the best conditions obtained thus far and were able to isolate the aldehyde (*R*)-**167a** in a 50% yield and with 93:7 *er*, which

reflected well on the test reaction results. We tried to isolate possible side products to get a grasp of the reasons behind the low yield, but did not succeed in this. At this point, we assumed that part of the material either polymerised or reacted further with acrolein at some point. For example, after the Mukaiyama–Michael addition step, the enamine **416** could react further[37] in another conjugate addition reaction to give **418**, if the hydrolysis of the iminium ion **417** to the product (*R*)-**167a** was slow enough (Scheme 69).[57,192]



Scheme 69: A proposed catalytic cycle of the Mukaiyama–Michael reaction. The on-cycle is coloured in blue. Possible off-cycles that slow down the progress of the reaction are marked in orange. The red arrow points to a possible side product **418**.

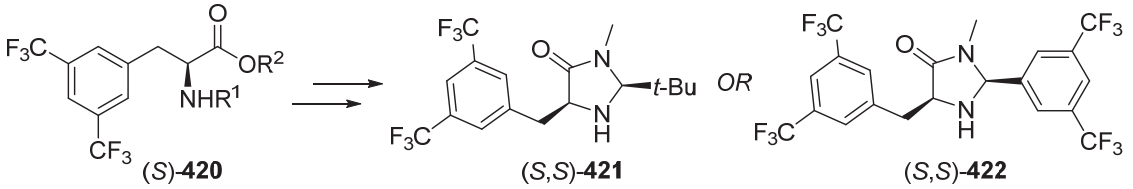
Further tests included the lowering of the temperature to –30 °C. Unfortunately, the change did not enhance the *er* and simply lowered the conversion (Table 9, entry 10). A slight positive change in the enantioselectivity was seen when water was excluded from the reaction, but, as when the water was present, the reaction was not of practical use due to the low conversion (Table 9, entry 11). The reason for the low conversions were not clear to us.[57,192]

We speculate that the hydrolysis of TIPS ether became slower at low temperatures in the conjugate addition step between **165a** and iminium ion **414** (or **415**)[196] (Scheme 69). In addition, it is possible that there were off-cycle intermediates, which slowed down the progress of the reaction and eventually jammed the catalytic cycle.[118] These hemiaminal intermediates **415** and **419** could form between the iminium ions **414**/**417** and either water or even hydroquinone,

which was present in acrolein as a stabiliser*. The stability of the enamine **417** at this temperature was also a question.[57,192]

We also ran a background reaction test without the catalyst (*R*,*R*)-**31i**, using 4-NO_2-benzoic acid (Table 9, entry 12). Even though we did not have any experimental data of the pK_{aH} value of (*R*,*R*)-**31i**–TFA salt, we were confident that it would be higher than that of 4-nitrobenzoic acid.[197] We did not see any product formation within 144 hours, which thus suggested that (*R*,*R*)-**31i**–TFA salt would not be able to catalyse the Mukaiyama–Michael reaction *via* acid catalysis.

The conditions obtained thus suggested that, in order to increase the enantioselectivity, we should synthesise more catalysts to understand the electronic requirements of the optimum catalyst. We selected the two promising leads, 2,5-diarylpyrrolidine and pyroglutamic-acid-derived pyrrolidine, as the core structures for our optimisation processes. Developing novel imidazolidinone catalysts was abandoned at this stage for two reasons. Firstly, our group has been strongly biased to the catalyst systems described earlier. Secondly, the imidazolidinone synthesis route would require amino acid-derived starting materials, which might not be commercially available. For example, enantiopure bis-CF_3-substituted phenylalanine (*S*)-**420** or relevant derivatives would have required additional steps in order to start the synthesis of the most interesting imidazolidinones (*S*,*S*)-**421** or (*S*,*S*)-**422** (Scheme 70).



Scheme 70: The amino acid-derived starting material (*S*)-**420** that would have been needed in the synthesis of novel imidazolidinone catalysts (*S*,*S*)-**421** or (*S*,*S*)-**422**.

4.3 2,5-Diarylpyrrolidine catalyst development

The early screenings suggested that the emphasis should be put on the catalysts with electron-withdrawing substituents. Thus, *para*–F-, –SO_2Me- and –NO_2-substituted catalysts were set as first goals (Figure 4). In addition to electronic properties, the current commercial availability and the price of the starting materials forced us to aim our synthesis attempts to only certain types of catalysts: at this point, we wanted to avoid additional steps and chose mono-*para*-substituted starting materials instead of di-*meta*-substituted ones. Apart from the above-mentioned criteria, the synthesis of a pentafluorophenyl and a *para*-OMe-substituted catalysts were also in our plannings, the latter to serve as proof for the argument that electron-donating substituents are inferior to enan-

* According to Merck's (Sigma Aldrich) certificate of analysis of acrolein, 0.25–0.35% of hydroquinone has been added as a stabiliser.

tioselectivity in the examined Mukaiyama–Michael reaction. In addition, the scaling up of catalyst (*R*,*R*)-**31i** to gram scale was studied.

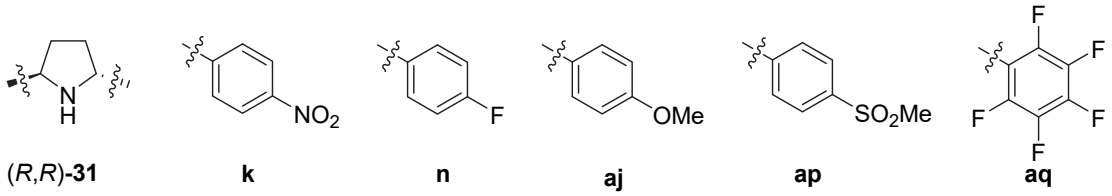
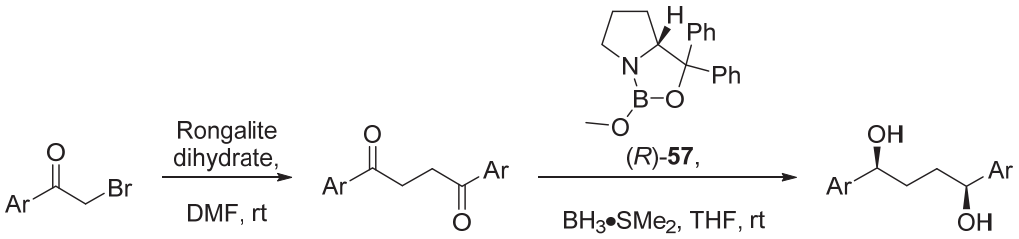


Figure 4: The novel 2,5-diarylpyrrolidine targets.

From the 2,5-diarylpyrrolidine synthesis routes presented in Chapter 2, we chose the one developed by the groups of Chong and Steel.[55,65] We started our efforts by synthesising the diketones using the method developed by Jarvis *et al*.[58] and managed to produce OMe-, NO_2- and SO_2Me-substituted diketones **34n, 34d** and **34o** in yields ranging from satisfactory to good (34%, 55% and 66%, respectively). To our delight, we obtained the F-substituted diketone **34g** in a very good, 88% yield (Table 10, entries 1–4).

In the case of diketone **34p**, we were forced to begin the synthesis "one step behind" with 2′,3′,4′,5′,6′-pentafluoroacetophenone due to the lack of a commercial source for the corresponding bromoethanone **423**. Despite trying the literature procedure several times[198], we faced severe problems both in the bromination and in the diketone formation steps, and we obtained only traces of the desired diketone compound. Spending too much time on optimisation of these reactions was not the primary goal of our plans, which, to our disappointment, meant that the synthesis of (*R*,*R*)-**31aq** had to be postponed.

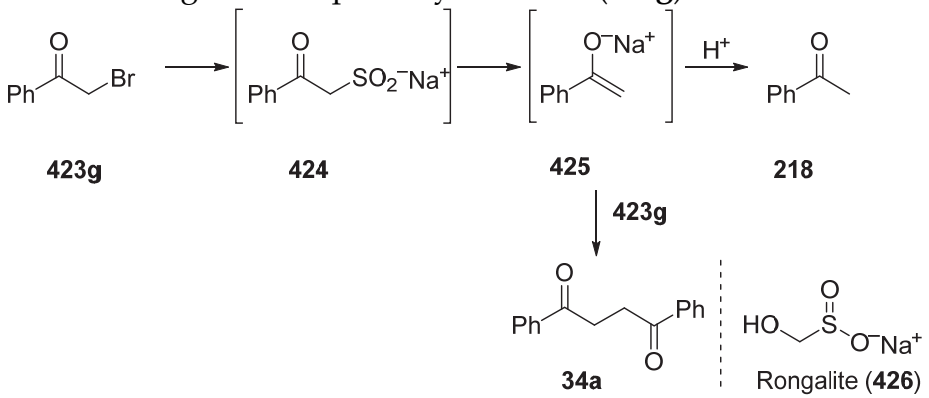
Table 10: The synthesis of diketones and diols.



Entry	Ar	Yield[a] (%)	Yield[b] (%)	*dr*[c]
1	4-NO_2-Ph	**d:** 55	**d:** 89	90:10
2	4-F-Ph	**g:** 88	**g:** 95[d]	95:5
3	4-OMe-Ph	**n:** 34	**n:** 90[d]	93:7
4	4-SO_2Me-Ph	**o:** 66	**o:** –	–
5	Pentafluoro-Ph	**p:** –[e]	**p:** –	-
6	3,5-$(CF_3)_2$-Ph	**b:** 37	**f:** 99	84:16

a) Yields of the diketones **34**. b) Yields of the diols **55**. c) *dr* estimated from the ^{13}C spectrum. d) (*R*,*R*)-enantiomer was synthesised. e) Synthesis attempted using the crude **34p**.

Jarvis *et al.* noticed that the major side product in their diketone synthesis was acetophenone (**218**), which was hypothesised to originate from the protonation of the enolate intermediate **425** (Scheme 71).[58] Thus, we tried to pump up the reported yield of **34b** (45%)[56] by adding molecular sieves to the reaction mixture to remove the most obvious proton source, water, present in Rongalite. To our disappointment, this did not give the desired improvement, the yield being 37% (Table 10, entry 6). This suggested that either the removal of water was not efficient enough or there was another proton source that could not be removed by molecular sieves, i.e. either the hydroxyl proton of Rongalite (**426**) or the α-proton of the starting material phenacyl bromide (**423g**).



Scheme 71: A proposed mechanism for the formation of diketone **34a** by Jarvis and co-workers and the acetophenone side product.[58]

We noticed that some of the diketones were crystalline, and, to our delight, we were able to characterise them by x-ray crystallography (Figure 5). From the solved structures, we saw that the packing caused the butane chains of diketones **34b** and **34g** to arrange in a classical zigzag way, whereas in NO_2-diketone **34d**, the skeleton was in a *gauche* arrangement. One could hypothesise that the *para*-NO_2 substituent made the carbonyl carbon extremely electron-poor, polarising the $C_{carbonyl}$-C_α-bond in such an extent that it favoured the *gauche* conformation over the *anti*-periplanar conformation. As interesting as it would have been, we did not try to crystallise **34d** from different solvents to see if we could have obtained other polymorphs with *anti*-periplanar conformation. In addition, we did not examine the phenomenon by other analytical means, and thus, the role of the *gauche* effect to the packing remained an open question.

The diketones were then subjected to asymmetric CBS reduction, which gave the corresponding diols in excellent yields (Table 10). It was noteworthy that, using the standard acidic work-up conditions, the yields of diols (*R*,*R*)-**55g** and (*R*,*R*)-**55n** were significantly lower. A simple neutralisation of the reaction mixture after the acidic quench raised the yields up to a very high level, suggesting that these diols were prone to elimination under acidic work-up conditions. Lastly, we were again forced to drop out another catalyst candidate because the diketone **34o** could not be reduced under standard borane-reduction conditions due to solubility issues of it in THF.

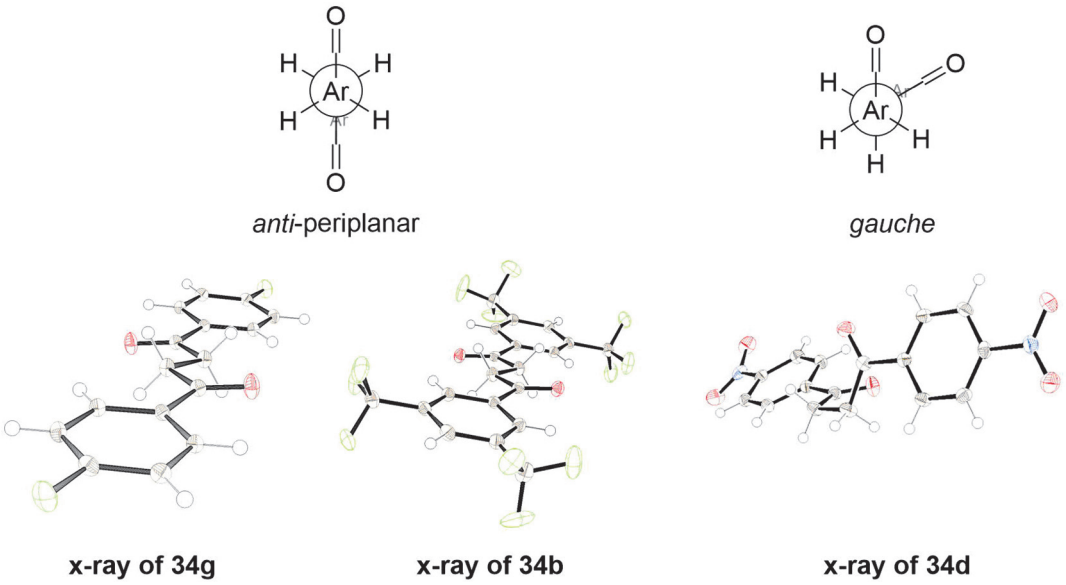


Figure 5: X-ray crystal structures of the diketones **34g, 34d** and **34b**.

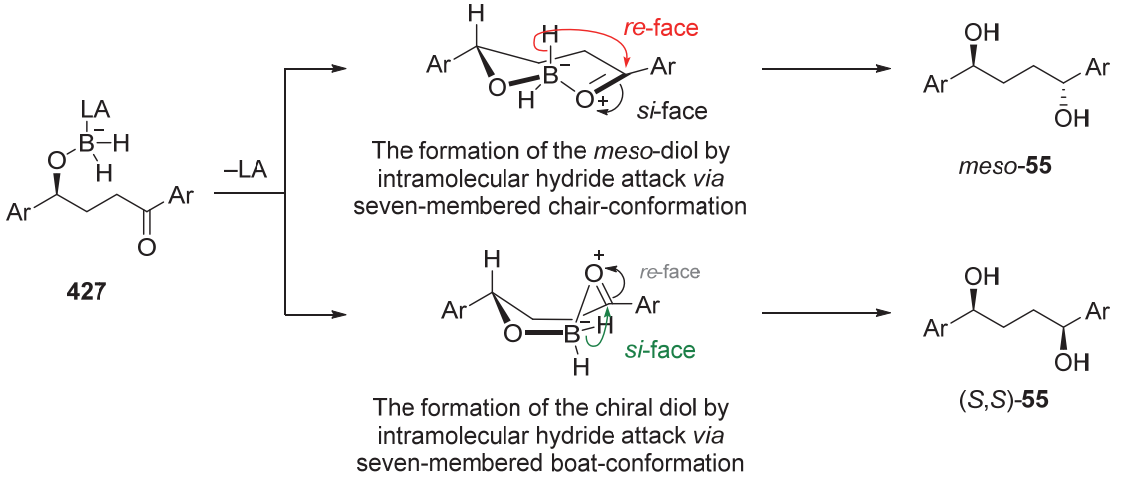
The diastereomeric ratios of the synthesised diols were roughly estimated by integrating the ^{13}C NMR spectra, which indicated that the *dr*'s were very good to excellent (Table 10). The results were not fully consistent with the ones published by Denmark *et al.*, who claimed that the *dr*'s of OMe-substituted diol (*R*,*R*)-**55n** and 3,5-$(CF_3)_2$-substituted diol (*R*,*R*)-**55f** after standard CBS reduction were 78:22 and 63:37, respectively.[66] Even though we did not analyse our samples by HPLC, which would have given more accurate estimates, we knew that our results were reliable enough, as the upcoming steps showed us later. In addition, a closer look at the procedures revealed that Denmark and co-workers did the reactions in milligram scales only, giving the presence of residual moisture a greater role in this air- and moisture-sensitive reaction.*

The presence of *meso*-diastereomers suggested that there was a competing reduction reaction, possibly an intramolecular hydride transfer *via* seven-membered chair conformation (Scheme 72). An intramolecular hydride attack *via* boat conformation, as well as the catalysed intermolecular asymmetric reduction, would have led to the desired chiral diastereomer (*S*,*S*)-**55**. Despite this, the enantiomeric ratios of the final catalysts were excellent (see Section 8.3).

We were able to get x-ray-quality crystals from most of the diols (Figure 6). Regarding the *para*-substituted diols (*R*,*R*)-**55d** and (*R*,*R*)-**55g**, the chiral stereoisomers were more crystalline than the achiral *meso*-diastereomers. The F-substituted diol (*R*,*R*)-**55g** crystallised in a way that forced the butane chain of the molecule in an *anti*-periplanar–*gauche*–*anti*-periplanar conformation. On the other hand, the packing of NO_2-substituted diol (*R*,*R*)-**55d** made the butane chain align in a *gauche*–*anti*-periplanar–*gauche* orientation. One obvious reason that caused the differences in the packings rose from the fundamental changes

* In the case of (*R*,*R*)-**55f**, the authors claimed that the diketone **34b** was not fully consumed before they quenched the reaction, a tell-tale that, most probably, moisture affected the reaction and, thus, lowered the diastereoselectivity.[66]

in intermolecular hydrogen bonding. (*R*,*R*)-**55g** formed hydrogen bonds only between hydroxyl groups, whereas, with diol (*R*,*R*)-**55d**, this was not observed: the latter formed the network solely between OH groups (donor) and NO_2 groups (acceptor).



Scheme 72: Intramolecular reduction *via* possible seven membered ring chair-conformation. For the comparison, a boat-conformation, leading to the desired chiral diastereomer, is shown. LA= Lewis acid.

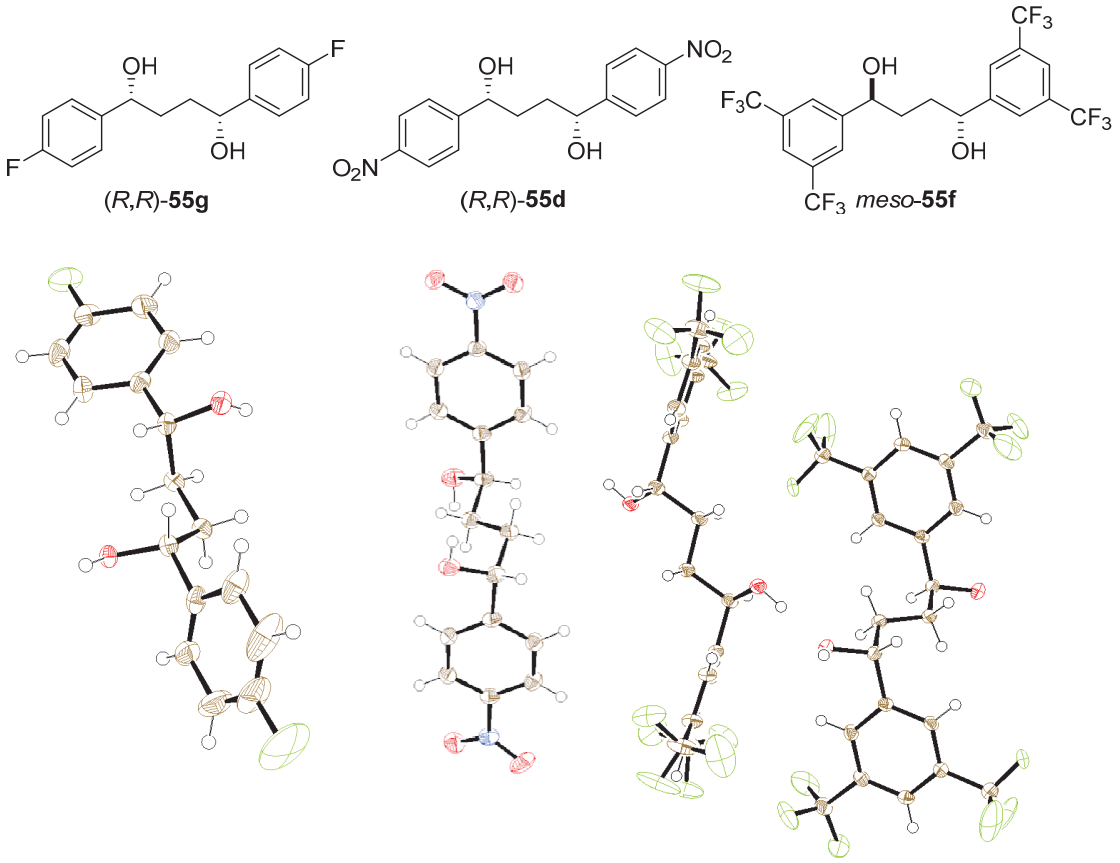


Figure 6: The structures of diols (*R*,*R*)-**55d**, (*R*,*R*)-**55g** and *meso*-**55f**.

Contrary to (*R*,*R*)-**55d** and (*R*,*R*)-**55g**, the *meso*-diastereomer of bis-CF_3-substituted diol **55f** was more crystalline (Figure 6). The packing forced the molecule to orient in two different conformations in the unit cell, which was different from the previous examples. One molecule had its butane chain in a *gauche*–*anti*-periplanar–*gauche* orientation, whereas the other was in an all-*anti*-periplanar conformation. This created a fascinating-looking intermolecular hydrogen-bonding network where "closed clubs" of four OH groups could be seen (see subsection 8.9.6).

In addition to structure determination's point of view, being able to get crystalline material was good news for the future: in multigram scales, enhancing the *dr* of the diol mixtures would be more facile *via* recrystallisation than by column chromatography. Indeed, Denmark and co-workers managed to get diastereomerically pure 3,5-$(CF_3)_2$-substituted diol (*R*,*R*)-**55f** after several recrystallisations, which, on the other hand, led to a poor overall yield (40%).[66] Chong *et al*. were also able to crystallise diastereomerically pure (1*S*,4*S*)-1,4-diphenylbutane-1,4-diol ((*S*,*S*)-**55a**), but noticed the risk of an epimerisation in the prolonged crystallisations.[55] With these scales, we were confident that we would be able to separate the diastereomers after the next step[56] more efficiently and thus minimise the loss of material. Therefore, we did not study the recrystallisation processes more diligently.

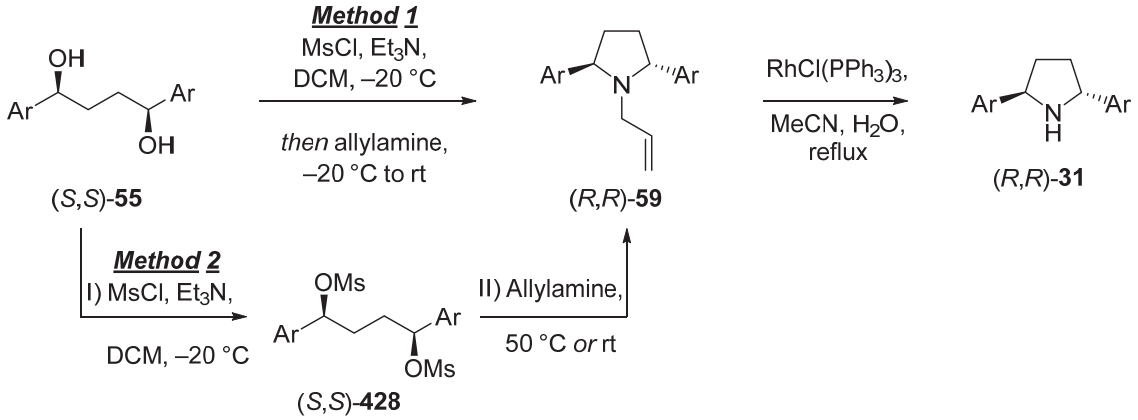
In the next step, we subjected the diols to a one-pot reaction. This included a dimesylation, which was followed by a cascade of two S_N2 reactions, to furnish the pyrrolidine core of the desired catalysts (Table 11, entry 2). F-substituted pyrrolidine (*S*,*S*)-**59g** formed in an excellent, 75% yield, and there were no difficulties in the chromatographic separation of the unwanted *cis*-diastereomer.

Unfortunately, the syntheses of pyrrolidines (*R*,*R*)-**59d** and (*S*,*S*)-**59n** were not easy tasks. In the case of OMe-substituted pyrrolidine **59n**, either side reactions or the instability of the *trans*-diastereomer made it impossible for us to obtain pure *trans*-**59n**. The *cis*-diastereomer, however, was stable and was isolated in a 31% yield (Table 11, entry 3). Denmark faced similar difficulties with the same substrate, noticing that the dimesylate formed from (*R*,*R*)-**55n** was too unstable to be isolated: this might partly explain the side product formation, even though we did the S_N2 cascade in the same pot without isolation attempts.[66] Nevertheless, we decided to postpone synthesis of (*S*,*S*)-**31aj**, which with this route would have required at least the optimisation of the leaving group. In the worst case, we would have needed to also change the nucleophile, a fact that would have led to additional endgame studies.

We faced yet another problem in the synthesis of NO_2-substituted pyrrolidine (*R*,*R*)-**59d**. After several attempts with standard reaction conditions, the yields of the desired pyrrolidine were poor. After a thorough investigation, we found out that a substantially large amount of the dimesylate did not react. Once isolated, the solvation of (*S*,*S*)-**428a** with DCM, as well as with other common organic solvents, proved challenging, suggesting that the solubility might have been the issue in the cascade reaction. To solve the sudden issue, we

dissolved the crude dimesylate product in dry DMF and let it react with allylamine. Fortunately, the reaction was finished in 38 hours at room temperature, and at 50 °C already within 17 hours. After a challenging separation of the diastereomers, the desired (*R*,*R*)-**59d** was obtained in a good, 59% yield (Table 11, entry 1).

Table 11: The synthesis of *N*-allylpyrrolidines **59** and the final pyrrolidine catalysts **31**.



Entry	Ar	Yield (%)[a]	Yield (%)[b]
1	4-NO_2-Ph	**d:** 59 (82)	**k:** 52 (96)[c]
2	4-F-Ph	**g:** 75[c] (91)	**n:** 95[c]
3	4-OMe-Ph	**n:** 31[d]	**aj:** –
4	3,5-$(CF_3)_2$-Ph	**b:** 70 (88)	**i:** 91

a) Yield of the diastereomerically pure compounds **59**, combined yield of the diastereomers in parentheses. b) Yield of the pyrrolidines **31**. c) Yield of the (*S*,*S*)-enantiomer. d) Yield of the *cis*-diastereomer.

The above-mentioned finding made us try to further optimise the cyclisation reactions of both (*R*,*R*)-**55g** to (*S*,*S*)-**59g** and (*S*,*S*)-**55f** to (*R*,*R*)-**59b**. We were especially interested in enhancing latter transformation, which was known to be rather low yielding step in the synthesis route to (*R*,*R*)-**55i**.[56] Contrary to what we had hoped, the first transformation was not successful with the new approach: the dimesylate was so reactive that it polymerised during the work-up. Alternatively, dimesylate (*S*,*S*)-**428c** proved to be perfectly stable after the work-up, the latter transformation thus succeeding to give (*R*,*R*)-**59b** in a very good 70% yield and perfect diastereomeric purity after chromatography (Table 11, entry 4).

The final step of the synthesis route was a deallylation reaction with Wilkinson's catalyst. With F-substituted pyrrolidine (*S*,*S*)-**31n**, as well as with NO_2-substituted pyrrolidine (*S*,*S*)-**31k**, the yield was almost quantitative (Table 11, entries 1–2). It was noteworthy that the yield of the latter reaction was lower

when we used an old batch of Wilkinson's catalyst, and slightly colourful impurities started emerging when we used chlorinated solvents in transfers of **31k**.

In a gram-scale synthesis of CF_3-substituted pyrrolidine (*R*,*R*)-**31i**, some problems arose, probably due to deactivation of Wilkinson's catalyst during the reaction. It was also possible that the CF_3 substituents created additional sterical hindrance near the allyl chain, thus hampering the deallylation. Despite these small obstacles, (*R*,*R*)-**31i** was obtained in excellent yield when the unreacted starting material was recycled. Additionally, we were able to get x-ray-quality crystals of the free amine (Figure 7).

Figure 7: The X-ray structure of the catalyst (*R*,*R*)-**31i**. On the left, an ORTEP-presentation (ellipses with 50% probability), and on the right, a spacefill presentation (CSD-MULBED).[57,167]

4.4 Pyroglutamic-acid-derived catalyst development

As was seen from the early screening studies of the desired Mukaiyama–Michael reaction, the pyroglutamic-acid-derived catalyst systems with electron-withdrawing substituents gave promising results (see Section 4.2). Based on these results, we set our primary goals in the synthesis of catalysts (*R*,*R*)-**32e**, (*R*,*R*)-**32f** and (*R*,*R*)-**32g** (Figure 8a). Compared with 2,5-diarylpyrrolidine catalysts, this novel catalyst type had a more modular core, enabling the synthesis of even larger variety of catalysts with varying substituents.

The modularity of the core had its challenges because of the conformational freedom present in the bond between the C2 and the oxygen-containing tertiary carbon C2'. Inspired by the research by Gilmour and co-workers, we wanted to synthesise a fluorinated catalyst (*R*,*R*)-**429a** to control the bond rotation with the help of the *gauche* effect.[199,200] In principle, an iminium ion conformation could be favoured, where one of the sides of the electrophile would be shielded by one of the C2' aromatic rings (synclinal-*endo*-**430**, Figure 8b). This could enhance the enantioselectivity of the studied Mukaiyama–Michael reaction. In synclinal-*exo*-**430** conformation, this hindrance would be less pronounced, but without further knowledge about the conformational preferences of the hypothesised system, we were ready to undertake the challenge of synthesising catalyst (*R*,*R*)-**429a**.

We started the synthesis work with the usual reaction sequence from (*R*)-pyroglutamic acid ((*R*)-**127**) to pyrrolidine (2*R*)-**129**.[172] We continued with a known organocuprate addition to get pyrrolidine (*R*,*R*)-**130e** in very good, 79%

yield (Scheme 73a).[37] The pentafluorophenyl variant (*R*,*R*)-**130f** was synthesised in the same manner in a 40% yield, but in a scale that was enough for us to carry on with the rest of the steps. We did not examine the reasons for the poor performance of the transformation thoroughly, but probably some unwanted S_NAr reactions lowered the yield.

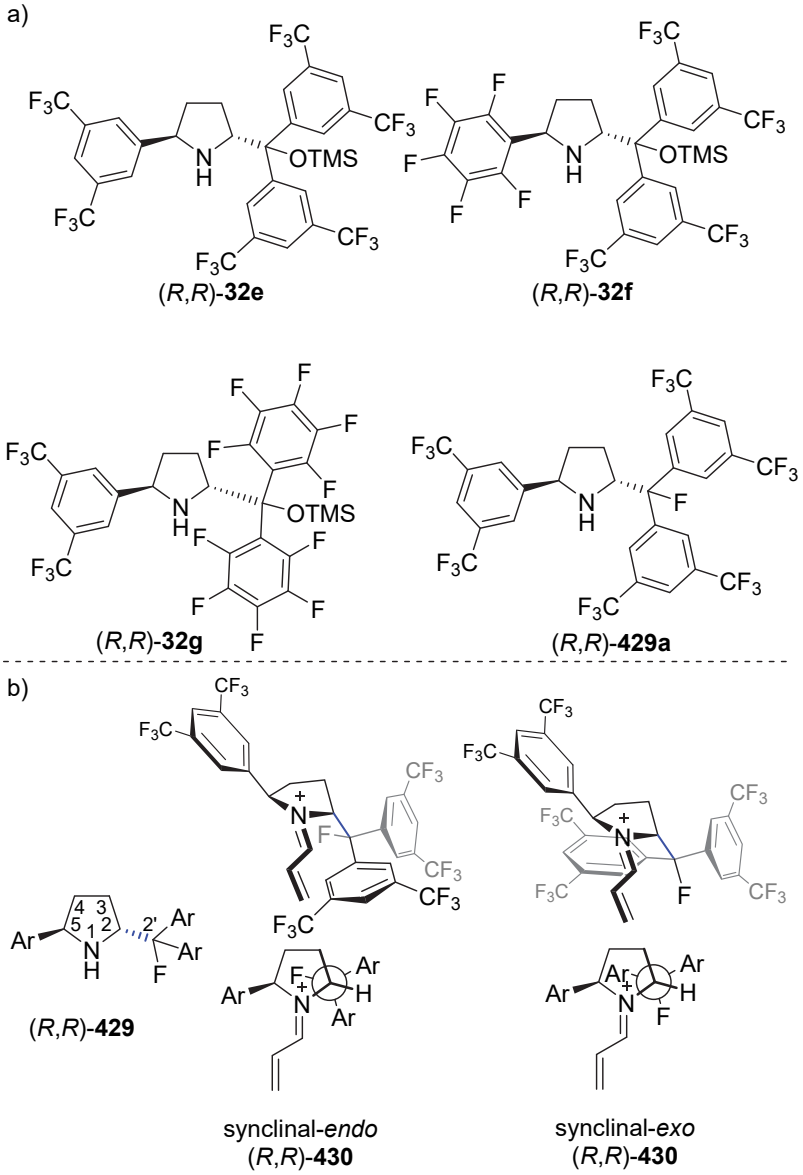
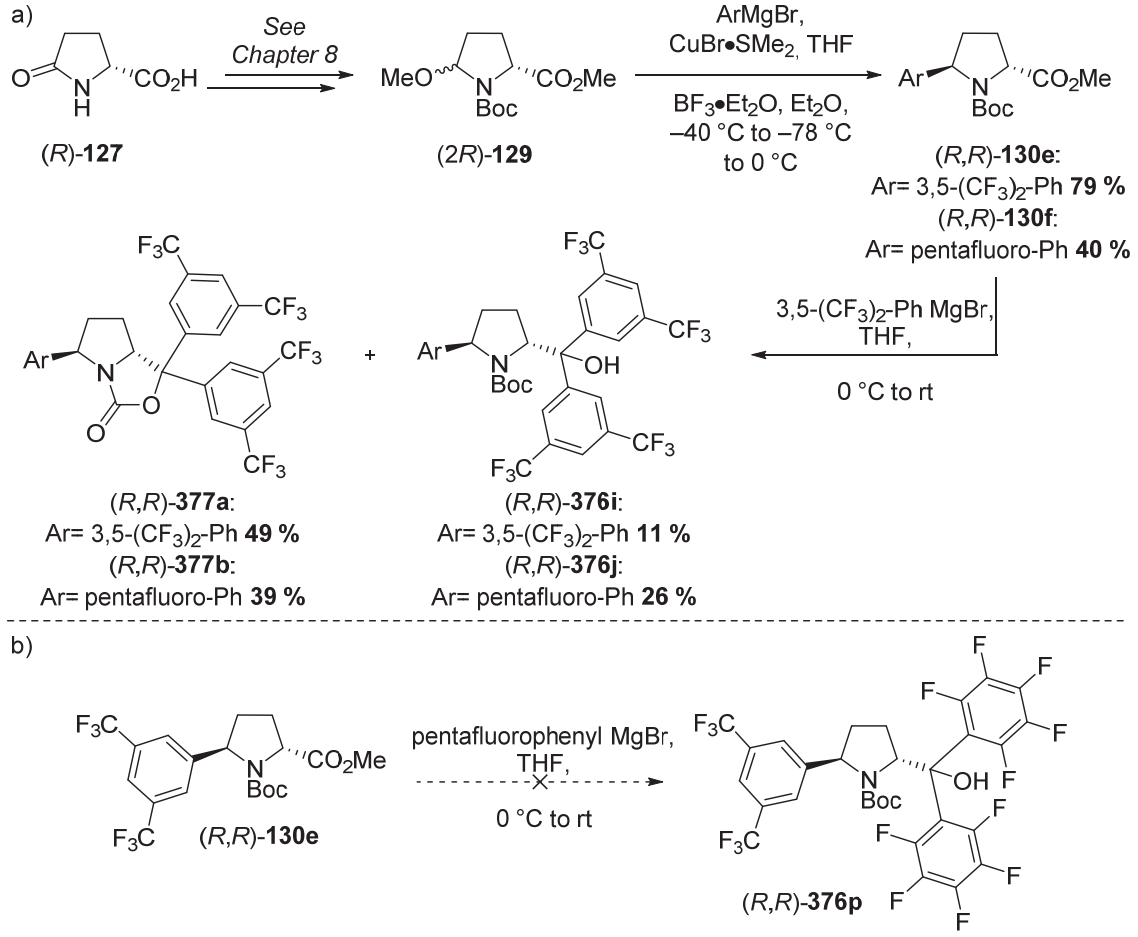


Figure 8: a) Primary pyroglutamic-acid-derived catalyst targets. b) The possible conformations of the iminium ion (*R*,*R*)-**430**, formed between (*R*,*R*)-**429a** and acrolein (**116**), due to the *gauche* effect.

The following double Grignard reactions with 3,5-$(CF_3)_2$-PhMgBr turned out to be challenging ones. When we subjected (*R*,*R*)-**130e** and (*R*,*R*)-**130f** to these reactions, they resulted in complex mixtures of various compounds (Scheme 73a). After careful purifications and analyses, we found out that, along with the desired Boc-compounds (*R*,*R*)-**376i** and (*R*,*R*)-**376j**, carbamates (*R*,*R*)-**377a** and (*R*,*R*)-**377b** also formed. The latter ones, results of intramolecular acyl substitu-

tion reactions, were the main products and, to our delight, were usable in the synthesis of the final catalysts as well.



Scheme 73: a) Early steps in the synthesis of pyroglutamic-acid-derived catalysts (*R*,*R*)-**32**. b) Unsuccessful synthesis attempt of (*R*,*R*)-**376p**.

We also recovered 7% of unreacted starting material and 19% of epimerised starting material 2-*epi*-**130e**, which mostly explained the low combined total yield of the transformation with (*R*,*R*)-**130e** (Scheme 73a). The low total yield of the reaction with (*R*,*R*)-**130f** was partially due to the sensitivity of (*R*,*R*)-**376j** and because of putative S_NAr side reactions. In both cases, optimising the amount of the Grignard reagent would probably have led to better results. However, at this point we were satisfied to the amount of obtained materials, which were enough to carry on with the following synthesis steps.

We also tried a double Grignard reaction with pentafluorophenylMgBr to (*R*,*R*)-**130e** (Scheme 73b)**.** Unfortunately, we were not able to get any pure product (*R*,*R*)-**376p**, even after repeated purification attempts. We hypothesise that the tertiary alcohol was prone to elimination due to electron-donating properties of the *ortho*- and *para*-F-substituents *via* resonance, making (*R*,*R*)-**356p** too unstable to be isolated in practice. Thus, we were forced to abandon the synthesis of the catalyst (*R*,*R*)-**32g**.

The Boc compounds (*R*,*R*)-**376i** and (*R*,*R*)-**376j** were then deprotected under acidic conditions to give amino alcohols (*R*,*R*)-**369b** and (*R*,*R*)-**369c** in good yields (Scheme 74a). To our delight, the methanolysis of carbamate (*R*,*R*)-**377a** also gave (*R*,*R*)-**369b** in excellent 91% yield. However, the latter reaction conditions with carbamate (*R*,*R*)-**377b** favoured the formation of unwanted S_NAr products (*R*,*R*)-**377c** and (*R*,*R*)-**369d** (Scheme 74b). It was a tempting idea to diverge from the original plan and push towards a catalyst (*R*,*R*)-**32h**, possessing an interesting mix of electronics. However, we decided to focus on the original plan and save this approach for possible future attempts.

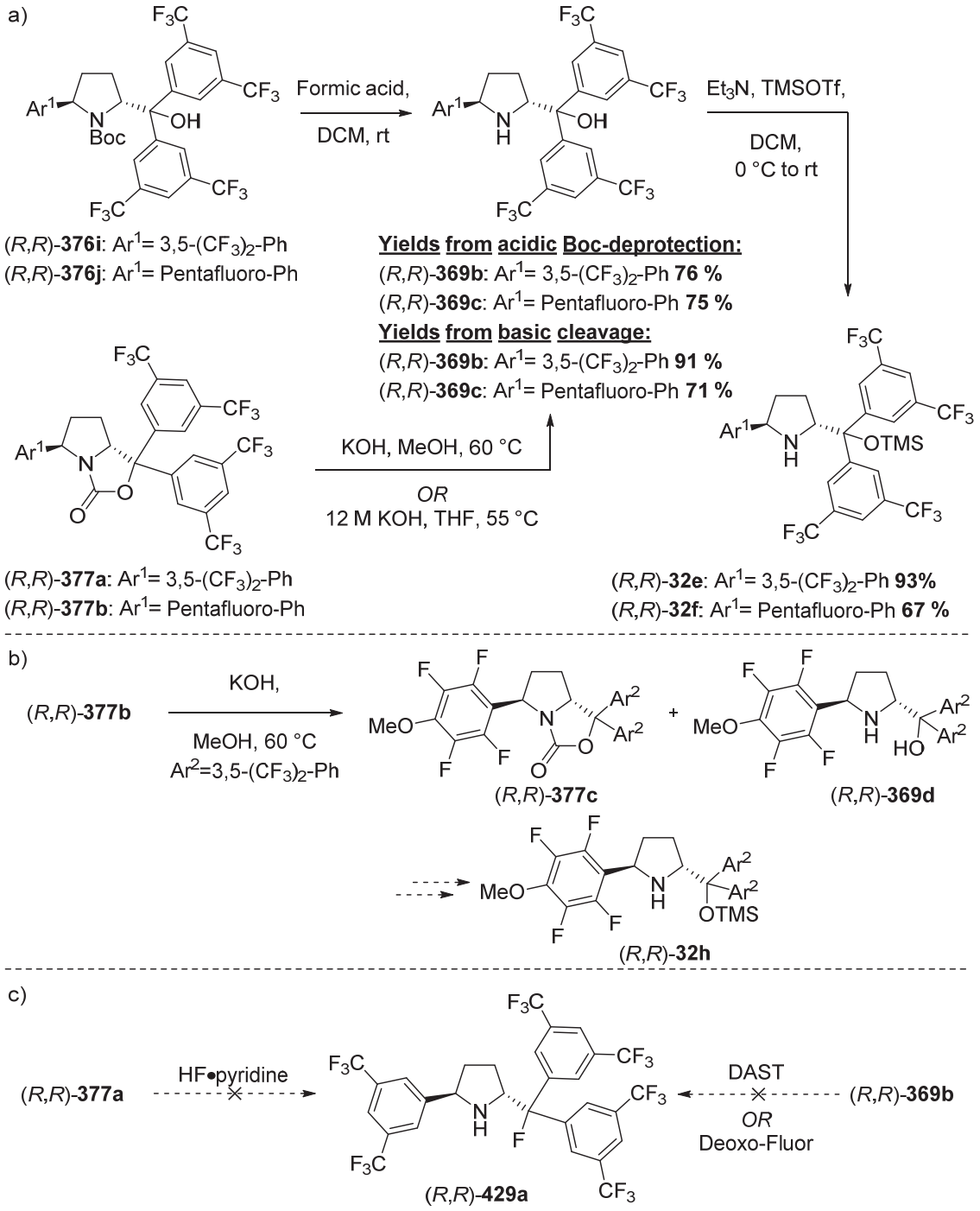
To suppress the S_NAr product formation, we switched the solvent from MeOH to THF, used aqueous KOH solution and lowered the temperature from 60 °C to 45 °C. We immediately noticed that the formation of the side products decreased, but the reaction was sluggish. Raising the temperature to 55 °C and the amount of base to 55 equivalents pushed the reaction to completion overnight. After the purification, (*R*,*R*)-**369c** was obtained in a good, 71% yield (Scheme 74a). Finally, the desired catalysts (*R*,*R*)-**32e** and (*R*,*R*)-**32f** were synthesised in 93% and 67% yields.

We then aimed our attempts towards the deoxyfluorinated catalyst (*R*,*R*)-**429a** (Scheme 74c). Following the procedure of Yang *et al*., the carbamate (*R*,*R*)-**377a** was let to react with a 70:30 mixture of HF–pyridine, both as neat and in a DCM solution.[201] To our disappointment, in both cases, (*R*,*R*)-**377a** was completely inert to the transformation. Possibly the Lewis basicity of the carbamate carbonyl was so low due to electron-withdrawing aromatic rings, which made the protonation of it unfavourable.

We also tried the traditional deoxofluorination reagent DAST and its variant Deoxo-Fluor with aminoalcohol (*R*,*R*)-**369b** (Scheme 74c). The starting material was mostly consumed in both cases, but again, only to give complex reaction mixtures and negative results regarding the fluorination. It was evident that the tertiary alcohol could not readily eliminate due to electron-withdrawing CF_3 groups, meaning that we would probably need to rethink our synthesis strategy in order to get (*R*,*R*)-**429a**.

4.5 New catalyst screening studies

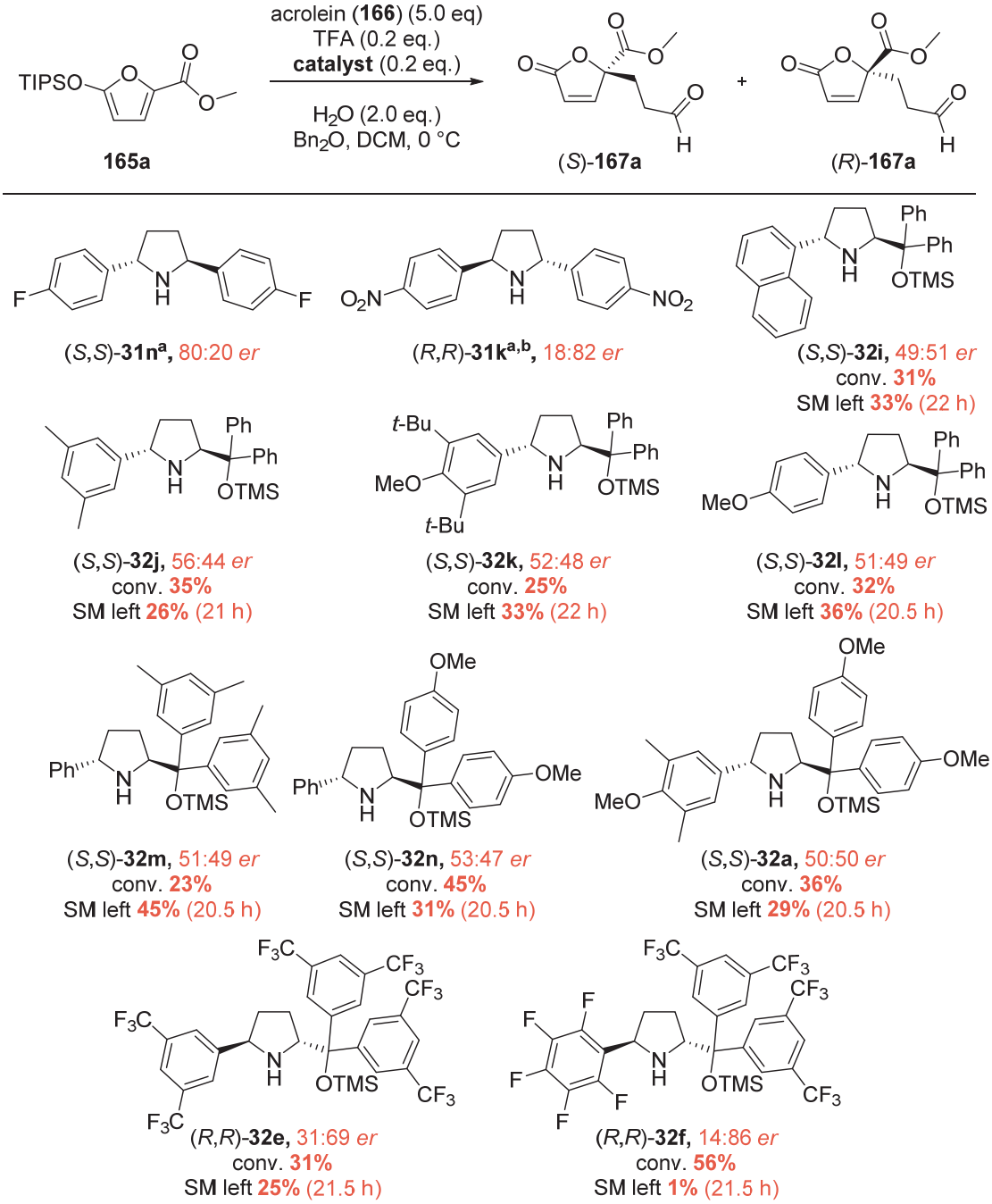
Despite some unsuccessful attempts in the synthesis of novel iminium catalysts, overall, we were satisfied to get catalysts (*R*,*R*)-**31k**, (*S*,*S*)-**31n**, (*R*,*R*)-**32e** and (*R*,*R*)-**32f** for the second round tests. In addition, we had an access to a handful of pyroglutamic-acid-derived catalysts with electron-rich aryls ((*S*,*S*)-**32a, i–n**), synthesised for the purposes of a previous project.[37] Thus, we also tested their performance to support our claims that the studied reaction worked the best with a catalyst with electron-poor aryls.



Scheme 74: a) The final steps in the synthesis of pyroglutamic-acid-derived catalysts **32**. b) The side-product formation in the basic cleavage reaction of (*R*,*R*)-**377b**. c) Unsuccessful deoxyfluorination attempts.

With the new 2,5-diarylpyrrolidine catalysts, there was a notable jump from the "undecorated" phenyl catalyst (*S*,*S*)-**31a** (62:38 *er*) to the 4-F-Ph catalyst (*S*,*S*)-**31n** (80:20 *er*, Scheme 75). With 4-NO_2-Ph catalyst (*R*,*R*)-**31k**, the *er* was only marginally better (18:82 *er*). The results were thus worse than with CF_3 catalysts (*R*,*R*)-**31l** and (*R*,*R*)-**31m**, both of them giving an 85:15 *er* (see Scheme 68 in Section 4.2). Thus, these findings suggested that there was no obvious linear rela-

tionship between the electron-withdrawing ability of the *para*-substituent to the enantioselectivity of the reaction. On one hand, this supported the choice of the CF_3-substituted catalyst system, but on the other hand, made us more puzzled.

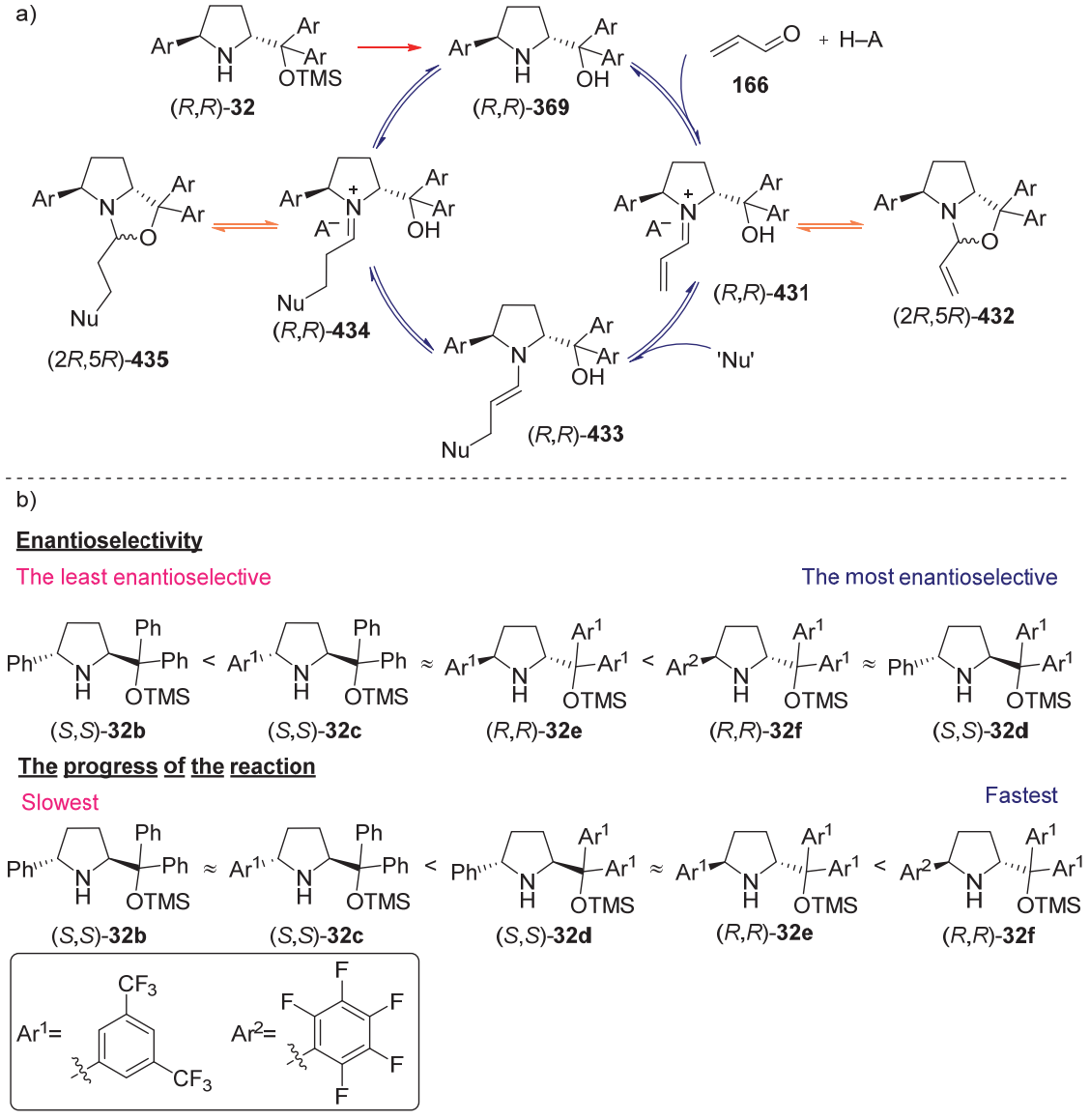


Scheme 75: Catalyst screening studies, see Section 8.6 for details. a) Conversion not determined. b) SM was never fully consumed.

As we expected, the pyroglutamic-acid-derived catalysts with electron-rich aryls did not perform well at all. We obtained racemic mixtures practically in every case, catalyst (*S*,*S*)-**32j** being the best with a 56:44 *er* (Scheme 75). Interestingly, the bulkiness of the left-hand-side aryl group did not affect the enantioselec-

tivity of the reaction at all: despite the big 1-naphthyl-group (catalyst (*S*,*S*)-**32i**), the *er* was still essentially 50:50, which even underperformed the triple-phenyl catalyst (*S*,*S*)-**32b** (see Scheme 68 in Section 4.2).

From the novel electron-deficient catalysts, (*R*,*R*)-**32e** with six CF_3 groups gave only a 31:69 *er* (Scheme 75). To our surprise, it did not outperform the quintuple-CF_3 catalyst (*S*,*S*)-**32d** and gave almost the same result as the catalyst (*S*,*S*)-**32c** with only two CF_3 groups (see Scheme 68 in Section 4.2). Pentafluorophenyl-catalyst (*R*,*R*)-**32f** gave a higher *er* than (*R*,*R*)-**32e**, but did not score as high *er* as the catalyst (*S*,*S*)-**32d**.



Scheme 76: a) Parasitic hemiaminal intermediates, which slow down the reaction after a hypothetical desilylation of the pyroglutamic-acid-derived catalysts. b) Rankings of the pyroglutamic-acid-derived catalysts based on the enantioselectivity and the progression of the reaction.

After examining the ^{1}H NMR spectra of the reaction mixtures, and calculating the conversions, we noted that there was still starting material left after ~20

hours in most of the reactions. An exception was the experiment where we used the pentafluorophenyl catalyst (*R*,*R*)-**32f**. In this case, the reaction finished with a conversion similar to 2,5-diarylpyrrolidine catalyst (*R*,*R*)-**31i**. The detailed explanation for the slow reactions was unknown to us, but the electronics of the catalysts seemed to play the dominant role in the reactivity, sterics having an ancillary role.

One possible explanation for the slow reactions could also be the hydrolysis of the TMS group of the catalyst during the reaction.[202] It is well known that 1,2-aminoalcohols form parasitic hemiaminal ether intermediates of type (2*R*,5*R*)-**432** and (2*R*,5*R*)-**435** in secondary-amine-catalysed reactions (Scheme 76a).[34,203,204] However, identifying these intermediates from the recorded reaction mixture NMR spectra was an impossible task, leaving this as an open question.

The main results from pyroglutamic-acid-derived catalyst screenings were summarised in Scheme 76b. Placing strongly electron-withdrawing substituents on the right-side aryls of the catalyst had the strongest effect to enantioselectivity, but also to the progression of the reaction. The left-side aryl seemed to fine-tune these observables in a tricky way. The enantioselectivity was lower with an aryl containing strongly electron-withdrawing CF_3 substituents than with a less-electron-poor pentafluorophenyl and phenyl groups. In addition, aryl with strongly electron-withdrawing CF_3 groups, as well as phenyl, did not make the reaction progress as fast as the pentafluorophenyl group.

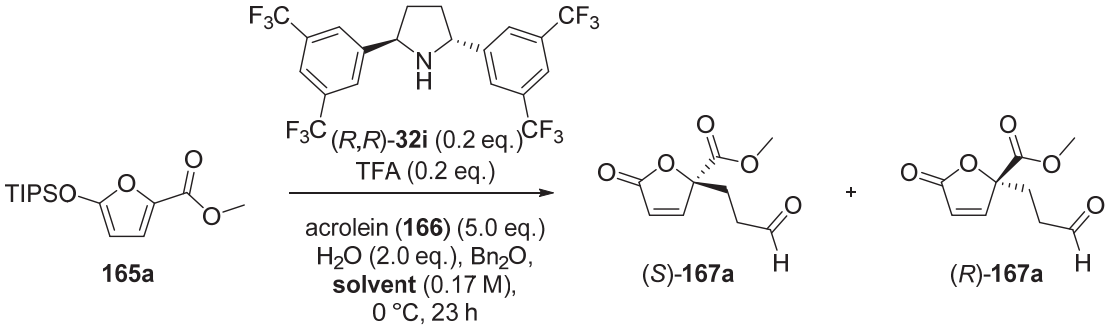
4.6 Solvent screening studies

Lastly, we tested a series of common laboratory solvents to see their effect on the reaction performance. The results showed that our initial sophisticated guess of using DCM as the solvent was correct. The conversions were lower with every tested solvent compared with DCM. Especially low conversions were detected with low-dielectric-constant solvents toluene, Et_2O, EtOAc and THF. $CHCl_3$ provided a 29% conversion, which was still low (Table 12, entries 1–5). With high-dielectric-constant solvents MeOH, DMF and DMSO, the conversions were on the same level compared with $CHCl_3$ (Table 12, entries 6–9). Unfortunately, we could not determine a conversion for the reaction run with ACN due to severely overlapping side product peaks in the product area of the ^{1}H NMR spectrum.

The *er*'s were not bettered, the best one being 22:78 with $CHCl_3$ (Table 12, entry 3). Interestingly, both THF and ACN changed the stereoselectivity so that (*S*)-**167a** was the major enantiomer formed in the reactions (Table 12, entries 5 and 7). Probably these solvents, especially THF, altered the stereodetermining transition state of the reaction by changing the essential non-covalent interactions between the silyloxyfuran and the iminium ion, while still maintaining the catalyst control in some extent. Goodwin also noticed the same phenomenon in her Mukaiyama–Michael solvent screening studies, the effects being less dra-

matic, though.[189] Nevertheless, more experiments were still needed to study and confirm these rather peculiar results.

Table 12: Solvent and additional conditions screening studies.



Entry	Solvent	Dielectric constant[205,206]	Conversion (%)[a]	*er*[b]
1	toluene	2	8	32:68
2	Et_2O	4	~0	–[c]
3	$CHCl_3$	5	29	22:78
4	EtOAc	6	7	50:50
5	THF	8	15	73:27
6	MeOH	33	25	41:59
7	ACN	36	–[d]	56:44
8	DMF	37	26	49:51
9	DMSO[e, f]	47	27	51:49
10	DCM[f, g]	9	43	7:93
11	DCM[h]	9	49	15:85
12	DCM[i]	9	41	26:74

a) Conversion from starting material to product. b) *er* corresponds to the ratio of (*S*)-**167a**:(*R*)-**167a**. c) The amount of product was too low to be detected by GC. d) Could not be determined reliably by ^{1}H NMR. e) Reaction run at rt. f) 19 hours. g) Concentration of the reaction 0.34 M. h) 0.04 eq. of Et_3N was added. i) 0.09 eq. of Et_3N was added.

We also conducted a few other test reactions. In the first one, we changed the concentration of the reaction from 0.17 M to 0.34 M (Table 12, entry 10). The conversion of the reaction got slightly lower, possibly due to a greater tendency for a side product formation in the more concentrated conditions, while the *er* stayed the same (compare to Section 4.2, Table 9). In the second one, we tried to minimise the possible effect of acidic impurities originating from acrolein by adding small amounts of triethylamine to the reaction mixture, a manoeuvre inspired by Companyó and Burés.[193] With 0.04 equivalents of Et_3N, the conversion was on a common level, while, with 0.09 equivalents, the conversion was already significantly lower. Unfortunately, the *er* in both of the reactions got worse, suggesting that either the approach was not suitable for our reaction or the amounts of base should have been smaller. However, a complete screening

of conditions in the manner of Burés and Companyó to find the optimum pH of the reaction mixture would have taken a lot of time. Thus, we decided to prioritise our work, leave this option for the future and move on to a total synthesis route development project, presented in Chapter 5.

4.7 The future of the method

The results prompted us to think briefly about the future of the method. Compared with the preceding work by Pansare and co-workers, we were able to improve the *er* of the studied Mukaiyama–Michael reaction from 87:13 to 93:7. Furthermore, the yield was enhanced from 24% to 50%.[178] Despite the success, there was still some room for improvement.

Regarding the catalyst development, computational studies should be conducted to get fresh, sophisticated ideas. For example, the importance of possible weak interactions between iminium ions and the silyloxyfuran **165a** in the potential transition states can hardly be hypothesised without computational methods. With the help of these, the selection of suitable aryls could become more elaborate. Just by picking aryl groups with different substituents based on their electronic properties, namely, roughly comparing their Hammett σ-values,[207] and testing through every possible combination does not seem to be a viable approach in the long run. However, before the computations, a new, wider set of both symmetrical and unsymmetrical *trans*-2,5-diarylpyrrolidines with electron-withdrawing, and, especially, electron-donating substituents should be synthesised in order to get a more valid training set (Scheme 77a).[37]

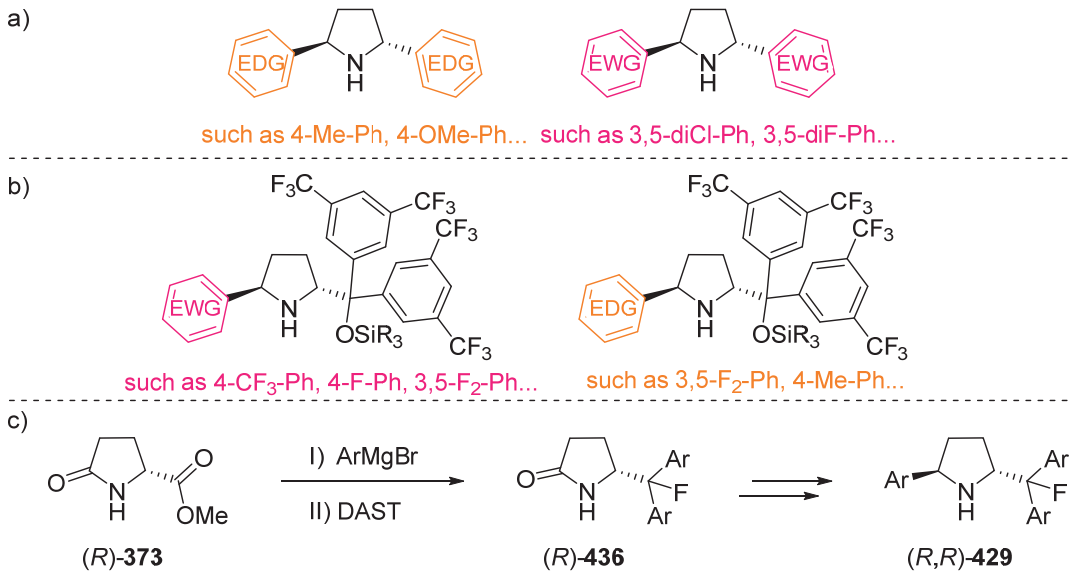
Regarding the pyroglutamic-acid-derived catalysts, the required experimental data for first computations should be enough compared to the previous studies.[37] Just by looking at the results, the enantioselectivity and reactivity of the studied reaction clearly depends on the strongly electron-poor aryl groups on the right side of the catalyst (when drawn in the standard orientation) and a less-electron-poor aryl group on the left. The first target for variations would then be the left-hand side of the pyrrolidine, keeping the right-hand side quadruple CF_3 substitution intact. Possible targets could then be found by reducing either the number of fluorine atoms from five or the number of CF_3 groups to one (Scheme 77b). A group that would donate electron density slightly to the aryl ring (e.g. Me) could also be tried.

In order to get a deoxyfluorinated catalyst, we could test a variety of other commercially available deoxyfluorination reagents. It should also be possible to conduct the deoxyfluorination reaction earlier in the synthesis route, which would require changes in the order of the reduction, organo cuprate and Grignard reactions (Scheme 77c).[208]

If the fine-tuning of the above-mentioned catalysts does not give any improvement, one of the options is to make more radical changes in the catalyst structure. For example, amide-linked catalysts[37], described in Section 6.2, could also be a potential lead to new catalysts.

After finding the optimum catalyst, pumping up the yield of the reaction would be the next task. The factor that keeps the amount of the desired product (*R*)-**167a** rather low should be revealed. Meticulous screening of solvents, counter acids, additives, temperature, concentration, and the amount of acrolein should be conducted. Also, control experiments with the pure (*R*)-**167a** under the general conditions should be carried out to see the propensity of (*R*)-**167a** to react either in side reactions or even in a retro-Michael reaction. Furthermore, the methyl ester and silyl moieties of the starting material silyloxyfuran could be varied.

After optimising the above-mentioned parameters, a further expansion of the substrate scope of the reaction could be done. MacMillan and co-workers already found β-monosubstituted enals to be suitable substrates.[188] However, β-disubstituted and α-substituted enals, as well as triple-bond-containing ynals, have not been tested. Demonstrating the utility of the method in a synthesis route of a chosen target could then be conducted.



Scheme 77: Proposals for the future in the case of a) *trans*-2,5-diarylpyrrolidines, b) pyroglutamic-acid-derived pyrrolidines and c) deoxyfluorinated catalysts.

4.8 Conclusions

We were able to improve the conditions of an organocatalytic enantioselective Mukaiyama–Michael reaction between a silyloxyfuran **165a** and acrolein (**166**). The reaction utilised a chiral secondary amine (pyrrolidine) as a catalyst and was thus an iminium-ion-catalysed reaction. Catalyst screening studies revealed two promising cores for the ideal catalyst: *trans*-2,5-diarylpyrrolidine and pyroglutamic-acid-derived pyrrolidine cores.

More thorough studies revealed that both the enantioselectivity and the conversion of the reaction were heavily dependent on the aryl substituents of

the catalysts and, thus, their electronical properties. The best catalysts for the reaction turned out to be the ones with electron-withdrawing CF_3 groups in their aryl rings, electron-donating groups being inferior choices. Eventually, 2,5-diarylpyrrolidine (*R*,*R*)-**31i** turned out to be the chosen catalyst for the reaction.

The synthesis of the novel catalysts was challenging, and we were forced to abandon some catalyst candidates due to unsolvable problems. However, we were also able to solve many of them and, gratifyingly, were able to scale up the synthesis route of (*R*,*R*)-**31i** to gram scale.

Both the counter acid and the solvent had their influences on both the conversion and enantioselectivity of the studied Mukaiyama–Michael reaction. The most fitting acid was trifluoroacetic acid, the solvent of choice being DCM. With this catalytic system, the reaction gave the desired aldehyde (*R*)-**167a** in an excellent, 93:7 *er* and in a 50% yield. We thus managed to reach a level that allowed the practical use of the method in asymmetric synthesis.

The fact was that there was still a lot to improve upon in the reaction conditions. We were not able to solve the problem that led to the low yield. In addition, we could not find the ultimate catalyst and did not have the computational resources at hand to understand the fundamentals related to the enantioselectivity of the reaction, the details that could have sped up the optimisation process. Even though the method was not fully matured, we decided to bear its flaws and move on, using the method in a total synthesis route described in Chapter 5.

5 CATALYTIC ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)–LYCOPERDIC ACID

5.1 Introduction and former total syntheses

Our next plan was to demonstrate the synthetical utility of the developed method in a total synthesis route of a natural product. As we presented in the beginning of Chapter 4, oxygen-containing tertiary stereoecenters with varying cores were widely present in natural products (Scheme 65). From the various alternatives, we chose (+)-lycoperdic acid ((+)-**168**) as our target due to its structural similarity to the Mukaiyama–Michael product aldehyde (*R*)-**167**.

(+)-**168** is a non-proteinogenic amino acid, which was isolated by Rhugenda-Banga *et al.* from a mushroom, *Lycoperdon perlatum*.[109] It is structurally similar to L-glutamic acid ((*S*)-**437**), one of the genetically encoded (proteinogenic) amino acids. It also shares structural similarities with dysiherbaines (–)-**396** and (–)-**438**, which were isolated from a marine sponge, *Dysidea herbacea*.[182,209] Both are well-known ionotropic glutamate receptor binders, L-glutamic acid being the endogenous ligand, as the name implies.[210]

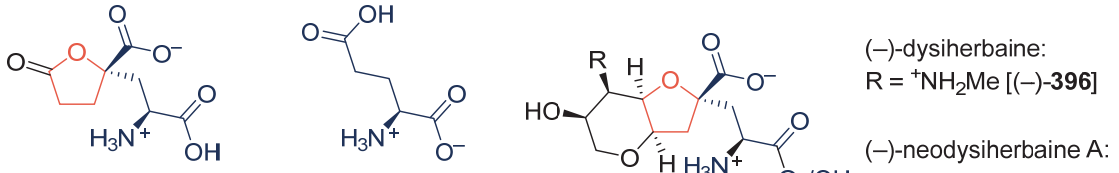
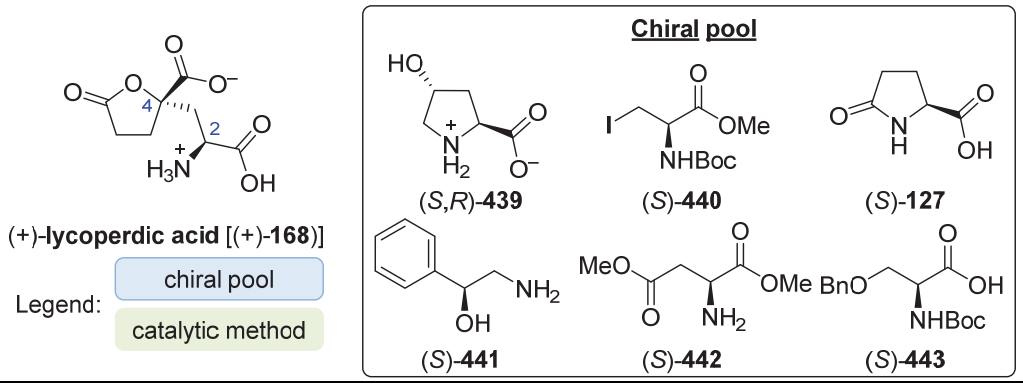


Figure 9: (+)-Lycoperdic acid and structurally similar amino acids L-glutamic acid and dysiherbaines.

All of the above-mentioned compounds have the five-carbon chain with the dicarboxylic acid moieties of glutamic acid in their structures, as well as an amino group at C2. Additionally, (+)-**168** and dysiherbaines have five-membered rings attached to C4, creating a tetrasubstituted tertiary stereocenter.

Despite the structural similarities, many total syntheses and promises to conduct pharmacological studies, the biological activity of (+)-**168** has remained a mystery for the scientific community.

Table 13: The stereocontrol of C2 and C4 stereocenters in the published routes to (+)-**168**.



Author	Number of Longest Linear Steps	Control of C4	Control of C2	Chiral Pool
Yoshifuji[211,212] 1992/1995	6	no stereocontrol	chiral pool	(*S*,*R*)-**439**
Hatakeyama[213] 2000	13	Sharpless asymmetric epoxidation	chiral pool	(*S*)-**440**
Hamada[214] 2002	6 (9)[a]	stereoselective hydroxylation	chiral pool	(*S*)-**127**
Tamura[215] 2005	10	chiral auxiliary	chiral auxiliary	(*S*)-**441**
Chamberlin[216] 2007	11 (15)[a]	stereoselective bromination	chiral pool	(*S*)-**127**
Reiser[217] 2013	6 (8)[b]	stereoselective radical cyclisation	chiral pool	(*S*)-**442**
Lopp[218] 2015	7[c]	asymmetric oxidation	chiral pool	(*S*)-**443**
Oikawa[219] 2019	11	no stereocontrol	enantioselective hydrogenation	–

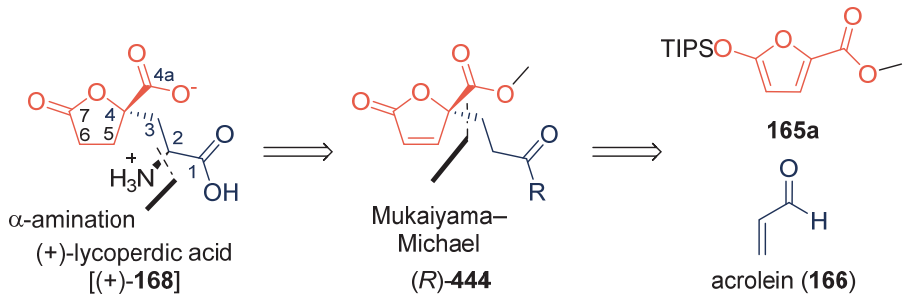
a) Steps in parentheses from (*S*)-**127**. b) Formal total synthesis with six steps, which would have required two extra steps to (+)-**168**. c) Longest linear sequence from serine derivative (*S*)-**443**.

To date, there are seven total syntheses and one formal synthesis* for (+)-**168** (Table 13).[211–220] Half of the routes are less than 10 steps long, the longest route being as much as 15 steps long. To set the C4 stereocenter, a catalytic method was used in two of the routes, whereas a substrate-controlled manner was employed in four of them. In two routes, a stereocontrol could not be achieved.

The most popular way to construct the C2 stereocenter of (+)-**168** has included an amino acid derivative, suitable to the chosen strategy (Table 13). These have involved pyroglutamic acid ((*S*)-**127**) and hydroxyl proline (*S*,*R*)-**439**, which contain more than half of the required atoms of the target molecule *per se*. On one hand, the chiral pool approaches have offered fast ways to get at least one stereocenter with the correct absolute configuration, but on the other hand, they have led to routes that have required additional steps due to protecting group and/or oxidation state manipulations. Only recently, the group of Oikawa used a catalytic method to get the desired amino acid moiety by conducting an asymmetric hydrogenation.

5.1.1 Our retrosynthesis

We wanted to develop a route where we would achieve full stereocontrol by using organocatalytic methods, without relying on stoichiometric chiral pool molecules or chiral auxiliaries. Retrosynthetically, we envisioned that we would set the C2 stereocenter *via* α-amination reaction (Scheme 78). The arduous tertiary stereocenter at C4 would be accessible *via* the Mukaiyama–Michael reaction between a silyloxyfuran **165a** and acrolein (**166**).

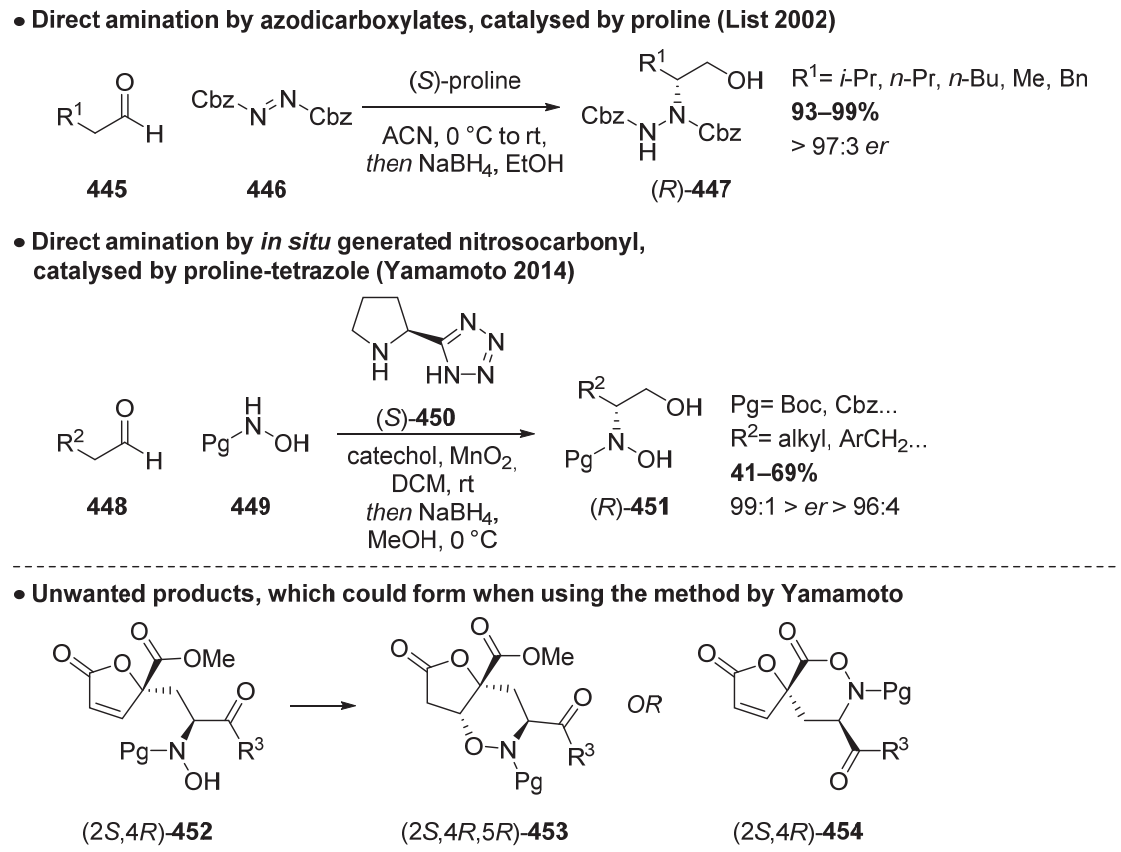


Scheme 78: Retrosynthesis of (+)-**168**.

We solved the biggest issues of the first challenge, the asymmetric Mukaiyama–Michael reaction, in the previous chapter (see Chapter 4) and were left with the inspiring challenge to demonstrate the viability of the method in a preparative scale as part of a synthesis route. The second challenge was the setting of the C2 stereocenter and the amino acid moiety with an α-amination reaction. We found the procedure by List to be the most feasible one since the organocatalyst, proline, would not require a separate synthesis campaign, and it would offer a

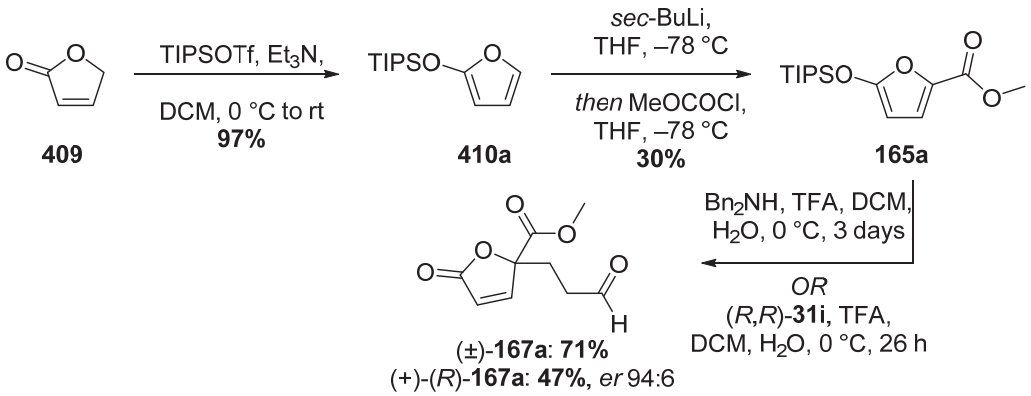
* Recently, Denton *et al.* published a total synthesis attempt[220] of (+)-**168**, based on the route by Tamura *et al.*[215] They reached the end-game studies, but eventually, were unable to synthesise the natural product reliably.

direct way to the amination (Scheme 79).[221] Another method of that kind was developed by Yamamoto and Maji, who used a proline-tetrazole catalyst (*S*)-**450** and *in situ* generated nitrosocarbonyl.[222] However, in our perspective, the yields obtained with this method were not appealing. In addition, the suitability of the hydroxyamine moiety with our possible substrate (*R*)-**444** was also questionable: the ester group at C4 could easily participate in a cyclisation reaction and the double bond in an intramolecular conjugate addition.



Scheme 79: Representative methods for direct organocatalysed α-aminations known in the literature.[221,222]

5.1.2 The first total synthesis route



Scheme 80: The first steps of the total synthesis route towards (+)-**168.**

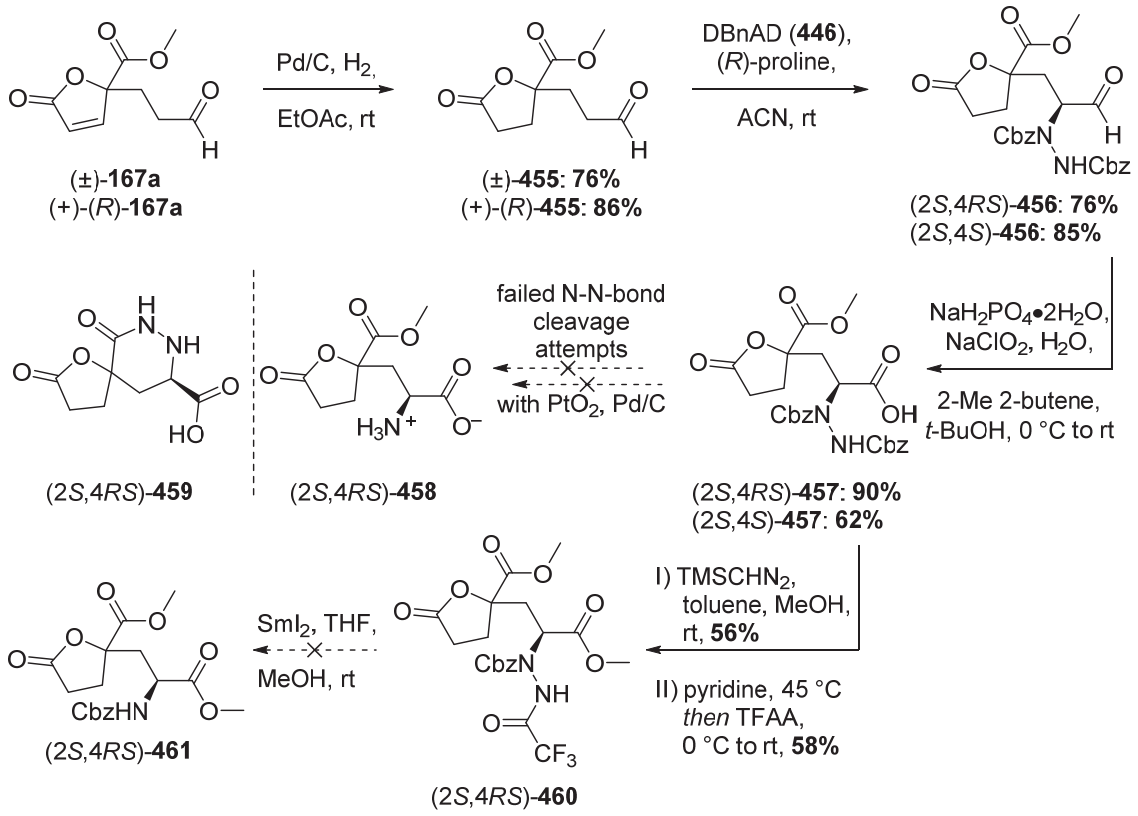
A few early tests of the first route were conducted by the author of this dissertation in his master thesis project,[192] but in this context, more optimised results obtained later were presented. We started the total synthesis campaign by silylating the furanone **409** with TIPSOTf and methoxycarbonylating the silyloxyfuran **410a** to **165a** according to the literature procedures (Scheme 80).[36,190] We conducted the main route scouting with achiral material and thus synthesised batches of racemic Mukaiyama–Michael aldehyde (±)-**167a** first. We utilised the achiral conditions developed earlier (dibenzylamine–TFA, see Table 8, Chapter 4), which, at best, gave a very good, 71% yield in gram scale. Due to the polymerising nature of acrolein, a careful work-up was always needed in bigger scales: evaporation of the crude to dryness easily led to decreased yields, and sometimes, the crude formed a yellow polymer cake on top of the column at the beginning of the purification. It is possible that the polymerisation could have been suppressed by reducing or oxidising the product aldehyde **167a** in the same pot,[36] but due to our total synthesis strategy, which required an aldehyde functionality in the following step, we chose not to add any extra oxidation state manipulations to the route.

To our disappointment, the synthesis of enantioenriched aldehyde (+)-(*R*)-**167a** did not proceed with a similar success. We got the compound in a 47% yield and with a 94:6 *er* (Scheme 80), which on the other hand were in unison with the results obtained earlier (see Chapter 4). The yield was significantly lower than in the racemic reaction, and the reasons behind this were not completely clear to us. In addition to the risk of polymerisation during the work-up, the reaction might have suffered from the impurities present in the reagent *per se*. A distillation of acrolein prior to every reaction could have removed most of the (acidic) impurities and the stabiliser, but due to the sensitive nature of acrolein towards polymerisation when unstabilised, we avoided this task.[223]

The double bonds of the aldehydes **167a** were then reduced in standard hydrogenation conditions with Pd/C, producing the aldehydes (±)-**455** and (+)-(*R*)-**455** in 76% and 86% yields, respectively (Scheme 81). The slight decreases from quantitative yields were probably due to the sensitivities of both the starting material and the product aldehydes: for example, a slight yellowish tinge could be seen in the crude products after the hydrogenation, which was absent from the pure product obtained after chromatographic purification.

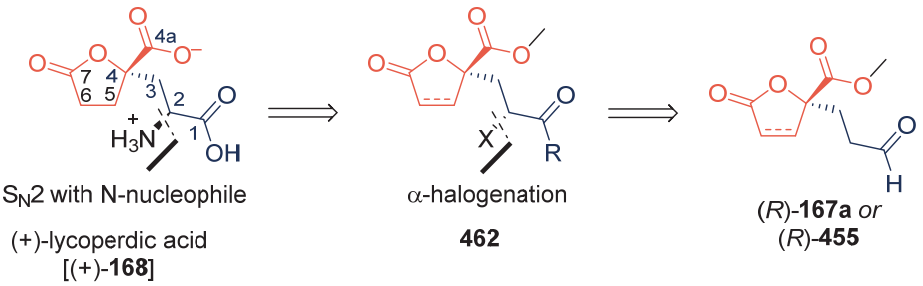
The aldehydes **455** were then α-aminated to the aminoaldehydes **456** with DBnAD according to List's protocol,[221] affording the diastereoenriched compound[57,192] with a slightly higher yield than (2*S*,4*RS*)-**456** (Scheme 81). Although being a straightforward method to conduct the α-amination, the characterisation and depicting the purity of the products by ^{1}H NMR was a painful task because of the rotamers caused by the Cbz groups. The aldehydes were then oxidised to the corresponding carboxylic acids using Pinnick oxidation. There was a slight difference in the yields between the diastereomeric mixture (2*S*,4*RS*)-**457** and diastereomerically enriched (2*S*,4*S*)-**457**, which left some room for optimisation of the reaction in the future.

Another challenging job was the *N*-*N*-bond cleavage, which proved to be impossible in our hands (Scheme 81). Hydrogenolysis, catalysed by Pd/C or PtO_2, yielded only complex mixtures, which we were not able to purify. Based on low resolution mass spectrometric studies of the crude product obtained after a reaction with Pd/C, a spiro compound (2*S*,4*RS*)-**459** was detected as one of the possible components. We also tried SmI_2-mediated cleavage with a commercially available reagent in the manner of Barbas *et al*.[224] We first made the corresponding methyl ester from acid (2*S*,4*RS*)-**457**, after which, we selectively trifluoroacetylated and cleaved off one of the Cbz groups to make hydrazine (2*S*,4*RS*)-**460** in decent yields. Unfortunately, SmI_2 was not able to cleave the aimed *N*-*N*-bond of (2*S*,4*RS*)-**460**, even when strictly deoxygenated conditions were applied. We had to face the truth that this type of α-amination was seemingly unreliable and impracticable, meaning we had to find another way to complete the total synthesis of (+)-**168**.



Scheme 81: Unsuccessful total synthesis route of (+)-**168**.

5.1.3 The second total synthesis route



Scheme 82: Retrosynthetic analysis of the second total synthesis route.

In the second attempt, we envisioned that we could conduct the α-amination by first halogenating the C2 stereoselectively and then using a suitable nitrogen nucleophile to displace the halogen atom with an S_N2 reaction (Scheme 82). Such a nucleophile would ideally be an azide anion. We could easily reduce the formed azide to the corresponding amine and Boc protect it *in situ* if needed. This would give us the fully protected natural product, which upon hydrolysis, would lead to (+)-**168**.

Our attention was drawn to organocatalytic α-chlorination[111,225] and α-bromination[112] reactions, the suitable substrate for the transformations being either (*R*)-**167a** or (*R*)-**455**. On the one hand, the furanone (*R*)-**455** would be ideal since the reduction of the double bond could be done at the same time as the azide reduction later in the route. On the other hand, lactone (*R*)-**167a** would be a safer option strategically because the risk of a conjugate addition by azide would then be avoided.[226]

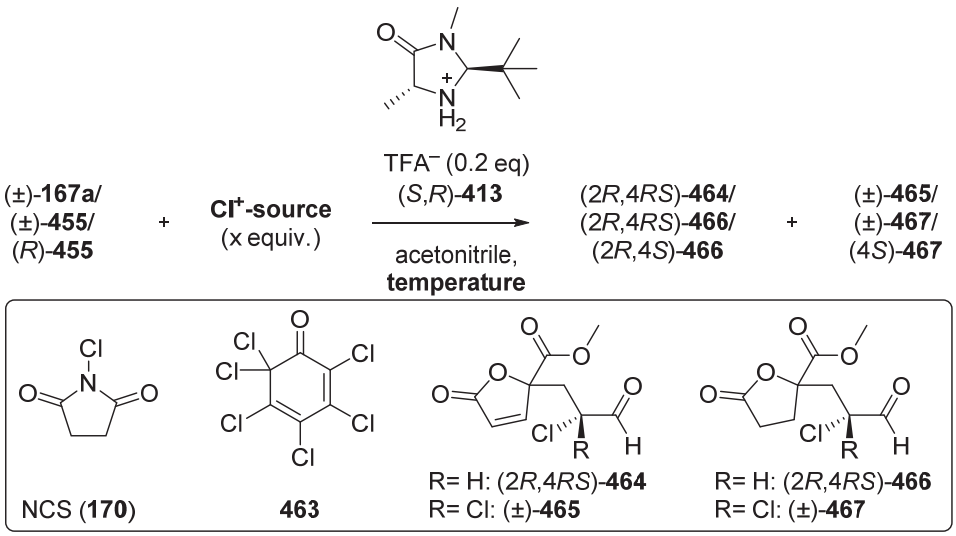
5.1.3.1 Screenings of the α-chlorination reaction

We started the initial α-chlorination screenings following the method of Christmann *et al.*, and used *N*-chlorosuccinimide (**170**) as the Cl^+-source.[227] As the reaction was completely new to us, we started the first experiments with (±)**–167a** as the starting material to avoid using chiral material in the early tests. The first reaction looked promising, giving an encouraging-looking pair of diastereomeric doublets (*dr* 1:1) in the aldehyde region of the ^{1}H NMR spectrum. In addition, the starting material was almost fully consumed within 3.5 hours. Lowering the temperature from 0 °C to –27 °C slowed down the completion of the reaction to 9 hours, but did not change the *dr* (Table 14, entries 1–2).

We also tested another chlorinating reagent, perchlorinated quinone **463**, and followed the methods published by MacMillan's group and Kokotos *et al.*[225,228] The reaction with **463** was finished in one hour at room temperature, giving the same *dr* as with NCS. In addition, the reaction putatively formed a small amount of dichlorinated aldehyde (±)-**465**, based on the singlet observed in the aldehyde region of the reaction mixture ^{1}H NMR spectrum. It was noteworthy that the amount of dichlorocompound (±)-**465** did not decrease when we lowered the amount of **463** from 1.2 equivalents to 1.0 (Table 14, entries 3–4).

To confirm that the correct product had truly formed, we tried to isolate the chloroaldehyde (2*R*,4*RS*)-**464** as pure. This turned out to be a terrible idea since the product was too unstable to be isolated by regular silica column chromatography, and we only got complex mixtures. Not having access to specialised silica used in the purification of similar compounds previously,[229] the only option was to oxidise (2*R*,4*RS*)-**464** in the same pot after the full consumption of (±)-**167a**.

Table 14: Screenings of the α-chlorination reaction.



Entry	Substrate	Cl^+ (eq)	t (h)	T (°C)	Conv. to prod. (%)[a]	Conv. to diCl (%)[a]
1	(±)-**167a**	**170** (1.1)	3.5	0	n.d.	n.d.
2	(±)-**167a**	**170** (1.1)	9	–27	n.d.	n.d.
3	(±)-**167a**	**463** (1.2)	1	rt	n.d.	*traces*
4[b]	(±)-**167a**	**463** (1.0)	1	rt	n.d.	*traces*
5	(±)-**455**	**170** (1.1)	6	0	75	1
6	(±)-**455**	**463** (1.1)	3.5	0	83	1
7	(±)-**455**	**463** (1.0)	4	0	81	1
8	(±)-**455**	**463** (1.2)	4	0	87	2
9[b,c]	(±)-**455**	**463** (1.1)	1	rt	(98)[d]	(~2)[e]
10	(*R*)-**455**	**463** (1.0)	0.5	rt	n.d.[f]	n.d.
11[b]	(*R*)-**455**	**463** (1.1)	5.5	0	(74)[d, g]	n.d.

a) Based on ^{1}H NMR using 1,2,4,5-tetramethylbenzene as an internal standard. b) Reaction mixture directly applied to the column. c) 0.75 mmol scale. d) Isolated yield of **464** + some impurities in parenthesis. e) A calculated estimate based on ^{1}H NMR spectrum after chromatography. f) *dr* 83:17, based on ^{1}H NMR of the reaction mixture. g) *dr* 90:10, based on ^{1}H NMR of the reaction mixture.

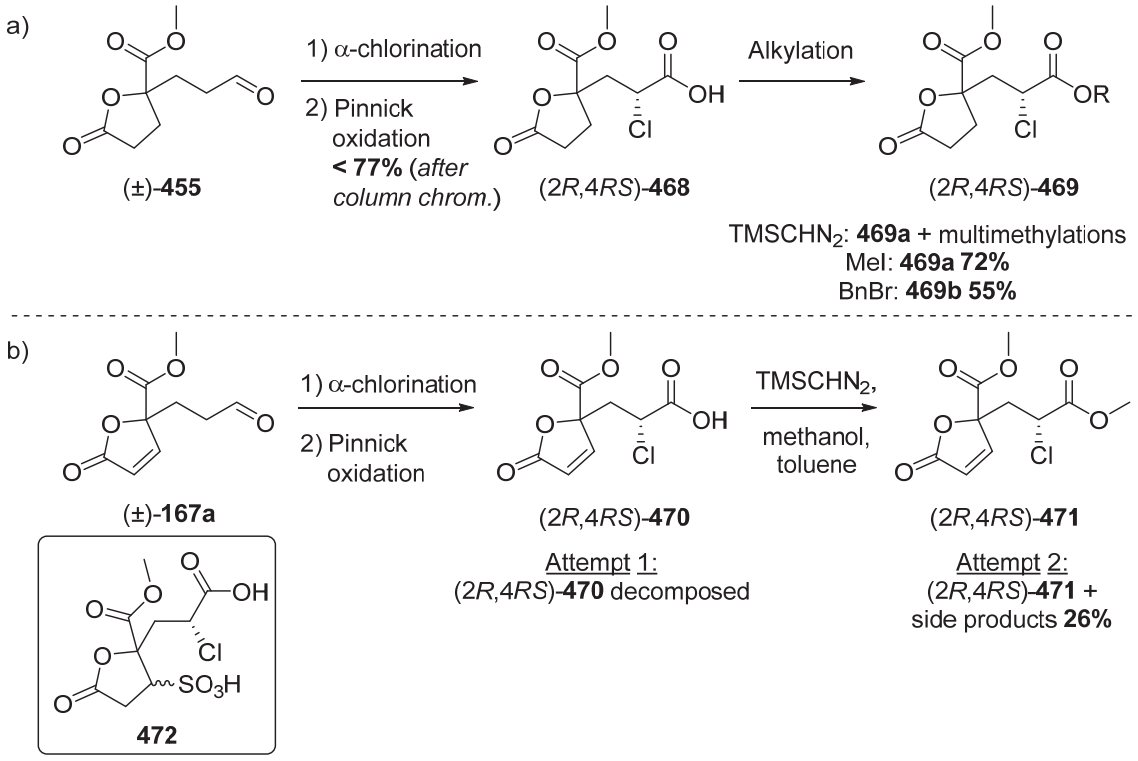
Before the oxidation attempts, we conducted α-chlorination studies with the aldehyde (±)-**455**. To our delight, reactions with both NCS and quinone **463** provided very good conversions, the latter giving slightly a better one. Interestingly, the conversions from (±)-**455** to (±)-**464**, as well as the amounts of dichlorinated aldehyde **467**, stayed roughly the same, even though we varied the amount of **463** between 1.0–1.2 equivalents **(**Table 14, entries 6–8).

Even though the results were seemingly great, we faced some peculiar problems from time to time. Roughly, half of the reactions did not go to full completion, even with longer reaction times. Many times the reaction mysteriously stalled to ~60–70% conversion and restarted only after adding more catalyst (*S*,*R*)-**413** and quinone **463**. Making the reaction mixture less concentrated did not have any effect, ruling out the possible solubility issues of the reagents. Ultimately, conducting the reaction at room temperature solved the problem, and the reaction was over in one hour. It was also noticed that (2*R*,4*S*)-**466** could be purified at least partially by column chromatography, but the diastereomers were not separable (Table 14, entry 9).

We then tried the reaction with enantioenriched starting material (*R*)-**455**. At room temperature, the reaction was finished within half an hour (*dr* 83:17), whereas at 0 °C, it was finished within 5.5 hours (*dr* 90:10, Table 14, entries 10–11). The stereoselectivity of the reaction was on an acceptable level, indicating that the synthesis route could be carried out without further optimisations. In addition, the reaction went to completion without stalling, suggesting that the earlier problems were probably related to the α-chlorination of the unwanted enantiomer (*S*)-**455**, which produced (2*R*,4*R*)-**466**. Lastly and unfortunately, the chloroaldehyde (2*R*,4*S*)-**466** showed its capricious nature by epimerising the C2 stereocenter during the column purification, forcing us to do the following oxidation in the same pot.

We continued the route scouting with (±)-**455** and chlorinated it with quinone **463** in the usual manner at room temperature (Scheme 83a). Without a work-up, we oxidised the aldehyde by Pinnick oxidation in the same pot, which gave us the acid (2*R*,4*RS*)-**468** in a 77% yield as a mixture of diastereomers and with some impurities. The acid seemed to be quite stable, tolerating even purification by column with DCM-methanol eluents. The isolation of the acid by extraction was tricky, though, due to its water solubility: usually the water phase needed a careful examination in order not to lose any material.

To study the separation of the diastereomers and to make chromatographical purification more facile, we alkylated the acid. With $TMSCHN_2$, the methylation was unreliable, since it also produced multimethylated compounds (Scheme 83a). To our delight, methylation of the crude (2*R*,4*RS*)-**468** with MeI under basic conditions yielded the desired diester (2*R*,4*RS*)-**469a** in a 72% yield. In addition, the benzyl ester (2*R*,4*RS*)-**469b** was synthesised in the same manner in a 55% yield. In both cases, the yields were calculated over two steps, and the products were isolated as mixtures of diastereomers and a few impurities originating from the Pinnick oxidation.



Scheme 83: One-pot sequences. a) α-chlorination was done with quinone **463**. b) In Attempt 1, quinone **463** was used, and in Attempt 2, NCS was used.

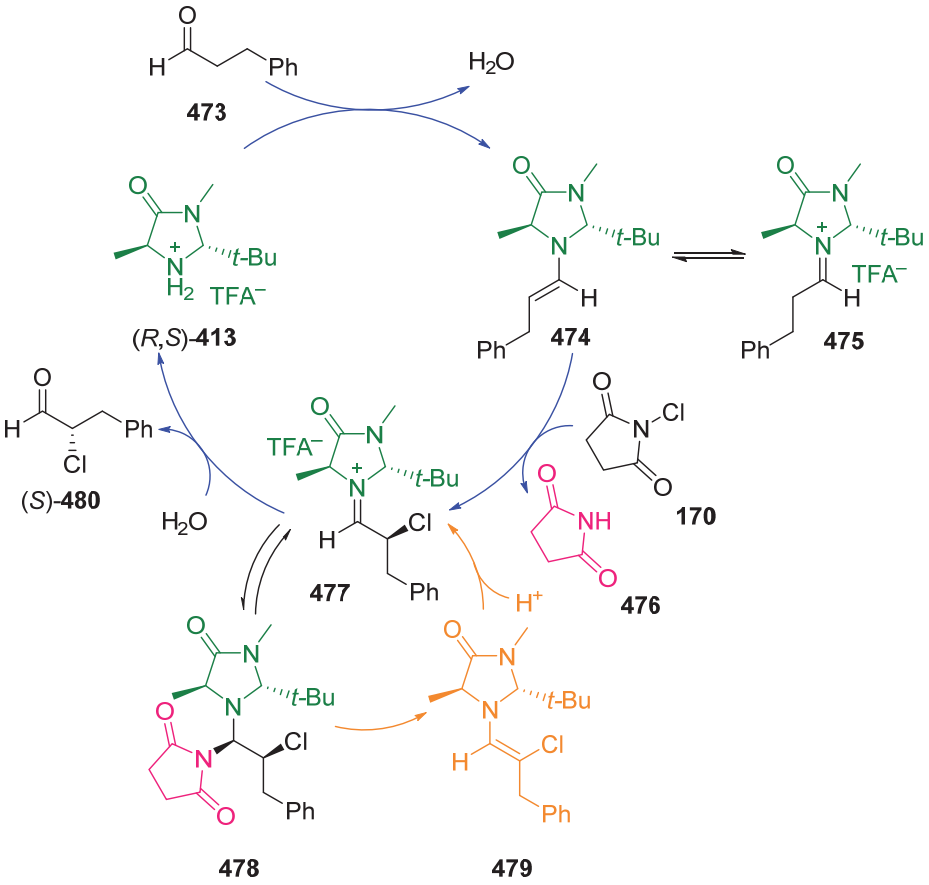
The one-pot sequence from (±)-**167a** to acid (2*R*,4*RS*)-**470**, using quinone **463** as the Cl^+-source in the α-chlorination, was also successful, based on the reaction mixture ^1H NMR spectrum. However, after the reaction was quenched with Na_2SO_3 and worked up, the double bond of (2*R*,4*RS*)-**470** was deemed to be gone, suggesting that either it got reduced or a sulphite-adduct **472** formed when Na_2SO_3 was added.[230]

We gave this reaction sequence yet another try by doing the chlorination with NCS, followed by Pinnick oxidation, without quenching the reaction when it was finished. The reactions gave the desired acid (2*R*,4*RS*)-**470**, although a noticeable amount of side products could be seen in the double bond region of the crude ^1H NMR spectrum. Nevertheless, to get an idea of the overall yield, we treated the crude acid with $TMSCHN_2$ to make the ester derivative (2*R*,4*RS*)-**471**, which would make the purification more facile. The yield of the sequence was really poor, 26% with impurities, meaning that we had to abandon this procedure.

It was evident that more efforts were needed in order to develop the α-chlorination/oxidation/methylation sequence starting from aldehyde (±)-**167a**. As the reactions worked well with (±)-**455**, we continued with this approach. Moreover, it could have been possible to improve the *dr* of the α-chlorination reaction by screening a set of different enamine catalysts, but we prioritised the development of the total synthesis route and decided to move on.

After some time had passed from our chlorination attempts, the group of Christmann published a mechanistic study about the α-chlorination with NCS

and challenges related to the practical use of the method.[119] The findings of the study were based on the proposals by Jørgensen[117] and by Blackmond,[118] that, during the reaction, an off-cycle intermediate, e.g. **478**, would form (Scheme 84). Christmann *et al*. managed to confirm this by being able to isolate these parasitic intermediates with several substrates and characterise them, even by means of x-ray crystallography. Changing the catalyst and Cl^+-source and tuning the counter acid suppressed the formation of the above-mentioned species, thus improving the performance of the reaction. These modifications could also make it possible for us to develop a more atom-economical approach to esters **469** and **471**, and we should take these into account in future.



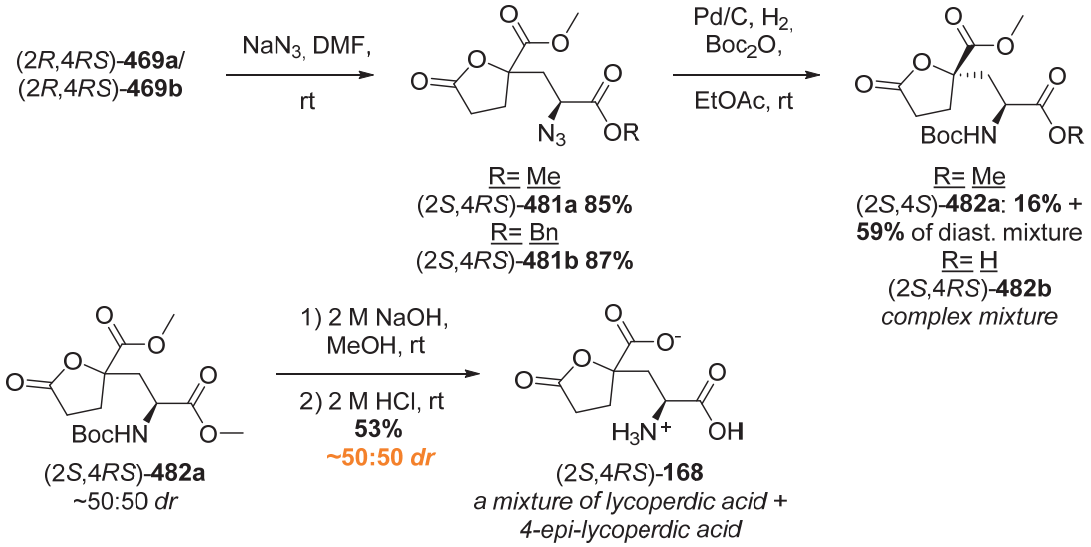
Scheme 84: Catalytic cycle describing the steps of α-chlorination (in blue).[117] The secondary cycle proposed by Blackmond[118] is in orange, the presence of which was ruled out by Christmann.[119]

5.1.3.2 Finalising the route

We continued the synthesis route development with diastereomeric mixtures of (2*R*,4*RS*)-**469a** and (2*R*,4*RS*)-**469b**. First, (2*R*,4*RS*)-**469b** was treated with NaN_3 at 60 °C overnight (Scheme 85).[111] The reaction conditions were too harsh since no clean product could be isolated. When the reaction was let to proceed at room temperature, the desired azide (2*S*,4*RS*)-**481b** was obtained in an 87% yield. Fortunately, azide (2*S*,4*RS*)-**481a** was also synthesised in the same manner, in an 85% yield. Both azides were isolated as mixtures of diastereomers.

We then subjected the azides to a standard hydrogenolysis–Boc-protection sequence (Scheme 85). With the azide (2*S*,4*S*)-4**81b**, the result was only a complex mixture. With (2*S*,4*RS*)-**481a**, we were able to get the desired diastereomer (2*S*,4*S*)-**482a** in a 16% isolated yield, along with a diastereomer mixture in a 59% yield. To our delight, more of the desired diastereomer could be isolated after repeated chromatographic purifications.

We conducted the first end-game studies and followed the general deprotection protocols of the previous total syntheses (Scheme 85). Deprotection with 6 M HCl at 50 °C removed the Boc group, but left the esters intact: the esters got hydrolysed only after refluxing the reaction mixture.[211,212] We were also able to remove the protecting groups by first saponifying the esters under basic conditions and then cleaving off the Boc group with 2 M HCl at room temperature.[215] The last obstacle was the ion exchange chromatography. After several attempts, we managed to get a 53% yield of a ~50:50-mixture of (+)-**168** and its diastereomer 4-*epi*-**168** when a ~50:50-mixture of (2*S*,4*RS*)-**482a** was used as a starting material.

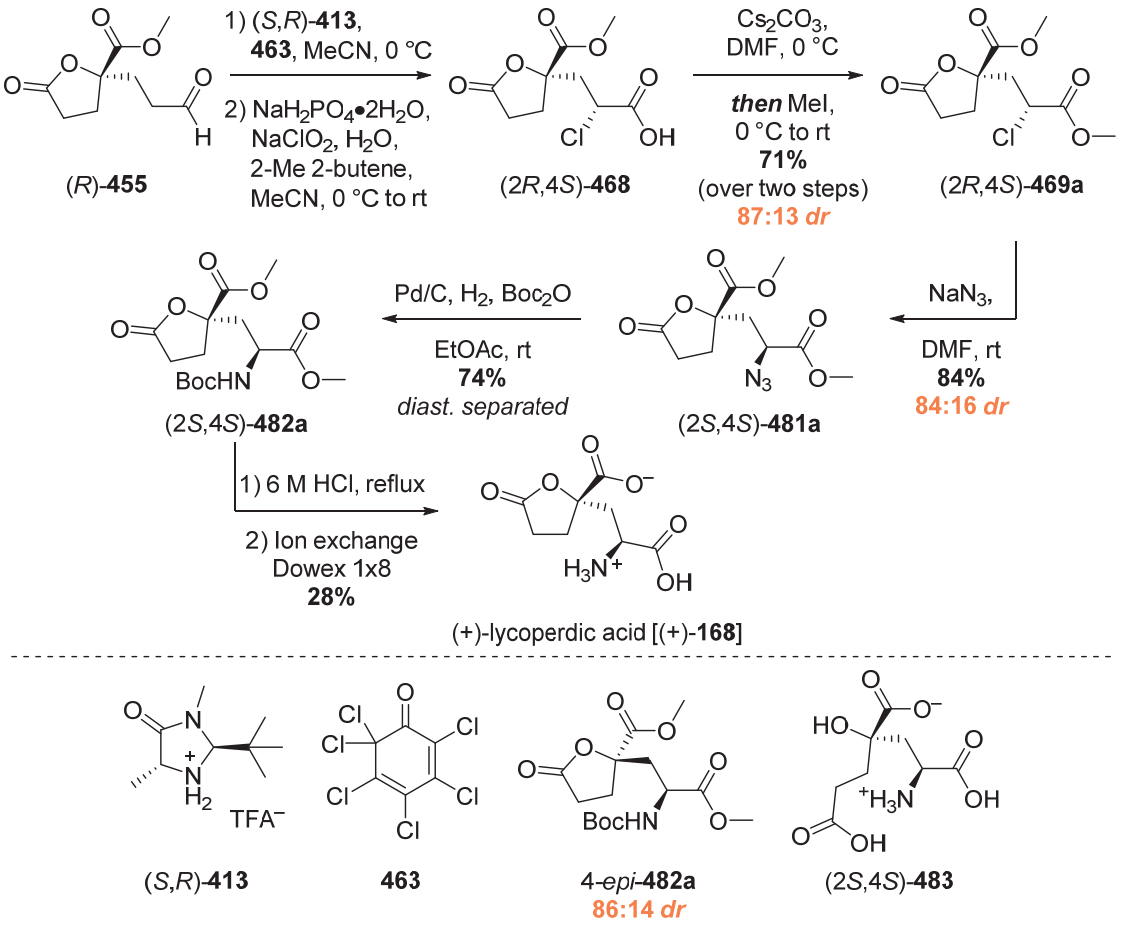


Scheme 85: Finalising the total synthesis route.

Encouraged by the great results, the stage was now set for the diastereoenriched synthesis of (+)-**168**. Starting from enantioenriched (*R*)-**455**, we synthesised the α-chloroester (2*R*,4*S*)-**469a** in a 71% yield over two steps with fine diastereoselectivity (*dr* 87:13, Scheme 86). We converted the diester to azide (2*S*,4*S*)-**481a** *via* the above-presented S_N2-reaction in an 84% yield and, finally, to the fully protected natural product (2*S*,4*S*)-**482a** in a 74% yield. In addition, we isolated a diastereomer mixture of (2*S*,4*S*)-**482a** and 4-*epi*-**482a** in a 9% yield with an 86:14 *dr*, 4-*epi*-**482a** being the major component.

We first saponified the diastereomerically pure (2*S*,4*S*)-**482a**, after which, we removed the Boc protection under acidic conditions (Scheme 86). To our disappointment, the basic treatment led to epimerisation of the C2 stereocenter, which was not detectable in our studies with the diastereomeric mixture earlier. However, the epimerisation did not occur when we refluxed (2*S*,4*S*)-**482a** in 6 M

HCl. After ion exchange chromatography, we got the crude (+)-**168**, along with few impurities, such as hydroxyl acid (2*S*,4*S*)-**483**. Recrystallisation twice from water gave the analytically pure sample of (+)-**168** in a 28% yield. It was noteworthy that the hydroxyl acid (2*S*,4*S*)-**483** could not be converted back to the lactone in refluxing benzene because of a side product formation.



Scheme 86: Finalising the route with enantioenriched aldehyde (*R*)-**455.**

5.2 Outlook and conclusions

We were able to develop an enantioselective total synthesis route for (+)-lycoperdic acid. The route utilised an organocatalytic Mukaiyama–Michael reaction between a silyloxyfuran **165a** and acrolein (**166**) as the key transformation, which was earlier developed by us. We were able to synthesise both the tertiary oxygen-containing C4 stereocenter with a 94:6 *er* and the full carbon core of the targeted natural product with this reaction.

We used an organocatalytic α-chlorination reaction in the diastereoselective construction of the amino acid moiety, i.e. the secondary amine-containing C2 stereocenter. The reaction was catalysed by MacMillan imidazolidinone (*S*,*R*)-**413**, while the perchlorinated quinone **463** acted as the Cl^+-source. One-

pot oxidation and a subsequent methylation provided the diester (2*R*,4*S*)-**469a** in excellent yield, the *dr* being 87:13.

Displacement of the chloride by an azide anion, hydrogenolysis and hydrolysis, afforded the desired natural product (+)-**168**. The synthesis route was thus seven steps long from the known silyloxyfuran **165a** and nine steps from a commercially available furanone **409**. The route was thus of average length compared to other published total synthesis routes of (+)-**168**. No chiral pool or auxiliaries were used, and the synthesis of the both stereocenters could be controlled by organocatalytic means. The step count could, in principle, be lowered by one step if both the α-chlorination/oxidation/methylation sequence could be conducted straight to aldehyde (*R*)-**167a** and a conjugate addition to the double bond of the furanone moiety by azide anion could be avoided.

The developed synthesis route includes modular intermediates, which could be used in the synthesis of various derivatives of (+)-lycoperdic acid. These compounds could be used in biological studies to see whether they are able to bind to target biomolecules. Such targets could be, for example, ionotropic glutamate receptors because of the structural similarities between (+)-**168**, L-glutamic acid ((*S*)-**437**) and (–)-dysiherbaine ((–)-**396**). At best, this could give important information about the structure-activity relationships of the prepared compounds and the function of the target biomolecule. This, in turn, would make it possible to develop more potent compounds, which ideally could be used as therapeutic agents to cure neurological diseases.[210] The modular intermediates could also diverge to novel synthesis routes for other targets. These could containing, even partially, the core structure of **167** or the oxygen-containing tertiary stereocenter. Some of the suitable molecules were already presented in Scheme 65, (+)-phorbic acid ((+)-**403**) and (–)-**396** being a couple of them.

6 ADDITIONAL TEST REACTIONS RELATED TO 2,5-DIARYLPYRROLIDINE SYNTHESIS AND THE STUDIED MUKAIYAMA–MICHAEL REACTION

6.1 Reduction of the diketones

During the 2,5-diarylpyrrolidine synthesis studies, we distinguished one clear target of improvement. The formation of the unwanted *meso*-isomers during the asymmetric CBS reduction should be suppressed in order to avoid cumbersome chromatographical separations of diastereomers. A change to another enantioselective method could possibly solve the problem. Instead of screening through the existing literature procedures, we tried to solve the diastereoselectivity problem using a novel strategy *via* enzymatic catalysis, using commercially available Codexis ketoreductases (KREDs). Enzymatic reduction would offer a way to avoid air- and moisture-sensitive reagents and transition metals.

We chose two substrates for the initial studies, namely diketones **34a** and **34b**. One of the reasons for the choice was that the pyrrolidine catalysts **31a** and **31i**, derived from **34a** and **34b**, have created the most interest in our group for the time being and optimising the associated synthesis routes has been important. **34a** also serves as a substrate lacking bulky substituents, causing less sterical clash in the active site of the enzyme.

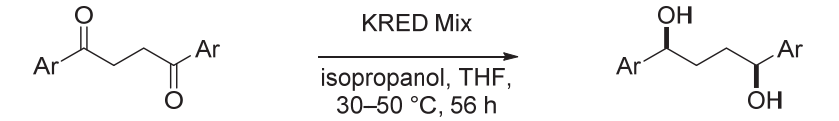
The first screening studies showed that some of the enzymes were able to catalyse the asymmetric reduction reaction of **34a** to **55a** (Table 15, entries 1-5). Enzymes P1-B02, P1-B12, P1-B10, P2-D11 and P2-D03 provided the most promising-looking results. The stereoselectivities were brilliant, as the amount of *meso*-diol **55a** or the minor enantiomer could hardly be detected on HPLC. Enzyme P2-D03 provided an interesting result: even though the *dr* was only 72:28, the *er* was 95:5 and the sense of enantioselectivity of the reaction was reversed compared with the other enzymes (Table 15, entry 5). Three of the reactions showed a full consumption of the starting material based on TLC, but only after we prolonged the reaction time to 56 hours and applied conditions known to

shift the equilibrium of the reaction towards the product. These included increasing the amounts of isopropanol and cofactor and raising the temperature from 30 °C to 50 °C.

Unfortunately, the CF_3-substituted diketone **34b** was inert to the reduction (Table 15, entry 6). Neither the addition of isopropanol and the cofactors nor raising the reaction temperature from 30 °C to 50 °C started the reduction reaction. This suggested that either the substrate was too bulky to fit into the active sites of the enzymes or the CF_3-groups formed unfavourable weak interactions with the amino acids of the active sites. However, the amino acid sequences and the detailed structures of the enzymes are unknown, making the reasoning of the outcome rather speculative.

We were ready to begin a more thorough research on the reaction conditions and conduct accurate quantitative reaction monitoring for the reduction of **34a** to **55a**. Before we had the chance to continue, Gotor-Fernández and coworkers published a paper, in which both commercially available Codexis enzymes and in-house-developed ketoreductases were used in the stereoselective 1,4-diketone reductions.[231] They also got excellent results with the abovementioned enzymes, as well as with their own enzymes. They were mainly able to reduce some *para*-substituted diketones, having problems in reactivity with *ortho*- and *meta*-substituted ones. Despite the reactivity problems, hopefully, these results will inspire researchers to develop efficient ketoreductases, which one day, can be used in a robust stereoselective enzyme-catalysed synthesis of chiral 1,4-diols despite the sterical and electronical factors of the substrate.

Table 15: Enzymatic reductions of diketones **34a** and **34b**.



34a: Ar= Ph
34b: Ar= 3,5-$(CF_3)_2$-Ph

55a: Ar= Ph
55b: Ar= 3,5-$(CF_3)_2$-Ph

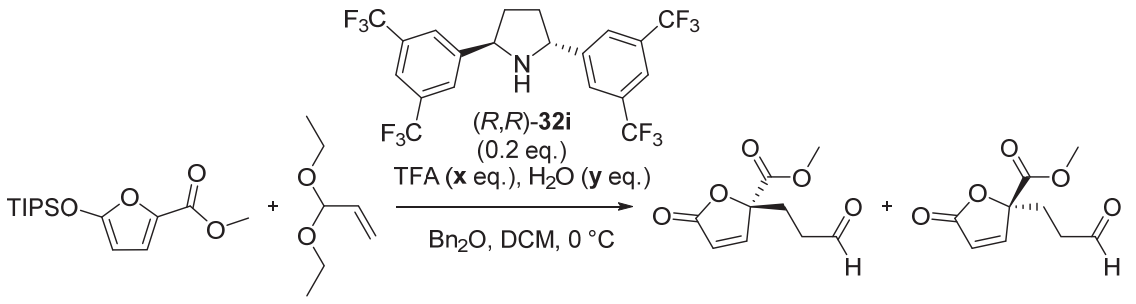
Entry	Substrate	Enzyme	*dr*[a]	*er*[b]
1	**34a**	P1-B02	>99:1	>99:1
2	**34a**	P1-B12	99:1	>99:1
3	**34a**	P1-B10	>99:1	>99:1
4	**34a**	P2-D11	98:2	>99:1
5	**34a**	P2-D03	72:28	5:95
6	**34b**	–	–	–

a) The ratio of (+/-)-**55**:*meso*-**55**, determined by chiral HPLC. b) The ratio between the major and minor enantiomers (stereochemistry of the major was not determined).

6.2 Mukaiyama–Michael reaction

Further changes in the studied Mukaiyama–Michael reaction rose from practical aspects. The limitations in the commercial availability of acrolein would be detrimental for the utility of the method in the future, a fact that prompted us to seek an alternative source for the chemical. Luckily, three commercially available options were available: dimethyl and diethyl acetals of acrolein and 2-vinyl-1,3-dioxolane.* We chose acrolein diethyl acetal since ethanol has a higher boiling point (78 °C) than acrolein (53 °C), allowing the distillation of acrolein after acidic deprotection, if necessary.[223,232] In addition, we wanted to try a more novel approach and use the diethyl acetal acrolein as the reagent, hoping it would release acrolein *in situ* to the reaction mixture. This aim supported the selection of diethyl acetal acrolein, which should be faster to hydrolyse than the more stable dioxolane.

Table 16: Mukaiyama–Michael reaction using diethyl acetal acrolein (**484**) as a reagent.



165a **484** (5.0 eq.) (*S*)-**167a** (*R*)-**167a**

Entry	TFA (eq.)	H_2O (eq.)	Time (h)	Conv. (%)[a]	*er*[b]	SM (%)[c]
1	0.2	2.0	17.5	17	–	50
			23	18	–	49
2	0.5	4.0	17.5	39	–	23
			23	40	7:93	23
3	0.5	6.0	17.5	45	–	19
			23	54	10:90	16
4	0.5	7.5	20	45	11:89	21

a) Conversion from starting material to product. b) *er* corresponds to the ratio of (*S*)-**167a**:(*R*)-**167a**. c) The amount of **165a** left after the specified time.

We used the same reaction conditions as in the "regular" reaction with acrolein, which should have released a maximum of two equivalents of acrolein in theory. As was anticipated, the reaction did not proceed well and resulted only in an 18% conversion within 23 hours (Table 16, entry 1). Doubling the amount of water to 4.0 equivalents and adding 0.5 equivalents of TFA was beneficial for

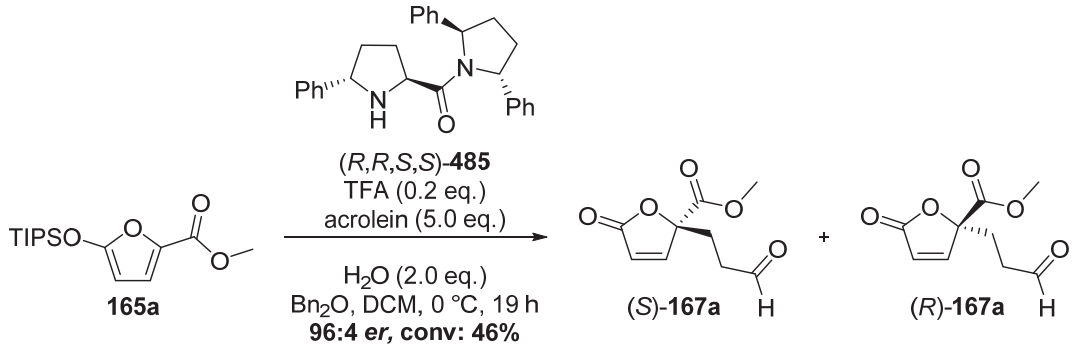
* Available in Merck (Sigma Aldrich) and TCI Europe.

the reaction. After 17.5 hours, the conversion had already risen to 39%, the enantioselectivity of the reaction being on the usual level (93:7 *er*). However, the reaction ceased to this level, leaving 23% of unreacted starting material (Table 16, entry 2).

Increasing the amount of water to 6.0 and 7.5 equivalents improved the conversion to 54% and 45%, respectively, but unreacted starting material still remained (Table 16, entries 3–4). Moreover, the addition of water lowered the enantioselectivity of the reaction: the *er*'s sunk to 90:10 and 89:11, suggesting that an acid-catalysed reaction was hampering the catalyst-controlled reaction.

There were at least two possible reasons for the lower efficiency of the reactions compared with the ones with acrolein. Ethanol was not able to participate in the silyl-group scavenging as efficiently as water, a fact that MacMillan and co-workers also brought up in their seminal Mukaiyama–Michael paper.[188] Ethanol could have also taken part in the formation of off-cycle hemiaminals, which trapped the catalyst and slowed down the progress of the reaction (see the catalytic cycle in Chapter 4, Scheme 69). We did not have time to examine the reaction more thoroughly, but the results looked promising, and with a bit of optimisation, diethyl acetal acrolein could most probably be used in the Mukaiyama–Michael reaction without the need for prehydrolysis and distillation.

In addition to the alternative acrolein source studies, we tested yet another type of catalyst that we had in stock, namely, the pyrrolidine (*R*,*R*,*S*,*S*)-**485**, an amide generated from (2*R*,5*R*)-2,5-diphenylpyrrolidine and pyroglutamic-acid-derived 5-phenylpyrrolidine (Scheme 87).[37] To our great surprise, the reaction gave (*S*)-**167a** with a 96:4 *er*, being the best result thus far. The conversion was also acceptable, 46% within 19 hours. Getting this result at this phase of the project felt bittersweet, but it nicely opened new avenues for the future iminium-ion catalysts. Needless to say, enhancing the *er* towards 99:1 would again require a whole set of new catalysts with differently substituted aryls.



Scheme 87: A Mukaiyama–Michael reaction test with a new type of pyrrolidine catalyst (*R*,*R*,*S*,*S*)-**485**.

6.3 Conclusions

As a solution for a diastereoselectivity problem encountered in the synthesis of 2,5-diarylpyrrolidine catalysts, we tried to develop an enzyme-catalysed reduction reaction of 1,4-diarylbutane-1,4-diones. We managed to find commercially available enzymes that showed promising results with one of our diketone-substrates. However, the subject was more popular than we had thought, and while our studies were still in progress, another research group had already published the method[231], which forced us to abandon the project.

We also managed to begin a research for substitutive conditions for the studied Mukaiyama–Michael reaction due to limitations related to the reagent acrolein. We got encouraging results from the initial tests with diethyl acetal acrolein, but due to limitations in time, we were forced to cease the work for now. The same time-related reason made us postpone another catalyst-development campaign, which would be based on the most enantioselective catalyst found just before crossing the finish line of this dissertation.

7 SUMMARY OF THE THESIS

Pyrrolidines are five-membered nitrogen-containing ring systems, which are widely seen in organic-chemistry-related subjects. Especially 2,5-diarylpyrrolidines and pyroglutamic-acid-derived 2-diarylmethyl-5-aryl- are interesting pyrrolidines, which have been used in asymmetric synthesis. In the early examples, *trans*-2,5-diphenylpyrrolidine was used as a chiral auxiliary in various methods, but lately, both pyrrolidine types have found their way to enantioselective organocatalysis. They have also been used in transition-metal-catalysed asymmetric reactions as a part of the metal-coordinating ligand.

Several synthesis routes for 2,5-diarylpyrrolidines, both stereoselective and racemic, have been published over the years. Two of them have been dominantly used: one relies on asymmetric reduction and S_N2 cascade reaction, while the other uses an asymmetric deprotonation/transmetalation/Negishi coupling sequence. In the case of the more novel pyroglutamic-acid-derived 2-diarylmethyl-5-aryl-pyrrolidines, few routes have been published, all of them originating from the chiral pool molecule pyroglutamic acid.

As was seen in the case of the studied Mukaiyama–Michael reaction, novel modular catalysts are always needed because even the most popular catalysts are not universal. Delightfully, we were able to find two modular pyrrolidine core leads, which were suitable for our reaction.

We were able to vary the electronics of the catalyst by substituent changes and, thus, study the demands of the ideal catalyst. However, modern computational methods and knowledge from physical organic chemistry should be used along with the experimental work to guide the catalyst-development campaigns to both shed light on the problem and get more value for the scientific work. In future, we will hopefully see the studied Mukaiyama–Michael reaction developed even further and used in many asymmetric synthesis routes, as the core of the product aldehyde is easily derivatisable.

Quite often, the utility of a newly developed method is demonstrated by using it in a synthesis route towards a chosen target. In our case, we chose a non-proteinogenic amino acid called (+)-lycoperdic acid. In our case, most of the route scouting was done with racemic and diastereomer mixtures of com-

pounds. On one hand, with this strategy, it was possible to screen with inexpensive substrates compared with the enantioenriched or diastereomerically pure compounds, and the robustness of the diastereomeric separations could be readily tested. On the other hand, due to the diastereomeric mixture approach, we missed the occurrence of epimerisation in the initial end-game studies. In addition, due to the possible differences in the reactivity between the enantiomers, we spent too much time on things that would not have caused problems with enantio- or diastereoenriched material in the first place, referring to the initial α-chlorination studies. However, we were able to finish a total synthesis of (+)-lycoperdic acid using a novel enantioselective route where the stereochemical control was based on organocatalysed reactions.

8 EXPERIMENTAL SECTION

8.1 General Information

All reactions were carried out under an argon atmosphere in flame-dried or oven-dried glassware. When needed, nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. THF, MeCN, Et_2O, toluene and CH_2Cl_2 were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). DMF was distilled over CaH_2 and stored over molecular sieves under argon. Pd/C was washed with acetone prior usage. TIPSOTf was prepared with Corey's procedure.[233] Furan-2(5*H*)-one (**409**) was prepared with Näsman's procedure.[191] *sec*-BuLi was titrated before each use (CAUTION: *sec*-BuLi is pyrophoric and its handling requires proper air and moisture sensitive techniques). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (*6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH*), ninhydrin (*0.3 g of ninhydrin, 100 mL of EtOH, 2 mL of AcOH*) or $KMnO_4$ solution (*1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1M NaOH, 100 mL H_2O*). For silica gel chromatography, the flash chromatography technique with Merck silica gel 60 (230-400 mesh) and CombiFlash Rf 200 with Redisep Gold columns (20–40 μm spherical silica, 400–632 mesh) were used. Deactivated silica gel for chromatography was prepared prior to use by adding Et_3N (~1% by weight) into a slush of silica and hexane. The slush was stirred, filtered, and the silica gel was allowed to dry in air.

All solvents were HPLC and p.a. grade unless otherwise noted. Degassing of solvents was carried out either by purging with argon gas for at least 30 min or by 3-5 freeze-thaw cycles (for H_2O). Dowex 1X8–400 ion exchange resin was converted from chloride form first to hydroxide form using 2M NaOH and finally to acetate form with 2M acetic acid according to the manufacturer's protocol.

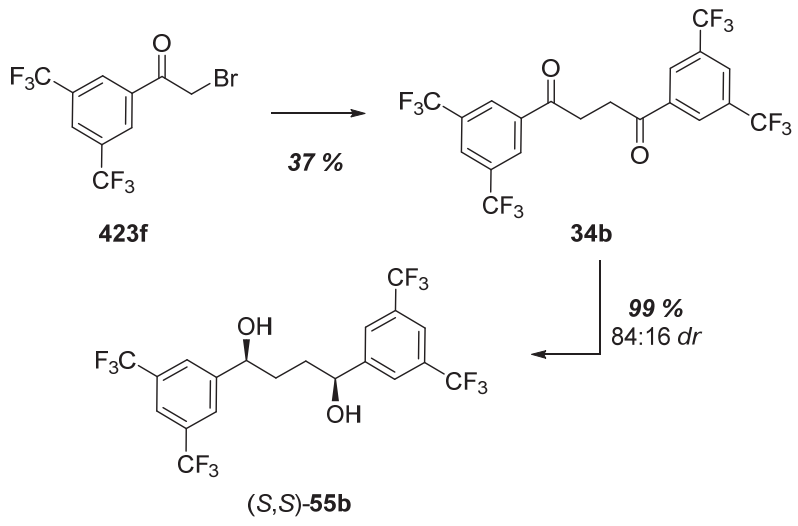
The ^{1}H NMR and ^{13}C NMR spectra were recorded in either $CDCl_3$, CD_2Cl_2, CD_3CN, $(CD_3)_2CO$, $(CD_3)_2SO$ or CD_3OD on Bruker Avance 500, 400 or 300 MHz spectrometers. The chemical shifts were reported in ppm relative to[234] $CHCl_3$ (δ 7.26), $CDHCl_2$ (δ 5.32), CHD_2CN (δ 1.94), CD_3CD_2HCO (δ 2.05), CD_3CD_2HSO (δ 2.50) or CHD_2OD (δ 3.31) for ^{1}H NMR. For the ^{13}C NMR spectra, $CDCl_3$ (δ 77.16), CD_2Cl_2 (δ 53.84), CD_3CN (δ 118.26), $(CD_3)_2CO$ (δ 29.84), $(CD_3)_2SO$ (δ 39.52) or CD_3OD (δ 49.00) were used as the internal standards. The enantiomeric ratios (*er*) of the compounds were determined in comparison to the corresponding racemic samples by HPLC using Waters 501 pump and Waters 486 detector or Agilent Technologies 7820A GC with SUPELCO Astec CHIRALDEX B-DM column. Melting points (mp) were determined in open capillaries using Stuart melting point apparatus. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. High resolution mass spectrometric data were measured using MicroMass LCT Premier Spectrometer or Agilent Technologies 6560 Ion Mobility ESI-Q-TOF LC/MS.

Single X-ray crystallography structural data for the compounds were collected with Agilent Supernova diffractometer equipped with Eos CCD detector, using mirror-monochromatised MoKα radiation (λ=0.71073 Å) and Agilent Supernova diffractometer equipped with Atlas CCD detector using mirror-monochromatised CuKα radiation (λ=1.5418 Å). The data reduction and absorption correction were made by program CrysalisPro[235]. The structures were solved by using either Superflip[236–238] charge flipping method or SHELXT[239] intrinsic phasing method, in OleX2[240], and refined with SHELXL[241] least squares method. The structures were drawn with ORTEP-3[242] showing thermal ellipsoids at 50% probability level. Crystallographic data of the structure CSD-MULBED can be obtained free of charge from the Cambridge Crystallographic Data Centre[167] *via* www.ccdc.cam.ac.uk/structures.

The syntheses of diarylpyrrolidines (*S*,*S*)-**31a**, (*S*,*S*)-**31l**, (*S*,*S*)-**31m** (*S*,*S*)-**31p**, pyroglutamic-acid-derived pyrrolidines (*S*,*S*)-**32a–d**, (*S*,*S*)-**32i–n**, amide catalyst (*R*,*R*,*S*,*S*)-**485** and catalyst (*S*,*R*)-**413** can be found from literature.[36,37,56,57,243] The MacMillan imidazolidinone (*S*,*S*)-**404** and diarylprolinol (*S*)-**30** were commercially available.

8.2 Synthesis of catalysts

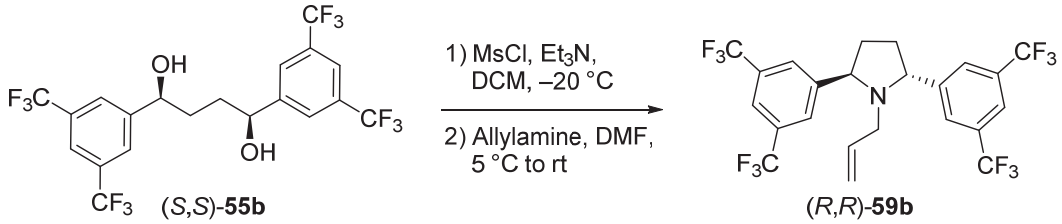
8.2.1 (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidine catalyst [(*R*,*R*)-31i]



Chem. Eur. J. **2014**, *20*, 5983–5993

In the synthesis of diol (*S*,*S*)-**55b**, a synthesis route of Pihko *et al.* was followed.[56] The *dr* of the (*S*,*S*)-**55b** was estimated from the ^{13}C spectrum integrating the signals at 73.4 ppm (*meso*-**55b**) and 73.0 ppm ((*S*,*S*)-**55b**).

8.2.1.1 (2*R*,5*R*)-1-allyl-2,5-bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidine [(*R*,*R*)-59b]



To a stirred slurry of diol (*S*,*S*)-**55b** (3.99 g, 7.76 mmol, 1.0 equiv) in DCM (75 mL) at –20 °C was added Et_3N (3.3 mL, 23.4 mmol, 3.0 equiv), followed by dropwise addition of MsCl (1.8 mL, 23.2 mmol, 3.0 equiv). After 3.5 h, 15 mL of sat. aq. NH_4Cl and H_2O (60 mL) were added. The mixture was extracted with DCM (30 mL) and the organic layer was dried (Na_2SO_4), filtered and concentrated to give the crude dimesylate (*S*,*S*)-**428c** which was used immediately in the next step without further purification.

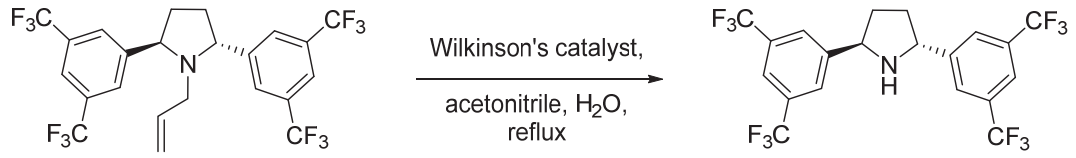
To a stirred solution of the crude dimesylate (*S*,*S*)-**428c** in DMF (11.0 mL) at 5 °C was added allylamine (9.0 mL, 120 mmol, 15 equiv). After the completion of the addition, the reaction mixture was allowed to warm to rt slowly along with the cooling bath. After 42 h, DCM (60 mL) and water (30 mL) were added. The layers were separated and the organic phase was washed with water (30 mL), sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). The combined aqueous phases were

back-extracted with DCM (2x30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated and the crude filtered through a plug of silica (3x10 cm, eluting with EtOAc-hexane 0:100 to 50:50). The product containing fractions were purified by CombiFlash chromatography (initial elution with 100% hexane) giving the desired *trans*-diastereomer (*R*,*R*)-**59b** (2.89 g, 5.40 mmol, 70%) as clear oil which solidified later after a freeze-thaw cycle in vacuum. In addition, *cis*-**59b** was isolated after elution with 50:50 EtOAc-hexane (728 mg, 1.36 mmol, 18%). Both diastereomers were clear oils, which solidified after freezing them and keeping under vacuum.

trans-pyrrolidine (*R*,*R*)-**59b**:
mp 47–48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (s, 2H), 7.77 (s, 4H), 5.61 (dddd, *J* = 17.4 Hz, 10.0 Hz, 7.5 Hz, 4.4 Hz, 1H), 5.00 (d, *J* = 9.8 Hz, 1H), 4.85 (dd, *J* = 17.3 Hz, 0.9 Hz, 1H), 4.56–4.48 (m, 2H), 3.01 (ddt, *J* = 14.6 Hz, 4.1 Hz, 2.0 Hz, 1H), 2.74 (dd, *J* = 14.7 Hz, 7.6 Hz, 1H), 2.69–2.54 (m, 2H), 2.02–1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 135.3, 131.9 (q, *J* = 33.2 Hz), 127.8 (m), 123.5 (q, *J* = 272.8 Hz), 121.4 (sept, *J* = 3.6 Hz), 117.3, 65.4, 50.4, 33.2.
Spectral data matches the data reported in literature.[56]

cis-**59b**:
R_f (EtOAc-hexane 6:94)= 0.46; IR (film, cm^{-1}): 1379, 1339, 1312, 1162, 1120, 893, 839, 706, 681; mp 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 4H), 7.81 (s, 2H), 5.62 (ddt, *J* = 17.0 Hz, 10.1 Hz, 6.9 Hz, 1H), 4.99–4.90 (m, 2H, *two overlapping signals*), 4.15–4.06 (m, 2H), 3.12 (d, *J* = 6.9 Hz, 2H), 2.45–2.28 (m, 2H), 1.93–1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 133.1, 132.1 (q, *J* = 33.2 Hz), 127.5 (app. d, *J* = 2.7 Hz), 123.6 (q, *J* = 272.6 Hz), 121.4 (sept, *J* = 3.8 Hz), 118.8, 66.8, 54.3, 34.5; HRMS (ESI$^+$): m/z calculated for $[C_{23}H_{17}F_{12}N_1H_1]^+$ = 536.1242, found 536.1233, Δ= 1.7 ppm.

8.2.1.2 (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidine [(*R*,*R*)-31i]



(*R*,*R*)-**59b** (*R*,*R*)-**31i**

A solution of *trans*-pyrrolidine (*R*,*R*)-**59b** (2.89 g, 5.40 mmol, 1.0 equiv) and Wilkinson's catalyst (0.250 g, 0.270 mmol, 0.05 equiv.) in acetonitrile (21.0 mL) and water (4.0 mL) was purged with argon for 30 min. The reaction mixture was heated to reflux for 14 h, and then allowed to cool to rt. Et_2O (60 mL) and brine (60 mL) were added and the aqueous phase was extracted with Et_2O (3x60 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was first purified by column chromatography after which the product-containing fractions were recrystallised twice from DCM-hexane. The

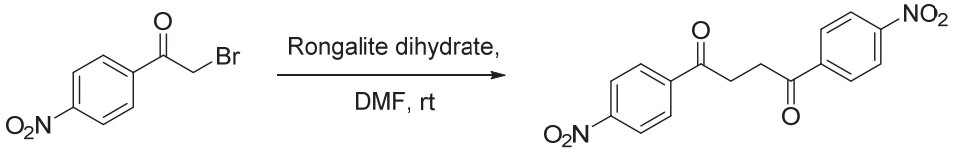
solid, impure (*R*,*R*)-**31i** was further purified by CombiFlash chromatography, giving 1.48 g of pure (*R*,*R*)-**31i.**

The mother liquors from recrystallisation (m= 1.08 g) contained mostly starting material (*R*,*R*)-**59b**. This material was resubjected to the reaction conditions as described above and purified by CombiFlash to give 0.948 g of (*R*,*R*)-**31i** (total yield of (*R*,*R*)-**31i**: 2.43 g, 4.90 mmol, 91%, *er* 99:1). The *er* was determined by ^{1}H NMR from the corresponding phosphoramidite derivatives (for details, see subsection 8.3.1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 4H), 7.79 (s, 2H), 4.72 (t, *J* = 6.6 Hz, 2H), 2.59–2.43 (m, 2H), 2.11 (brs, 1H), 1.98–1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 132.1 (q, *J* = 33.2 Hz), 126.7 (app. d, *J* = 2.5 Hz), 123.6 (q, *J* = 272.6 Hz), 121.3 (sept, *J* = 3.7 Hz), 61.7, 35.6.
Spectral data matches the data reported in the literature.[56]

8.2.2 (2*R*,5*R*)-2,5-bis(4-nitrophenyl)pyrrolidine catalyst [(*R*,*R*)-31k]

8.2.2.1 1,4-bis(4-nitrophenyl)butane-1,4-dione (34d)

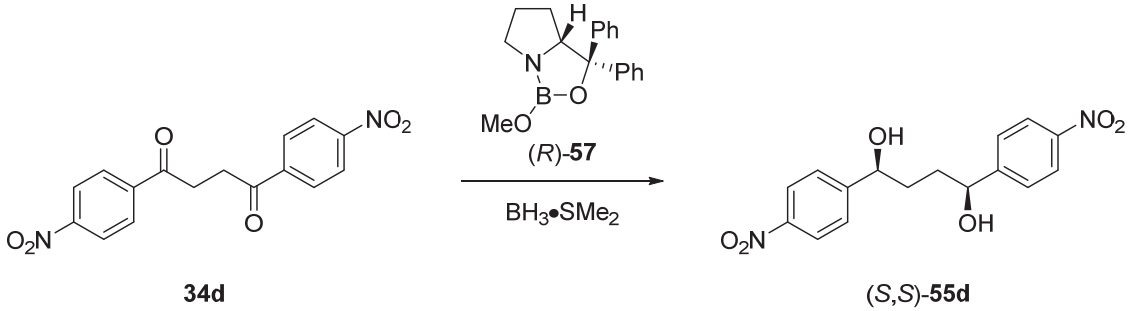


423a **34d**

A mixture of 2-bromo-1-(4-nitrophenyl)ethan-1-one (**423a**, 3.01 g, 12.3 mmol, 1.0 equiv), sodium hydroxymethanesulfinate dihydrate (Rongalite, 2.02 g, 13.1 mmol, 1.1 equiv) in DMF (8.0 mL) was stirred at rt for 69 h. Water (10 mL) was then added. The mixture was filtered through a sintered glass filter and the solid residue was washed with water (3 x 5 mL). The remaining residue was then washed successively with DCM (2 x 25 mL), then with EtOAc (25 mL), $CHCl_3$ (20 mL) and again with DCM (20 mL) to dissolve the remaining residue. The extracts were each dried (Na_2SO_4), analysed by TLC, filtered and concentrated. The extracts containing pure **34d** were pooled and concentrated, and the impure fractions were combined, concentrated, and the residue was purified by flash chromatography (EtOAc/hexane gradient from 20:80 to 100:0) to give the product **34d** as an off-white solid (1.12 g, 3.42 mmol, 55%).

R_f (EtOAc-hexane 40:60) = 0.40; IR (film, cm^{-1}): 2919, 1683, 1603, 1517, 1342, 1318, 1220, 996, 848, 737; mp 197–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38–8.33 (m, 4H), 8.21–8.17 (m, 4H), 3.53 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 150.7, 141.1, 129.3, 124.1, 33.2; HRMS (ESI$^-$): m/z calculated for $[C_{16}H_{11}N_2O_6]^-$ = 327.0623, found 327.0610, Δ= 4.0 ppm.

8.2.2.2 (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diol [(*S*,*S*)-55d]



34d (*S*,*S*)-**55d**

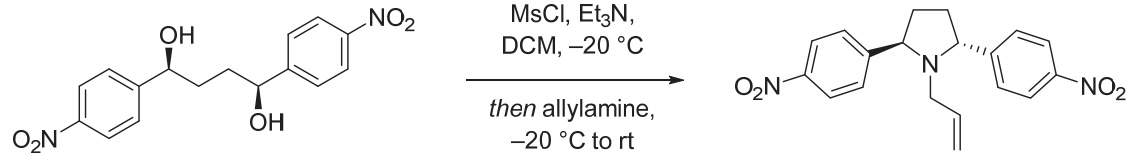
To a solution of (*R*)-2-(diphenylhydroxymethyl)pyrrolidine (0.110 g, 0.431 mmol, 0.20 equiv) in THF (2.6 mL) was added $B(OMe)_3$ (61 µL, 540 µmol, 0.25 equiv). The mixture was stirred for 1.5 h, and borane dimethylsulfide complex (0.51 mL, 5.11 mmol, 2.4 equiv) was added (*CAUTION: H_2 evolution*). A solution of diketone **34d** (0.708 g, 2.16 mmol, 1.0 equiv) was then dissolved in THF (49 mL) and the solution added to the reaction flask dropwise during ~40 minutes. After 16 h, the reaction was quenched with 2 M HCl (8 mL) until the gas evolution ceased (*CAUTION: H_2 evolution*). The reaction mixture was concentrated in vacuum and the residue was filtered through a glass sintered funnel and washed with EtOAc (50 mL). The filtrate was washed with H_2O (20 mL), the water phase extracted with EtOAc (2 x 10 mL), organics were combined, washed with brine (25 mL) and sat. aq. $NaHCO_3$ (25 mL) and finally dried with Na_2SO_4. After filtration and evaporation of the solvents, the crude was purified by flash chromatography (EtOAc-hexane gradient from 50:50 to 100:0) to give the diol (*S*,*S*)-**55d** as an off-white solid (0.639 g, 1.92 mmol, 89%).

R_f (EtOAc-hexane 60:40)= 0.39; IR (film, cm^{-1}): 3516, 2929, 1599, 1509, 1342, 1234, 1194, 1105, 1055, 1020, 1011, 847, 814, 765, 698, 530, 515, 496, 425; mp 167–169 °C; $[\alpha]_D$=–21.5 (*c* 1.0 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 8.21–8.16 (m, 4H), 7.58–7.54 (m, 4H), 4.78–4.75 (m, 2H, *obscured by the HDO/MeOH peak*), 1.91–1.71 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ 154.4, 148.5, 127.9, 124.4, 73.6, 36.1; (*Visible peaks from the minor diastereomer*): δ 154.4, 73.9, 36.3; HRMS (ESI^+): m/z calculated for $[C_{16}H_{16}N_2O_6Na_1]^+$ = 355.0901, found 355.0888, Δ= –3.7 ppm.

The diastereomeric ratio was estimated by integrating the diastereomeric ^{13}C-signals at 73.9 ppm (*minor*) and 73.6 ppm (*major*).

The opposite enantiomer was synthesised in the same manner using (*S*)-**57** as the catalyst with 98% yield. The compound exhibited the same spectral properties, but the optical rotation was opposite in sign: $[\alpha]_D$= +21.9 (*c* 0.98, MeOH).

8.2.2.3 (2*R*,5*R*)-1-allyl-2,5-bis(4-nitrophenyl)pyrrolidine [(*R*,*R*)-59d]



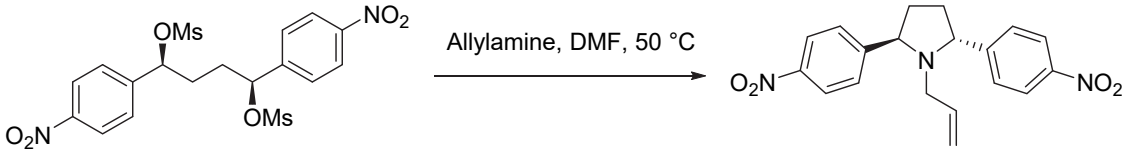
(*S*,*S*)-**55d** (*R*,*R*)-**59d**

A round-bottom flask was charged with diol (*S*,*S*)-**55d** (0.523 g, 1.57 mmol, 1.0 equiv), which was then dissolved in DCM (21 mL) and Et_3N (0.67 mL, 4.76 mmol, 3.0 equiv). The mixture was then cooled down to –20 °C, and MsCl (0.31 mL, 3.97 mmol, 2.5 equiv) was added dropwise. After 1 h, allylamine (12 mL, 0.157 mol, 100 equiv) was added in one portion. The reaction mixture was allowed to warm up to rt slowly along with the cooling bath under the flask. After 39 h, the reaction mixture was concentrated in vacuum. The residue was triturated with DCM (30 mL), filtered through a sintered glass funnel, and the solid residue was washed with DCM (30 mL) to give the unreacted mesylate (*S*,*S*)-**428a** (which was processed separately, see below). The filtrate was washed with H_2O (15 mL), brine (15 mL) and sat. aq. $NaHCO_3$ (15 mL). The combined water phases were extracted with DCM (10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane gradient from 10:90 to 50:50) to give the *trans*-pyrrolidine (*R*,*R*)-**59d** as a yellow solid (92.0 mg, 260 μmol, 17%). In addition, a 16:84-mixture of *trans*:*cis*-diastereomers was isolated (32.9 mg, 93.1 μmol, 6%).

trans-pyrrolidine (*R*,*R*)-**59d**:
R_f (EtOAc-hexane 40:60)= 0.64; IR (film, cm^{-1}): 2826, 1593, 1511, 1342, 1187, 1105, 1001, 942, 845, 789, 748, 696; mp 99–100 °C; $[\alpha]_D$= +143.8 (*c* 1.0 DCM); ^1H NMR (300 MHz, $CDCl_3$): δ 8.23–8.19 (m, 4H), 7.50–7.46 (m, 4H), 5.61 (dddd, *J* = 17.3 Hz, 10.1 Hz, 7.3 Hz, 4.4 Hz, 1H), 4.96 (app. dd, *J* = 10.2 Hz, 0.7 Hz, 1H), 4.87 (ddd, *J* = 17.1 Hz, 2.9 Hz, 1.8 Hz, 1H), 4.55–4.47 (m, 2H), 3.02 (ddt, *J* = 14.6 Hz, 4.2 Hz, 2.1 Hz, 1H), 2.82 (dd, *J* = 14.8 Hz, 7.4 Hz, 1H), 2.69–2.51 (m, 2H), 1.98–1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.0, 147.3, 135.6, 128.5, 123.9, 116.9, 65.5, 50.4, 33.2; HRMS (ESI$^+$): m/z calculated for $[C_{19}H_{20}N_2O_6]^+$ = 354.1448, found 354.1436, Δ= 3.4 ppm.

The unreacted dimesylate (*S*,*S*)-**428a** was purified as follows: The crude residue from above was dissolved in acetone and concentrated to afford solid (*S*,*S*)-**428a**. It was washed with hexane and water to give (*S*,*S*)-**428a** as a white solid (0.250 g, 0.512 mmol, 33%), which was used in the next reaction without further purification.

Dimesylate (*S*,*S*)-**428a:**
R_f (EtOAc-hexane 40:60)= 0.22; IR (film, cm^{-1}): 2938, 1523, 1345, 1328, 1168, 907, 862, 852, 696, 569, 520, 511; mp 140–141 °C; ^1H NMR (300 MHz, $(CD_3)_2CO$): δ 8.28 (d, 4H, *J* = 8.8 Hz), 7.76 (d, 4H, *J* = 8.7 Hz), 5.95–5.87 (m, 2H), 3.05 (s, 5.8H), 3.03 (s, 0.2H), 2.31–2.09 (m, 4H, *overlaps with NMR solvent peaks*); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 149.0, 147.2, 128.5, 124.7, 81.5, 38.8, 33.7; HRMS (ESI$^+$): m/z calculated for $[C_{18}H_{20}N_2O_{10}S_2Na_1]^+$= 511.0452, found 511.0453, Δ= –0.5 ppm.

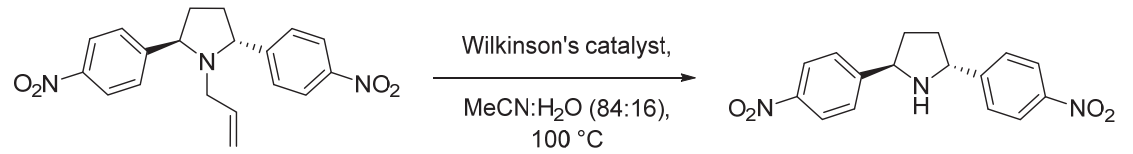


(*S*,*S*)-**428a** (*R*,*R*)-**59d**

Conversion of dimesylate (*S*,*S*)-**428a** to pyrrolidine (*R*,*R*)-**59d**: To a stirred solution of dimesylate (*S*,*S*)-**428a** (100 mg, 0.205 mmol, 1.0 equiv) in DMF (1.0 mL) at rt was added allylamine (0.17 mL, 2.22 mmol, 11 equiv). The reaction mixture was heated to 50 °C. After 17 h, the reaction mixture was concentrated and the residue was dissolved in DCM (10 mL) and washed with H_2O (5 mL), brine (5 mL) and sat. aq. $NaHCO_3$ (5 mL). The combined aqueous phases were back-extracted with DCM (2 x 10 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (EtOAc/pentane 10:90) to give pure *trans*-pyrrolidine (*R*,*R*)-**59d** as a yellowish solid (42.5 mg, 0.120 mmol, 59%) along with a 48:52-mixture of its *trans*:*cis*-diastereomers (16.7 mg, 47.3 µmol, 23%). The spectroscopic data matched with the data reported above.

The opposite enantiomer of (*R*,*R*)-**59d** was similarly synthesised in 51% yield. The compound exhibited the same spectral properties but opposite sign of optical rotation $[\alpha]_D$= –139.5 (*c* 0.98 in DCM).

8.2.2.4 (2*R*,5*R*)-2,5-bis(4-nitrophenyl)pyrrolidine [(*R*,*R*)-31k]



(*R*,*R*)-**59d** (*R*,*R*)-**31k**

A solution of *trans*-pyrrolidine (*R*,*R*)-**59d** (73.9 mg, 0.209 mmol, 1.0 equiv) and Wilkinson's catalyst (19.4 mg, 21.0 µmol, 0.10 equiv) in MeCN:H_2O (2.2 mL, 84:16) was purged with argon for 30 minutes. The reaction mixture was heated to 100 °C with stirring. After 17 h, the reaction mixture was concentrated and the residue was dissolved in DCM (15 mL) and washed with H_2O (10 mL). The aqueous phase was back-extracted with DCM (4 x 8 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was first purified by flash chromatography (EtOAc-hexane gradient from 20:80 to 60:40) and again with CombiFlash chromatography (EtOAc-hexane gradient from 0:100 to 31:69). The product was a reddish solid (34.0 mg, 0.109 mmol, 52%, *er* 99:1). The enantiomeric ratio was determined by ^{1}H NMR from the corresponding phosphoramidite derivatives (for details, see subsection 8.3.2).

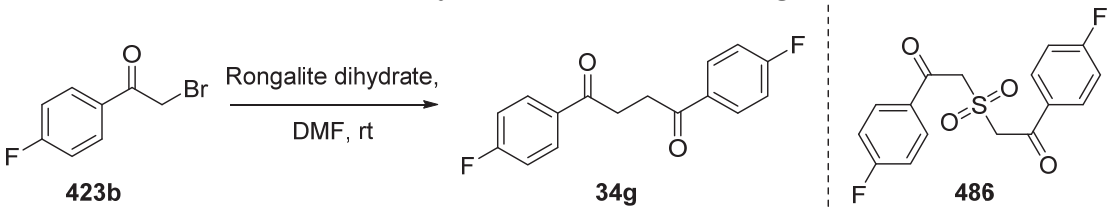
R_f (EtOAc-hexane 60:40)= 0.46; IR (film, cm^{-1}): 2931, 2852, 1595, 1509, 1338, 1106, 851, 750, 698, 510; mp 73–75 °C; $[\alpha]_D$= +121.1 (*c* 1.0 DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23–8.18 (m, 4H), 7.61–7.56 (m, 4H), 4.68 (app. t, *J* = 6.6 Hz, 2H), 2.57–2.41 (m, 2H), 1.96–1.81 (m, 3H, *overlaps with NH-proton and water peak*); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 153.1, 147.2, 127.2, 124.0, 62.0, 35.6; HRMS (ESI^+): m/z calculated for $[C_{16}H_{16}N_3O_4]^+$ = 314.1135, found 314.1113, Δ= 7.0 ppm.

The opposite enantiomer was synthesised in the above manner in 96% yield, optical rotation being $[\alpha]_D$= –153.8 (*c* 1.0 in DCM). Both enantiomers exhibited identical *er* (99:1) (for methods, see subsection 8.3.2).

8.2.3 (2*S*,5*S*)-2,5-bis(4-fluorophenyl)pyrrolidine catalyst [(*S*,*S*)-31n]

8.2.3.1 1,4-bis(4-fluorophenyl)butane-1,4-dione (34g)



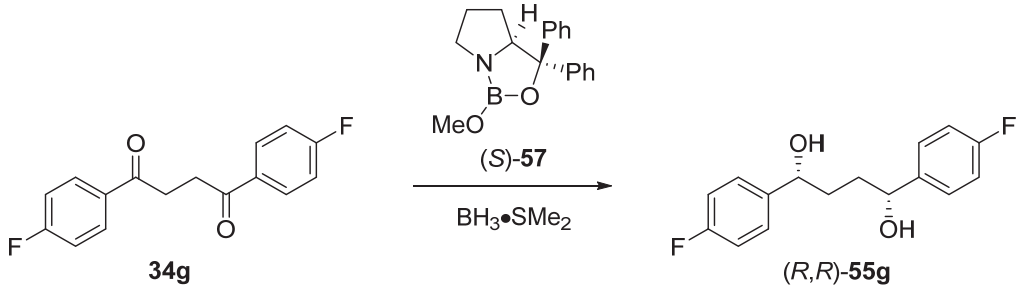
423b **34g** **486**

A mixture of 2-bromo-1-(4-fluorophenyl)ethan-1-one (**423b**, 2.60 g, 11.6 mmol, 1.0 equiv), sodium hydroxymethanesulfinate dihydrate (Rongalite, 2.00 g, 12.3 mmol, 1.1 equiv) and DMF (13 mL) at rt was stirred for 3 h. Water (26 mL) was added. The mixture was filtered through a glass sintered funnel and the solid was washed with water (4 x 6 mL). The residue was dissolved in DCM, the solution was concentrated, and the residue was purified by flash chromatography (EtOAc-hexane gradient from 0:100 to 80:20). The product was a white solid (1.40 g, 5.11 mmol, 88%). A small amount of sulfone side product **486** was also isolated as a white solid (82.6 mg, 0.244 mmol, 4%).

Diketone **34g**:
^1H NMR (300 MHz, $CDCl_3$): δ 8.09–8.02 (m, 4H), 7.18–7.11 (m, 4H), 3.42 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 165.7 (d, *J* = 254.7 Hz), 133.3 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.4 Hz), 115.8 (d, *J* = 21.7 Hz), 32.6.
Spectral data matches the data in literature.[244]

Sulfone **486**:
R_f (EtOAc-hexane 20:80)= 0.22; IR (film, cm^{-1}): 2949, 2907, 1698, 1680, 1596, 1509, 1330, 1283, 1244, 1204, 1159, 1132, 990, 835, 506; mp 155–156 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–7.99 (m, 4H), 7.23–7.17 (m, 4H), 4.96 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 166.9 (d, *J* = 258.4 Hz), 132.2 (d, *J* = 3.0 Hz), 131.9 (d, *J* = 9.8 Hz), 116.6 (d, *J* = 22.2 Hz), 59.9; HRMS (ESI^+): m/z calculated for $[C_{16}H_{12}F_2O_4S_1Na_1]^+$ = 361.0317, found 361.0306, Δ= 3.0 ppm.

8.2.3.2 (1*R*,4*R*)-1,4-bis(4-fluorophenyl)butane-1,4-diol [(*R*,*R*)-55g]



34g (*R*,*R*)-**55g**

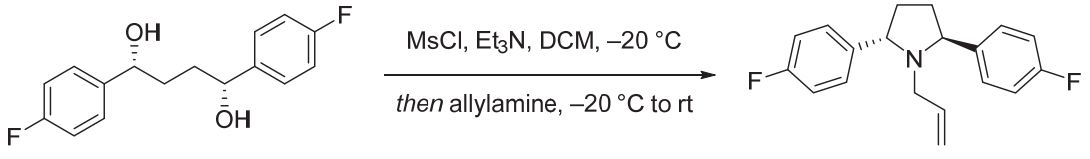
The procedure used for the preparation of (*S*,*S*)-**55d** was used with the following modifications: To a stirred solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (0.192 g, 0.190 mmol, 0.21 equiv) in THF (4.0 mL) was added $B(OMe)_3$ (0.10 mL, 0.897 mmol, 0.25 equiv). After 2 h, borane dimethylsulfide complex (0.86 mL, 9.07 mmol, 2.5 equiv) was added (*CAUTION: H_2 evolution*). A solution of diketone **34g** (1.00 g, 3.65 mmol, 1.0 equiv) in THF (20 mL) was then added dropwise over ~30 min. The reaction was then quenched, worked-up and the crude purified as described for (*S*,*S*)-**55d**, except that the quenched reaction medium was neutralised with $NaHCO_3$ before the evaporation of the solvents, to give (*R*,*R*)-**55g** as a white solid (0.967 g, 3.48 mmol, 95%).

R_f (EtOAc-hexane 50:50)= 0.44; IR (film, cm^{-1}): 3326, 1608, 1510, 1235, 1159, 1078, 1014, 827, 808, 578, 539, 526; mp 75–77 °C; $[\alpha]_D$= +46.1 (*c* 1.0 DCM); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.23 (m, 4H, *overlaps with $CHCl_3$*), 7.04–6.96 (m, 4H), 4.70–4.64 (m, 2H), 1.94–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3 (d, *J* = 245.5 Hz), 140.4 (d, *J* = 3.2 Hz), 127.5 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.3 Hz), 74.1, 36.1; HRMS (ESI^-): m/z calculated for $[C_{16}H_{15}F_2O_2]^-$ = 277.1046, found 277.1041, Δ= 1.8 ppm.

The diastereomeric ratio was estimated by integrating the diastereomeric ^{13}C-signals at 74.1 ppm (*major*) and 73.7 ppm (*minor*).

A racemic sample was synthesised in the same manner using borane dimethylsulfide complex as the sole reagent in 98% yield (*dr* ~60:40 *meso*:*dl*, estimated from the ^{13}C spectrum). ^1H NMR spectrum of the product matched that of an enantiopure sample. In ^{13}C NMR spectrum, peaks from *meso*-diastereomer were visible as follows: ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.28 (d, *J* = 245.4 Hz), 140.3 (d, *J* = 3.1 Hz), 127.5 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.4 Hz), 73.7, 35.2.

8.2.3.3 (2*S*,5*S*)-1-allyl-2,5-bis(4-fluorophenyl)pyrrolidine [(*S*,*S*)-59g]



(*R*,*R*)-**55g** (*S*,*S*)-**59g**

To a stirred solution of diol (*R*,*R*)-**55g** (0.297 g, 1.07 mmol, 1.0 equiv) in DCM (20 mL) was added Et_3N (0.45 mL, 3.23 mmol, 3.0 equiv). The mixture was cooled

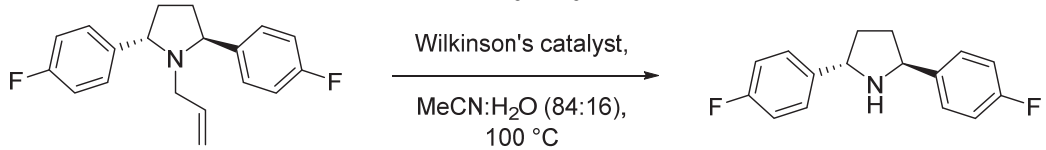
to –20 °C, after which MsCl (0.22 mL, 2.83 mmol, 2.7 equiv) was added dropwise. After 3 h, allylamine (8.1 mL, 0.108 mol, 100 equiv) was added. The reaction mixture was allowed to warm to rt slowly along with the cooling bath under the flask. After 19 hours, the volatiles were evaporated under reduced pressure. The residue was purified by CombiFlash chromatography (EtOAc-hexane gradient from 0:100 to 100:0) to give (*S*,*S*)-**59g** as a clear oil (0.241 g, 0.805 mmol, 75%). In addition, pure *cis*-**59g** was isolated as a clear oil (50.1 mg, 0,167 mmol, 16%).

trans-pyrrolidine (*S*,*S*)-**59g**:
R_f (EtOAc-hexane 5:95)= 0.82; IR (film, cm^{-1}): 1602, 1505, 1220, 1152, 1089, 1014, 917, 827, 534; $[\alpha]_D$= –95.8 (*c* 1.0 DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.25 (m, 4H, overlaps with $CHCl_3$), 7.05–6.97 (m, 4H), 5.61 (dddd, *J* = 17.2 Hz, 10.3 Hz, 7.3 Hz, 4.4 Hz, 1H), 4.97–4.86 (m, 2H, *two overlapping signals*), 4.33–4.26 (m, 2H), 2.94 (ddt, *J* = 14.7 Hz, 4.1 Hz, 2.0 Hz, 1H), 2.67 (dd, *J* = 14.7 Hz, 7.4 Hz, 1H), 2.57–2.42 (m, 2H), 1.93–1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (d, *J* = 244.6 Hz), 139.9 (d, *J* = 2.7 Hz), 136.7, 129.4 (d, *J* = 8.0 Hz), 115.9, 115.1 (d, *J* = 21.2 Hz), 65.0, 49.9, 33.3; HRMS (ESI$^+$): m/z calculated for $[C_{19}H_{20}F_2N_1]^+$ = 300.1558, found 300.1564, Δ= –2.0 ppm.

cis-**59g**:
R_f (EtOAc-hexane 0:100)= 0.35; IR (film, cm^{-1}): 2969, 2815, 1604, 1505, 1219, 1151, 1090, 922, 828, 786, 549, 521; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.39 (m, 4H), 7.07–6.99 (m, 4H), 5.66 (ddt, *J* = 17.0 Hz, 10.2 Hz, 6.9 Hz, 1H), 4.92 (dt, *J* = 10.2 Hz, 0.94 Hz, 1H), 4.88–4.80 (m, 1H), 3.87–3.78 (m, 2H), 3.01 (d, *J* = 6.9 Hz, 2H), 2.23–2.11 (m, 2H), 1.85–1.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, *J* = 244.2 Hz), 140.5 (d, *J* = 3.0 Hz), 133.8, 128.9 (d, *J* = 7.8 Hz), 117.6, 115.2 (d, *J* = 21.2 Hz), 66.3, 52.8, 34.5; HRMS (ESI$^+$): m/z calculated for $[C_{19}H_{20}F_2N_1]^+$ = 300.1558, found 300.1550, Δ= 2.7 ppm.

A racemic sample was also synthesised in the same manner using the ~60:40 diastereomer mixture of diol (±)-**S19** obtained above. The *cis*-**59g** was isolated in 52% yield (0.158 g, 0.527 mmol), whereas the (±)-*trans*-**59g** was obtained in 34% yield (0.105 g, 0.349 mmol). The spectral data matched that of the reported above.

8.2.3.4 (2*S*,5*S*)-2,5-bis(4-fluorophenyl)pyrrolidine [(*S*,*S*)-31n]



(*S*,*S*)-**59g** (*S*,*S*)-**31n**

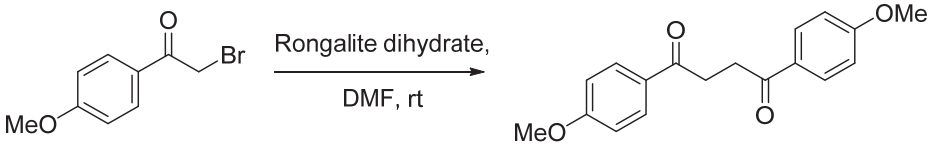
Following the procedure used for catalyst (*R*,*R*)-**31k**, the reaction of pyrrolidine (*S*,*S*)-**59g** (0.149 g, 0.498 mmol, 1.0 equiv) with Wilkinson's catalyst (26.1 mg, 28.2 µmol, 0.06 equiv) in MeCN:H_2O (3.8 mL, 84:16) afforded, after purification by flash chromatography (EtOAc-hexane gradient from 0:100 to 20:80) amine

(*S*,*S*)-**31n** as a yellowish oil that solidified upon storage in freezer (0.123 g, 0.474 mmol, 95%, *er* 99:1). The *er* was determined by ^{1}H NMR from the corresponding phosphoramidite derivatives (for details, see subsection 8.3.3).

R_f (EtOAc-hexane 20:80)= 0.39; IR (film, cm^{-1}): 2961, 2870, 1602, 1505, 1218, 1154, 1014, 828, 693, 569, 528; mp 32–34 °C; $[\alpha]_D$=–100.9 (*c* 1.0 DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.34 (m, 4H), 7.06–6.98 (m, 4H), 4.51 (app. t, *J* = 6.8 Hz, 2H), 2.47–2.29 (m, 2H), 1.97 (brs, 1H), 1.94–1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0 (d, *J* = 244.5 Hz), 141.5 (d, *J* = 3.0 Hz), 127.9 (d, *J* = 8.0 Hz), 115.3 (d, *J* = 21.2 Hz), 61.7, 35.8; HRMS (ESI$^+$): m/z calculated for $[C_{16}H_{16}F_2N_1]^+$ = 260.1245, found 260.1251, Δ= –2.3 ppm.

The racemic *trans*-(±)-**31n** was synthesised as above in 74% yield. The spectral data matched that of the reported above.

8.2.3.5 1,4-bis(4-methoxyphenyl)butane-1,4-dione (34n)

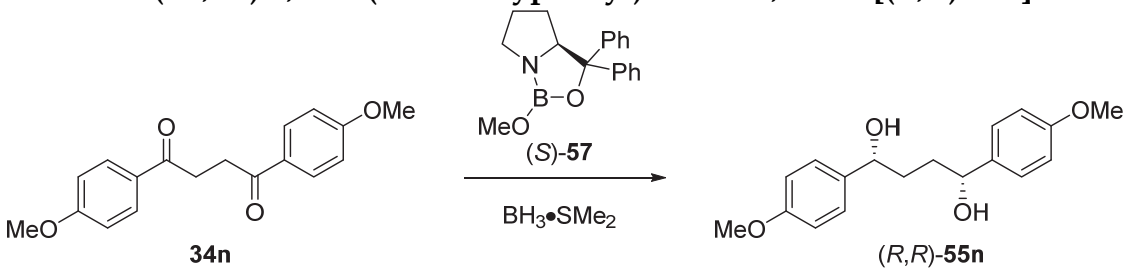


423c **34n**

A mixture of (**423c**, 2.99 g, 12.8 mmol, 1.0 equiv), sodium hydroxymethanesulfinate dihydrate (Rongalite, 2.12 g, mmol, 1.1 equiv) in DMF (10 mL) was stirred at rt for 32 h. Water (40 mL) was then added. The mixture was filtered through a sintered glass filter and the solid residue was washed with water (3x10 mL). The residue was dissolved in DCM, evaporated and the residue recrystallised twice with hot ~1:5 mixture of water:acetone. The remaining residue was a white solid (0.657 g, 2.20 mmol, 34%).

^{1}H NMR (300 MHz, ($CDCl_3$): δ 8.05–8.00 (m, 4H), 6.97–6.92 (m, 4H), 3.88 (s, 6H), 3.40 (s, 4H); ^{13}C NMR (75 MHz, ($CDCl_3$): δ 197.5, 163.7, 130.5, 130.2, 113.9, 55.6, 32.5.
The spectral data matches the date in literature.[245]

8.2.3.6 (1*R*,4*R*)-1,4-bis(4-methoxyphenyl)butane-1,4-diol [(*R*,*R*)-55n]



34n (*R*,*R*)-**55n**

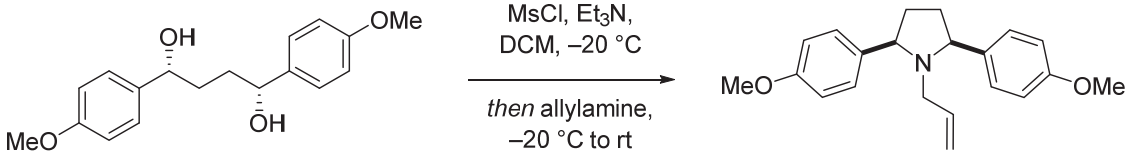
The procedure used for the preparation of (*R*,*R*)-**55g** was used with the following modifications: To a stirred solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (45.3 mg, 0.175 mmol, 0.21 equiv) in THF (4.0 mL) was added $B(OMe)_3$ (0.024 mL, 0.215 mmol, 0.25 equiv). After 1 h, bo-

rane dimethylsulfide complex (0.18 mL, 1.90 mmol, 2.3 equiv) was added (*CAUTION: H_2 evolution*). A solution of diketone **34n** (0.249 g, 0.834 mmol, 1.0 equiv) in THF (20+10 mL) was then added dropwise over ~30 min. The reaction was then quenched, worked-up and the crude purified as described for (*R*,*R*)-**55g** to give (*S*,*S*)-**55n** as a white solid (0.226 g, 0.748 mmol, 90%).

R_f (EtOAc-hexane 60:40)= 0.44; IR (film, cm^{-1}): 3363, 2951, 1611, 1513, 1248, 1173, 1024, 939, 828, 810, 550; $[\alpha]_D$= +25.3 (c 1.0 MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ 7.22–7.18 (m, 4H), 6.88–6.83 (m, 4H), 4.53 (t, *J* = 6.05 Hz, 2H), 3.77 (s, 4H), 1.90–1.71 (m, 2H), 1.68–1.53 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD, *major diastereomer peaks*): δ 160.4, 138.3, 128.3, 114.6, 74.7, 55.7, 36.4; (*Visible peaks from the minor diastereomer*): δ 138.4, 74.8, 36.5; HRMS (ESI$^+$): m/z calculated for $[C_{18}H_{22}O_4Na_1]^+$ = 325.1410, found 325.1397, Δ= 4.1 ppm.

The diastereomeric ratio was estimated by integrating the diastereomeric ^{13}C-signals at 74.8 ppm (*minor*) and 74.7 ppm (*major*).

8.2.3.7 1-allyl-2,5-bis(4-methoxyphenyl)pyrrolidine (*cis*-59n)

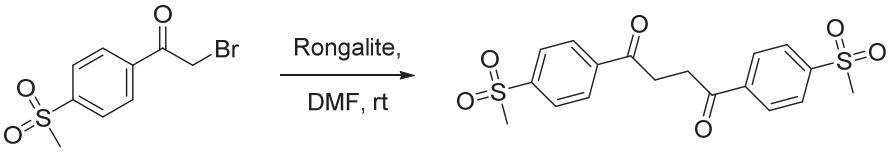


(*R*,*R*)-**55n** *cis*-**59n**

To a stirred solution of diol (*R*,*R*)-**55n** (94.6 mg, 0.31 mmol, 1.0 equiv) in DCM (5.0 mL) at –20 °C was added Et_3N (0.13 mL, 0.92 mmol, 3.0 equiv). MsCl (0.08 mL, 1.0 mmol, 3.3 equiv) was added dropwise to the turbid mixture, which clarified upon addition of the reagent. After 1 h, allylamine (2.4 mL, 31.4 mmol, 100 equiv) was added. The reaction mixture was allowed to warm to rt slowly along with the cooling bath under the flask. After 24 hours, the volatiles were evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc-hexane gradient from 0:100 to 20:80) to give *cis*-**59n** as an amorphous off-white solid (31.7 mg, 0.098 mmol, 31%). The desired *trans*-diastereomer could not be isolated as pure due to possible instability of the compound.

cis-**59n**:
R_f (EtOAc-hexane 10:90)= 0.45; IR (film, cm^{-1}): 2924, 1582, 1509, 1244, 1166, 1036, 937, 831, 816, 540; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.37 (m, 4H), 6.91–6.87 (m, 4H), 5.70 (ddt, *J* = 17.1 Hz, 10.2 Hz, 6.8 Hz, 1H), 4.92 (app. d, *J* = 10.1 Hz, 1H), 4.84 (app. d, *J* = 17.0 Hz, 1H), 3.82 (s, 6H), 3.78 (t, *J* = 5.5 Hz, 2H), 3.01 (d, *J* = 7.0 Hz, 2H), 2.19–2.08 (m, 2H), 1.85–1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 137.1, 134.0, 128.6, 117.3, 113.8, 66.2, 55.4, 52.4, 34.4; HRMS (ESI$^+$): m/z calculated for $[C_{21}H_{26}N_1O_2]^+$ = 324.1958, found 324.1954, Δ= 1.3 ppm.

8.2.3.8 1,4-bis(4-(methylsulfonyl)phenyl)butane-1,4-dione (34o)



423d **34o**

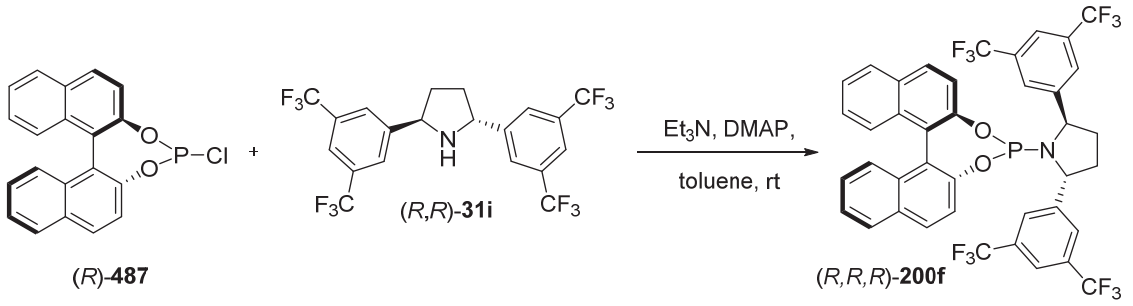
A mixture of 2-bromo-1-(4-(methylsulfonyl)phenyl)ethan-1-one (**423d**, 1.02 g, 3.61 mmol, 1.0 equiv), sodium hydroxymethanesulfinate dihydrate (Rongalite, 0.638 g, 4.06 mmol, 1.1 equiv) in DMF (4.0 mL) was stirred at rt for 6.5 h. Water (18 mL) was then added. The mixture was filtered through a sintered glass filter and the solid residue was washed with water (4 x 4 mL) and EtOAc (4 x 4 mL), leaving the remaining residue as a white solid (0.471 g, 1.19 mmol, 66%).

R_f (EtOAc-hexane 60:40)= 0.74; IR (film, cm^{-1}): 1678, 1315, 1287, 1150, 777, 753, 553, 516; mp 273 °C (decomp); ^1H NMR (300 MHz, $(CD_3)_2SO$): δ 8.25 (app d, J = 8.4 Hz, 4H), 8.10 (app d, J = 8.4 Hz, 4H), 3.51 (s, 4H), 3.29 (s, 6H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 198.2, 144.4, 140.1, 128.8, 127.4, 43.2, 32.9; HRMS (ESI^+): m/z calculated for $[C_{18}H_{18}O_6S_2Na_1]^+$= 417.0437, found 417.0416, Δ= 5.0 ppm.

8.3 Determination of the enantiopurity of the catalysts

The enantiomeric ratios of the catalysts were determined by synthesising diastereomeric phosphoramidite derivatives of the catalysts following the literature procedures.[37,56] The *dr* of the synthesised derivatives were determined by ^1H NMR, as the chemical shifts corresponding to the H-2 and H-5 of the diarylpyrrolidine ring were clearly distinguishable between the diastereomers. The obtained *dr* should thus correspond to the *er* of the parent catalyst.

8.3.1 (2*R*,5*R*)-2,5-bis(3,5-bis(trifluoromethyl)phenyl)-1-(dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)pyrrolidine [(*R*,*R*,*R*)–200f]



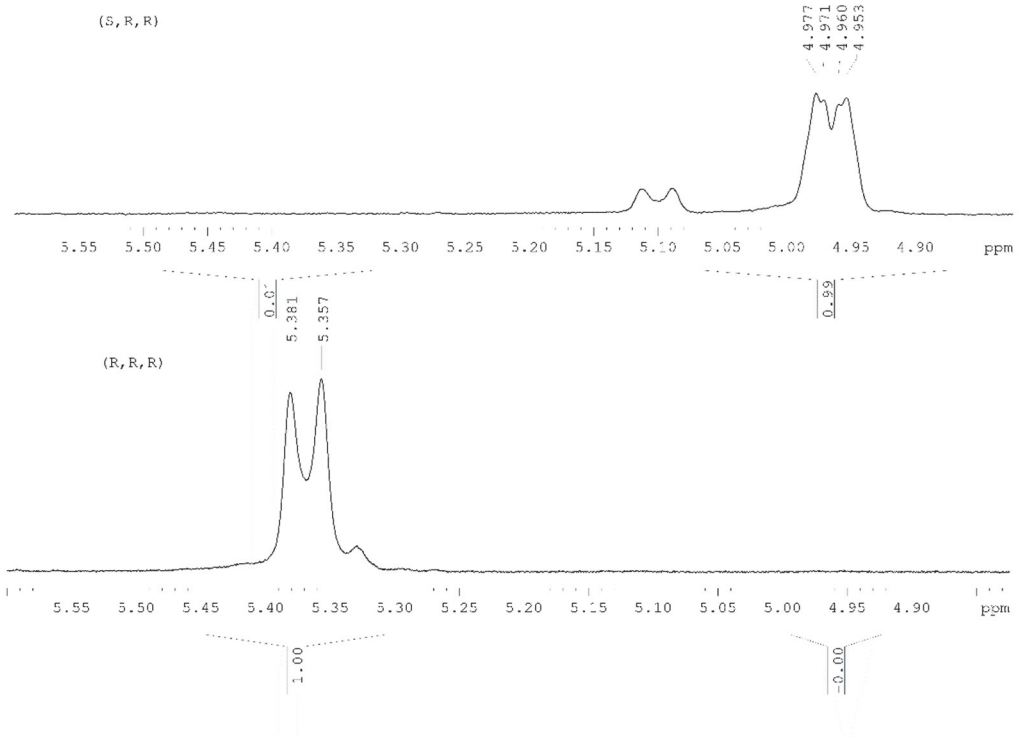
(*R*)-**487** (*R,R,R*)-**200f**

Catalyst (*R*,*R*)-**31i** (31.4 mg, 63 µmol, 1.0 equiv) and DMAP (3.1 mg, 25 µmol, 0.40 equiv) were weighed into a vial, after which (*R*)-**487** (0.5 M solution in toluene, 0.32 mL, 0.16 mmol, 2.5 equiv) and Et_3N (45 µl, 0.32 mmol, 5.0 equiv) were added. After 16 hours, an NMR sample of the reaction mixture was analysed to determine the *dr* and to ascertain the consumption of the starting material. The

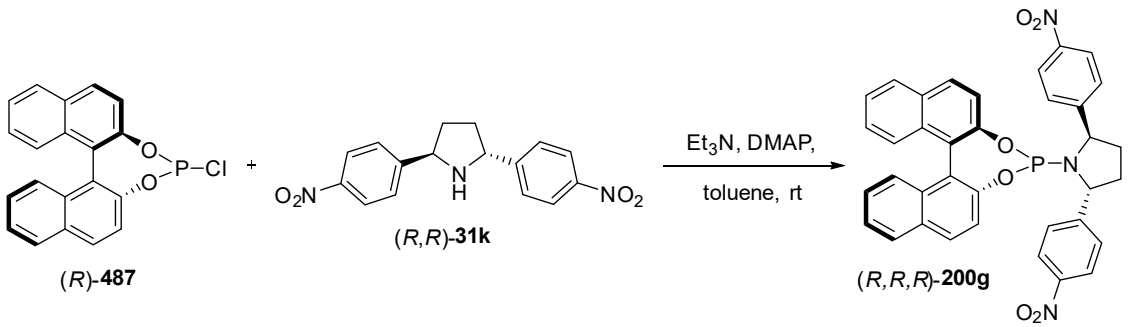
reaction mixture was then filtered through a small pad of silica (gradient elution Et_2O:pentane:Et_3N 20:80:2 to 100:0:2). The filtrate was concentrated under reduced pressure to afford the crude product (*R,R,R*)-**200f** as a white solid. *dr* >99:1.

R_f (Et_2O-hexane 10:90)= 0.70; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 5.37 (d, *J* = 7.3 Hz, 2H).

Similarly, (*S,R,R*)-**200f** was prepared using (*S*)-**487**. *dr* 99:1.
R_f (EtOAc-hexane 10:90)= 0.57; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 4.97 (dd, *J* = 5.2 Hz, 1.8 Hz, 2H).



8.3.2 (2*R*,5*R*)-1-(dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)-2,5-bis(4-nitrophenyl)pyrrolidine [(*R,R,R*)–200g]

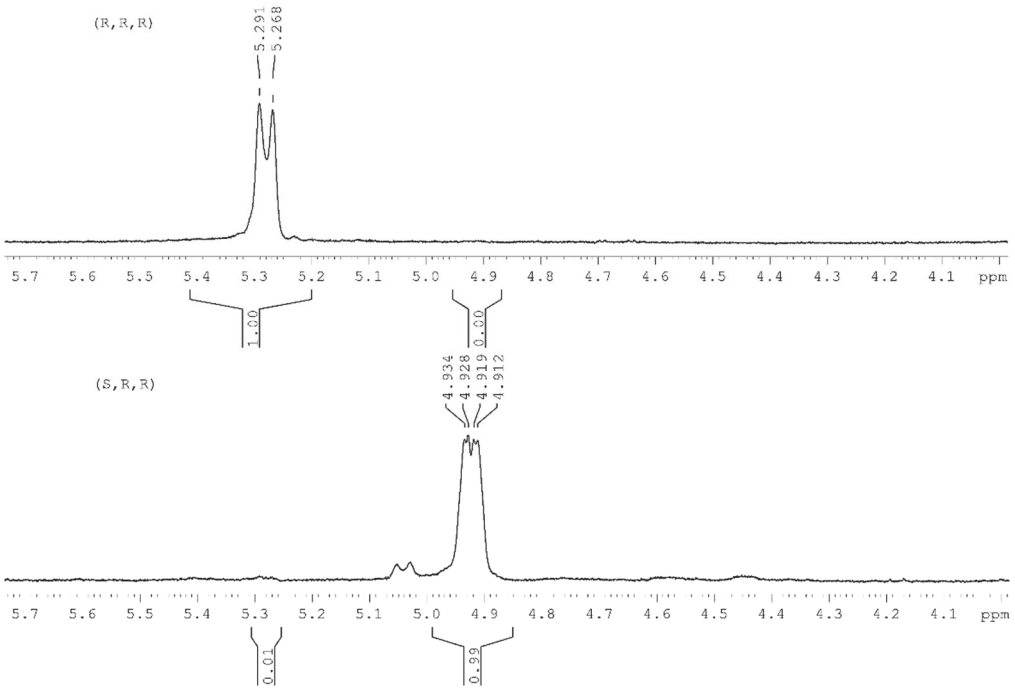


Catalyst (*R,R*)-**31k** (7.1 mg, 23 µmol, 1.0 equiv) and DMAP (1.5 mg, 12 µmol, 0.54 equiv) were weighed into a vial, after which (*R*)-**487** (0.5 M solution in tolu-

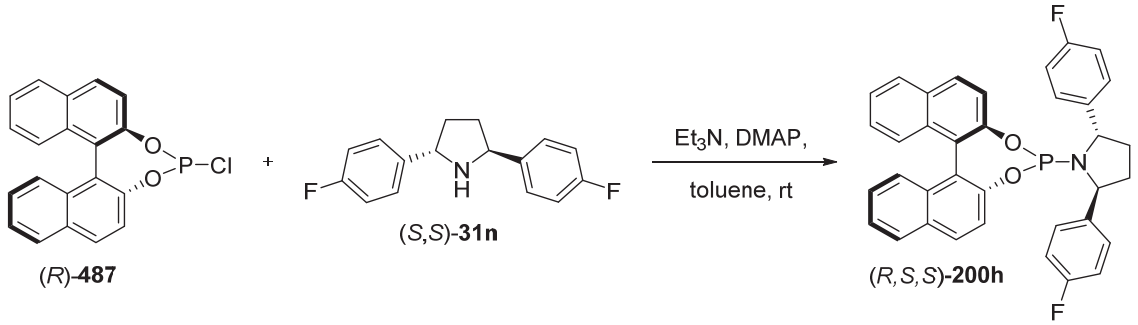
ene, 0.11 mL, 55 µmol, 2.4 equiv) and Et_3N (16 µl, 0.11 mmol, 5.0 equiv) were added. After 4 hours, an NMR sample of the reaction mixture was taken to analyse the *dr* and to see the total consumption of the starting material. The reaction mixture was then filtered through a small pad of silica (eluting first with Et_2O:pentane:Et_3N 50:50:2, followed by Et_2O:Et_3N 100:2). The filtrate was concentrated under reduced pressure to afford the crude product (*R,R,R*)-**200g** as a reddish white foam. *dr* >99:1.

R_f (EtOAc-hexane 20:80)= 0.42; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 5.28 (d, *J* = 6.8 Hz, 2H).

Similarly, (*S,R,R*)-**200g** was prepared using (*S*)-**487**. *dr* 99:1.
R_f (EtOAc-hexane 20:80)= 0.26; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 4.92 (dd, *J* = 4.8 Hz, 1.9 Hz, 2H).



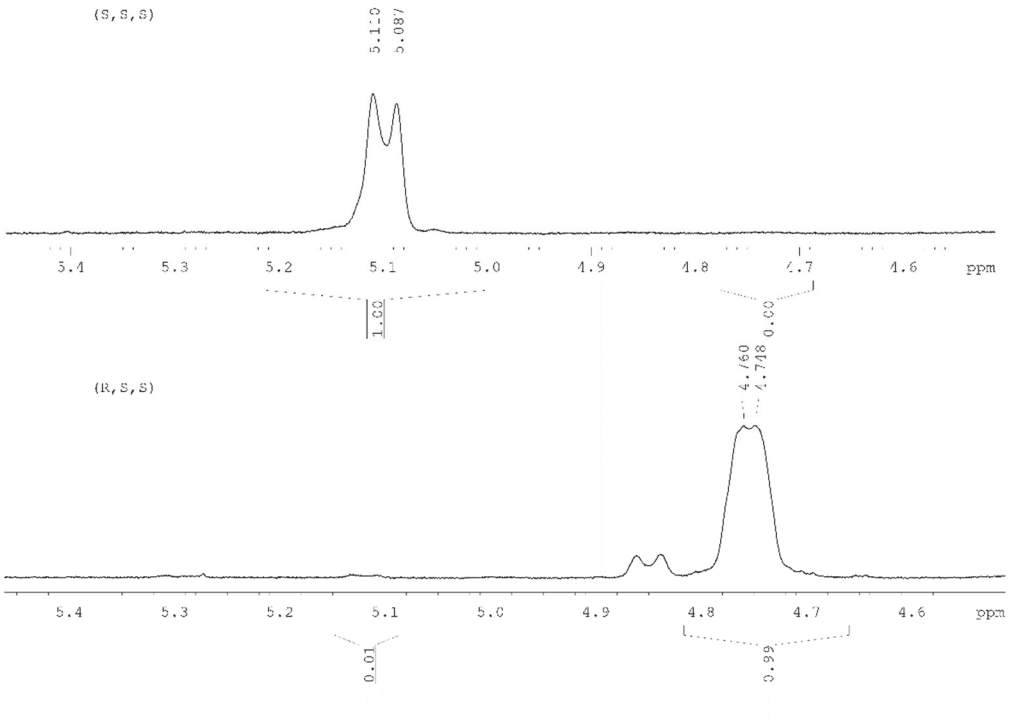
8.3.3 (2*S*,5*S*)-1-(dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)-2,5-bis(4-fluorophenyl)pyrrolidine [(*R*,*S*,*S*)–200h]



Catalyst (*S*,*S*)-**31n** (23.0 mg, 89 µmol, 1.0 equiv) and DMAP (4.4 mg, 36 µmol, 0.40 equiv) were weighed into a vial, after which (*R*)-**487** (0.5 M solution in toluene, 0.39 mL, 0.20 mmol, 2.2 equiv) and Et_3N (62 µl, 0.44 mmol, 5.0 equiv) were added. After 5 hours, an NMR sample of the reaction mixture was taken to analyse the *dr* and to see the total consumption of the starting material. The reaction mixture was then filtered through a small pad of silica (gradient elution Et_2O:pentane:Et_3N 20:80:2 to 60:40:2). The filtrate was concentrated under reduced pressure to afford the crude product (*R*,*S*,*S*)-**200h** as a white foam. *dr* 99:1.

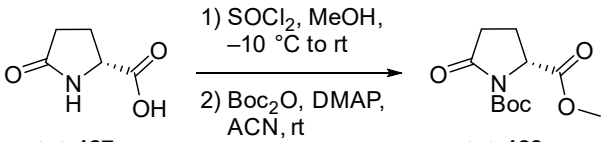
R_f (EtOAc-hexane 10:90)= 0.31; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 4.75 (d, *J* = 3.6 Hz, 2H)

Similarly, (*S*,*S*,*S*)-**200h** was prepared using (*S*)-**487**. *dr* >99:1.
R_f (EtOAc-hexane 10:90)= 0.47; ^1H NMR (300 MHz, $CDCl_3$, *characteristic* C*H*N peak): δ 5.10 (d, *J* = 6.9 Hz, 2H).



8.4 Synthesis of pyroglutamic-acid derived catalysts

8.4.1 1-(*tert*-butyl) 2-methyl (*R*)-5-oxopyrrolidine-1,2-dicarboxylate [(*R*)-127]



(*R*)-**127** (*R*)-**128**

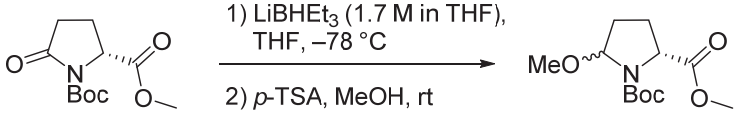
To a stirred solution of (*R*)-pyroglutamic acid (5.04 g, 38.4 mmol, 1.0 equiv) in MeOH (120 mL) at –15 °C was added dropwise $SOCl_2$ (3.1 mL, 42.1 mmol, 1.1 equiv). The reaction mixture was allowed to reach room temperature and was stirred 18 hours. The solvent and $SOCl_2$ were evaporated and the residue was dissolved in DCM (50 mL) and water (10 mL), after which sat. aq. $NaHCO_3$ was added until the pH was set to ~8 based on pH paper. The phases were separated and the water phase extracted with 10 mL of DCM. The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated to give the crude ester (m= 1.79 g), which was used in the next reaction without further purification.

To a stirred solution of the crude obtained above in ACN (30 mL) at room temperature was added DMAP (157 mg, 1.27 mmol, 0.1 equiv) and Boc_2O (3.34 g, 15.0 mmol, 1.2 equiv) and the reaction mixture was stirred 25 hours. The reac-

tion was quenched with 1M aq. $KHSO_4$-solution (25 mL), the phases were separated, the water phase was extracted with EtOAc (2x20 mL), the combined organics were washed with brine (20 mL) and dried (Na_2SO_4). After filtration and concentration, the crude was purified by column chromatography (EtOAc-hexane 30:70 to 50:50) to give the desired product (*R*)-**128** (2.97 g, 12.2 mmol, 32% yield over two steps).

$[\alpha]_D$= +32.2 (*c* 3.6 $CHCl_3$), (lit.[246] $[\alpha]_D$=+ 31.7 (*c* 3.37 $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (dd, *J* = 9.5 Hz, 2.9 Hz, 1H), 3.75 (s, 3H), 2.59 (dd, *J* = 17.8 Hz, 9.7 Hz, 1H), 2.45 (ddd, *J* = 17.5 Hz, 9.5 Hz, 3.6 Hz, 1H), 2.29 (dq, *J* = 13.3 Hz, 9.7 Hz, 1H), 2.00 (ddt, *J* = 13.1 Hz, 9.6 Hz, 3.3 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 171.9, 149.3, 83.6, 58.9, 52.6, 31.2, 27.9, 21.5.
The spectroscopic data and the optical rotary power matched those reported in the literature.[246]

8.4.2 1-(*tert*-butyl) 2-methyl (2*R*)-5-methoxypyrrolidine-1,2-dicarboxylate [(2*R*)-129]



(*R*)-**128** (2*R*)-**129**

To a stirred solution of (*R*)-**128** (2.87 g, 11.8 mmol, 1.0 equiv) in THF (43 mL) at –78 °C was added dropwise $LiBHEt_3$ (1.7 M in THF, 8.2 mL, 1.2 equiv). The reaction mixture was stirred at –78 °C for 1 hour, after which the reaction was quenched with sat. aq. $NaHCO_3$ solution (25 mL). The reaction vessel was placed in a bath at 0 °C and stirred for 45 minutes and 20 minutes at room temperature. The quenched mixture was diluted with Et_2O (40 mL), the phases were separated, the water phase extracted with Et_2O (2 x 40 mL), the combined organics washed with brine (40 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvents, the crude hemiaminal was used in the next step without further purification.

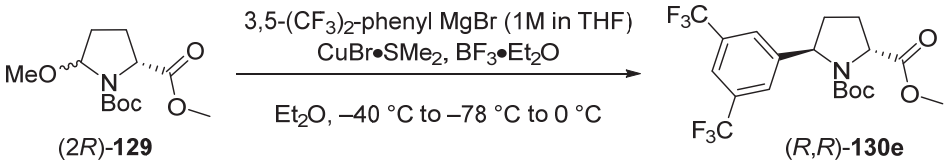
To a stirred solution of the crude, obtained above, in MeOH (50 mL) at room temperature was added *para*-toluenesulfonic acid monohydrate (247 mg, 1.27 mmol, 0.1 equiv) and the reaction mixture was stirred for 19 hours. The reaction was quenched by adding sat. aq. $NaHCO_3$ (40 mL), after which the solvents were evaporated. The remainder was mixed with Et_2O (40 mL) and the phases were separated. The water phase was extracted with Et_2O (2 x 40 mL), the combined organics were washed with brine (40 mL), dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by column chromatography (EtOAc-hexane 0:100 to 30:70) to give the desired product (2*R*)-**129** as a mixture of diastereomers (2.76 g, 10.7 mmol, 90% yield over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.30–5.13 (1H), 4.39–4.22 (1H), 3.74–3.71 (3H), 3.43–3.35 (3H), 2.52–2.25 (1H), 2.21–1.76 (3H), 1.49–1.41 (9H).

The spectroscopic data matched those reported in the literature.[247]

8.4.3 (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)-methyl)-5-(3,5-bis(trifluoromethyl)phenyl)pyrrolidine [(*R*,*R*)-32e]

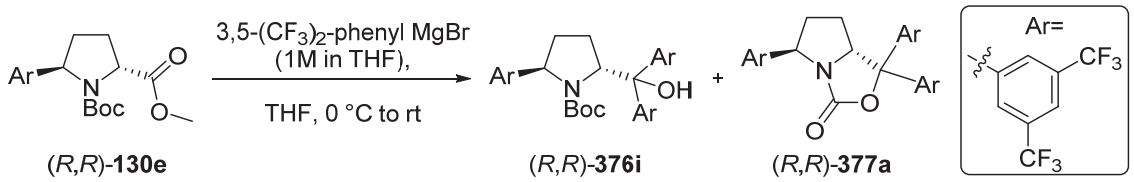
8.4.3.1 1-(*tert*-butyl) 2-methyl (2*R*,5*R*)-5-(3,5-bis(trifluoromethyl)phenyl)-pyrrolidine-1,2-dicarboxylate [(*R*,*R*)-130e]



To a stirred suspension of CuBr•SMe_2 (3.46 g, 16.7 mmol, 3.1 equiv) in Et_2O (43 mL) at –40 °C was added dropwise freshly prepared 3,5-$(CF_3)_2$-phenyl MgBr (1M in THF, 16.5 mL, 16.5 mmol, 3.1 equiv). The mixture was stirred for 1 hour at –40 °C after which it was cooled down to –78 °C. BF_3•Et_2O (2.1 mL, 17.0 mmol, 3.2 equiv) was added, followed by (2*R*)-**129** (1.40 g, 5.40 mmol, 1.0 equiv) as a solution in Et_2O (8.0 mL). The reaction mixture was stirred for 20 minutes at –78 °C, after which the reaction vessel was transferred in a cooling bath at 0 °C and stirred for 22 hours. The reaction was quenched with an aqueous solution of sat. NH_4Cl and 25% NH_4OH (1:1, 22 mL) and stirred for 30 minutes allowing the mixture to warm up to room temperature. The mixture was diluted with Et_2O (80 mL) and water (40 mL), after which the phases were separated. The water phase was extracted with Et_2O (2 x 60 mL) and the combined organic phases were dried (Na_2SO_4), filtered and the solvents were evaporated. The crude was purified by column chromatography (EtOAc-hexane 0:100 to 30:70) to give the desired product (*R*,*R*)-**130e** as a yellow solid (1.88 g, 4.26 mmol, 79%).

$[\alpha]_D$= +70.9 (*c* 0.68 $CHCl_3$), (lit.[37] $[\alpha]_D$= –60.6 (*c* 0.67 $CHCl_3$) for the opposite enantiomer); mp 74–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$, *mixture of rotamers*): δ 7.76 (s, 0.5H), 7.73 (s, 0.5H), 7.61 (s, 2H), 5.25 (d, *J* = 8.7 Hz, 0.5H), 5.10 (dd, *J* = 8.8 Hz, 1.7 Hz, 0.5H), 4.66 (dd, *J* = 8.6 Hz, 1.7 Hz, 0.5H), 4.57 (dd, *J* = 8.8 Hz, 0.90 Hz, 0.5H), 3.77 (s, 3H), 2.64–2.47 (m, 1H), 2.32–2.16 (m, 1H), 2.05–1.98 (m, 1H), 1.88–1.74 (m, 1H), 1.39 (s, 4.5H), 1.17 (s, 4.5 H); ^{13}C NMR (75 MHz, $CDCl_3$, *mixture of rotamers*): δ 173.1, 172.9, 154.0, 153.8, 147.5, 146.4, 131.95 (q, *J* = 33.2 Hz), 131.93 (q, *J* = 33.2 Hz), 125.9 (app. d, *J* = 2.6 Hz), 125.7 (app. d, *J* = 2.5 Hz), 123.5 (q, *J* = 272.8 Hz), 123.4 (q, *J* = 272.7 Hz), 121.1 (sept, *J* = 3.6 Hz), 120.9 (sept, *J* = 3.7 Hz), 81.1, 81.0, 61.1, 60.9, 60.4, 60.1, 52.4, 52.3, 33.5, 32.5, 28.2, 28.1, 28.0, 27.4.
The spectroscopic data and the optical rotary power matched those reported in the literature.[37]

8.4.3.2 *tert*-butyl (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)-methyl)-5-(3,5-bis(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate [(*R*,*R*)-376i] and (5*R*,7a*R*)-1,1,5-tris(3,5-bis(trifluoromethyl)phenyl)-tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one [(*R*,*R*)-377a]



(*R*,*R*)-**130e** (*R*,*R*)-**376i** (*R*,*R*)-**377a**

To a stirred solution of freshly prepared 3,5-$(CF_3)_2$-phenyl MgBr (1M in THF, 7.4 mL, 7.4 mmol, 3.7 equiv) at 0 °C was added dropwise (*R*,*R*)-**130e** (874 mg, 1.98 mmol, 1.0 equiv) as a solution in THF (12.5 mL). The mixture was stirred for 1 hour at 0 °C, after which it was warmed up to room temperature and stirred for 22 hours. The reaction mixture was then cooled down to –78 °C and water (2 mL) was added. The mixture was let to warm up to room temperature and sat. aq. NH_4Cl (10 mL) was added. The mixture was diluted with Et_2O (40 mL), the phases were separated and the water phase extracted with Et_2O (2 x 40 mL). The combined organics were washed with water (20 mL), the combined water phase back-extracted once with Et_2O (40 mL) and the combined organics washed with brine (40 mL), dried (Na_2SO_4), filtered and the solvents evaporated. The crude was purified by CombiFlash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give the Boc-compound (*R*,*R*)-**376i** (179 mg, 0.21 mmol, 11%) as a foamy solid and the carbamate (*R*,*R*)-**377a** (736 mg, 0.96 mmol, 49%, *elutes with some impurities*) as a foamy solid. In addition, 7% (63.4 mg, 0.144 mmol) of the starting material was isolated as well as its diastereomer 2-*epi*-**130e** [(2*S*,5*R*)-**130e**] as a reddish oily compound (169 mg, 0.382 mmol, 19%).

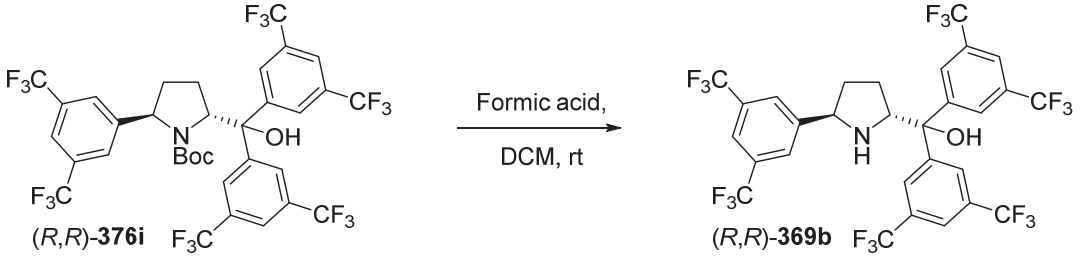
Boc-compound (*R*,*R*)-**376i**:
R_f (EtOAc-hexane 10:90)= 0.59; IR (film, cm^{-1}): 2983, 1652, 1364, 1275, 1172, 1124, 900, 708, 681; mp 70–72 °C; $[\alpha]_D$= +31.7 (*c* 1.0 DCM); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.91 (s, 2H), 7.90 (s, 1H), 7.85 (s, 2H), 7.80 (s, 1H), 7.51 (s, 2H), 7.13 (brs, 1H), 5.28 (dd, *J* = 8.8 Hz, 4.2 Hz, 1H), 4.60 (dd, *J* = 8.3 Hz, 3.9 Hz, 1H), 2.24 (dq, *J* = 14.1 Hz, 8.8 Hz, 1H), 1.91 (ddt, *J* = 13.8 Hz, 8.4 Hz, 4.2 Hz, 1H), 1.56–1.50 (m, 1H), 1.47–1.40 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 147.5, 147.1, 145.4, 132.4 (q, *J* = 33.5 Hz), 132.1 (q, *J* = 33.5 Hz), 131.8 (q, *J* = 33.5 Hz), 128.1 (app. d, *J* = 3.5 Hz), 127.7 (app. d, *J* = 2.5 Hz), 125.3 (app. d, *J* = 3.1 Hz), 123.3 (q, *J* = 272.8 Hz), 123.3 (q, *J* = 272.9 Hz), 123.2 (q, *J* = 272.7 Hz), 122.5–122.4 (m), 122.3–122.2 (m), 121.3 (sept, *J* = 4.1 Hz), 83.1, 81.3, 67.7, 63.6, 33.0, 28.4, 27.6; HRMS (ESI^+): m/z calculated for $[C_{34}H_{25}N_1O_3F_{18}Na_1]^+$ = 860.1445, found 860.1465, Δ= –2.4 ppm.

Carbamate (*R*,*R*)-**377a**:
R_f (EtOAc-hexane 10:90)= 0.44; IR (film, cm^{-1}): 1760, 1368, 1276, 1171, 1124, 1060, 900, 844, 706, 680; mp 147–149 °C; $[\alpha]_D$= +93.8 (*c* 1.0 DCM); ^{1}H NMR (500 MHz,

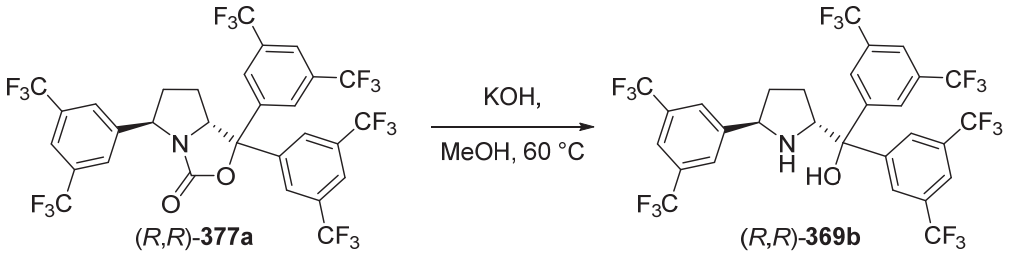
$CDCl_3$): δ 7.99 (s, 3H), 7.95 (s, 1H), 7.88 (s, 2H), 7.83 (s, 1H), 7.72 (s, 2H), 5.21 (t, *J* = 8.3 Hz, 1H), 4.84 (dd, *J* = 11.3 Hz, 4.9 Hz, 1H), 2.83 (dt, *J* = 13.7 Hz, 7.6 Hz, 1H), 2.07–1.99 (m, 1H), 1.91 (dt, *J* = 11.6 Hz, 5.8 Hz, 1H), 1.37–1.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 144.2, 143.9, 141.1, 133.4 (q, *J* = 30.7 Hz), 133.1 (q, *J* = 34.1 Hz), 132.6 (q, *J* = 30.4 Hz), 126.1 (app. d, *J* = 3.5 Hz), 125.8 (app. d, *J* = 2.7 Hz), 125.6 (app. d, *J* = 3.3 Hz), 124.0 (sept, *J* = 3.6 Hz), 123.3 (sept, *J* = 3.7 Hz), 123.2 (q, *J* = 272.8 Hz), 122.8 (q, *J* = 273.2 Hz, *two signals*), 122.0 (sept, *J* = 3.6 Hz), 84.2, 68.8, 62.3, 34.9, 30.9; HRMS (ESI^+): m/z calculated for $[C_{30}H_{15}N_1O_2F_{18}Na_1]^+$ = 786.0713, found 786.0712, Δ= 0.13 ppm.

2-*epi*-**130e** [(2*S*,5*R*)-**130e**]:
R_f (EtOAc-hexane 10:90)= 0.12; IR (film, cm^{-1}): 2980, 1748, 1698, 1367, 1276, 1156, 1124, 1074, 898, 757, 733, 708, 681 ; $[\alpha]_D$= +16.0 (*c* 1.0 DCM); ^1H NMR (300 MHz, $CDCl_3$, *mixture of rotamers*): δ 8.08 (brs, 2H), 7.74 (s, 0.53H), 7.71 (s, 0.47H), 5.05 (app. dd, *J* = 6.4 Hz, 3.7 Hz, 0.5H), 4.84 (t, *J* = 7.1 Hz, 0.5H), 4.54 (dd, *J* = 7.5 Hz, 3.4 Hz, 0.5H), 4.40 (t, *J* = 7.1 Hz, 0.5H), 3.80 (s, 3H), 2.45–2.35 (m, 1H), 2.31–2.20 (m, 1H), 2.10–1.87 (m, 2H), 1.38 (s, 4.2H), 1.10 (s, 4.8H); ^{13}C NMR (75 MHz, $CDCl_3$, *mixture of rotamers*): δ 173.3, 153.9, 153.7, 147.2, 146.0, 131.7 (q, *J* = 33.1 Hz), 126.9, 126.6, 123.6 (q, *J* = 272.6 Hz), 120.9, 120.8, 81.2, 80.9, 62.5, 61.7, 60.9, 60.4, 52.4, 52.2, 35.5, 34.3, 29.0, 28.9, 28.2, 27.9; HRMS (ESI^+): m/z calculated for $[C_{19}H_{21}F_6N_1O_4Na_1]^+$ = 464.1267, found 464.1282, Δ= –3.2 ppm.

8.4.3.3 Bis(3,5-bis(trifluoromethyl)phenyl)((2*R*,5*R*)-5-(3,5-bis-(trifluoromethyl)phenyl)-pyrrolidin-2-yl)methanol [(*R*,*R*)-369b]



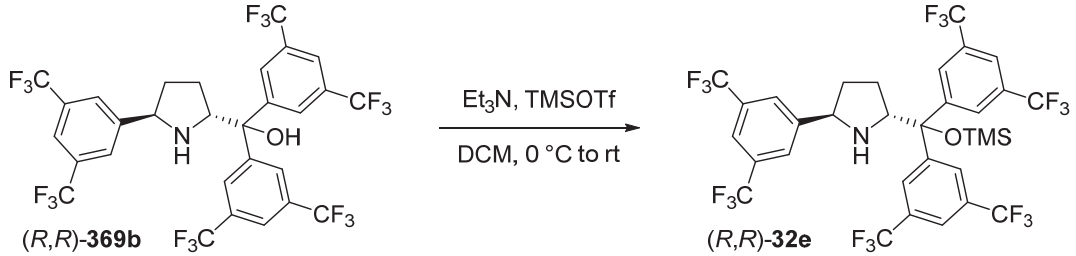
To a stirred solution of (*R*,*R*)-**376i** (51.5 mg, 0.061 mmol, 1.0 equiv) in DCM (1.0 mL) was added formic acid (1.0 mL, 26.5 mmol, 430 equiv) dropwise at room temperature. After 4 hours of reaction, more formic acid (2.0 mL, 53.0 mmol, 860 equiv) was added to drive the reaction towards completion. The reaction mixture was stirred for 19 hours in total, after which DCM and formic acid were evaporated. The residue was dissolved in Et_2O (5.0 mL) and washed with sat. aq. $NaHCO_3$ (3 mL). The phases were separated and the water phase was extracted with Et_2O (3 x 5 mL). The combined organics were dried (Na_2SO_4), filtered and the solvents evaporated. The crude was purified by CombiFlash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give (*R*,*R*)-**369b** as a yellowish foam (34.3 mg, 0.047 mmol, 76%).
The spectroscopic data matched those reported below.



To a stirred solution of (*R*,*R*)-**377a** (200 mg, 0.26 mmol, 1.0 equiv) in methanol (4.0 mL) was added KOH (230 mg, 4.04 mmol, 15.0 equiv) at room temperature. The mixture was warmed up to 60 °C and stirred for 7 hours. The reaction was worked up by adding water (4.0 mL) to the reaction mixture and extracting the water phase with Et_2O (4 x 5 mL). The combined organics were dried (Na_2SO_4), filtered and the solvents evaporated. The crude was purified by column chromatography (EtOAc-hexane 0:100 to 15:85) to give (*R*,*R*)-**369b** as a white foam (176 mg, 0.24 mmol, 91%).

R_f (EtOAc-hexane 10:90) = 0.50; IR (film, cm^{-1}): 1371, 1274, 1166, 1119, 988, 897, 844, 706, 680; mp 40–42 °C; $[\alpha]_D$= +68.5 (*c* 0.99 DCM); ^1H NMR (300 MHz, $CDCl_3$): 8.12 (s, 2H), 8.02 (s, 2H), 7.81 (s, 3H), 7.75 (s, 2H), 4.78 (dd, *J* = 8.4 Hz, 6.5 Hz, 1H, *overlaps with NH-signal*), 4.76 (brs, 1H, *overlaps with CH-signal*), 4.53 (dd, *J* = 7.7 Hz, 6.5 Hz, 1H), 2.46–2.38 (m, 1H), 2.03–1.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9, 146.7, 146.0, 132.6, (q, *J* = 33.4 Hz), 132.2 (q, *J* = 33.4 Hz), 126.6 (app. d, *J* = 2.9 Hz), 126.2 (app. d, *J* = 3.6 Hz), 125.8 (app. d, *J* = 2.7 Hz), 123.8 (q, *J* = 272.8 Hz), 123.3 (q, *J* = 272.7 Hz), 123.3 (q, *J* = 272.9 Hz), 122.1–121.8 (m, *three overlapping signals*), 76.9, 65.2, 62.3, 35.1, 27.8; HRMS (ESI^-): m/z calculated for $[2M–H^+]^-$ = $[C_{58}H_{33}N_2O_2F_{36}]^-$ = 1473.1967, found 1473.2001, Δ= –2.3 ppm.

8.4.3.4 (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-5-(3,5-bis(trifluoromethyl)phenyl)pyrrolidine [(*R*,*R*)-32e]

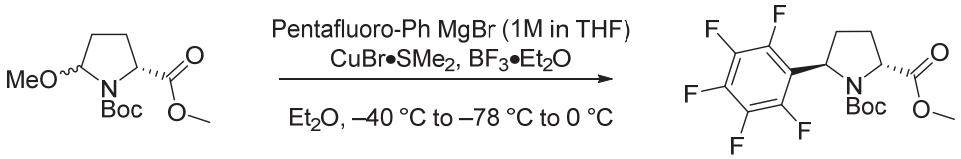


To a stirred solution of (*R*,*R*)-**369b** (153 mg, 0.21 mmol, 1.0 equiv) in DCM (2.0 mL) at 0 °C was added Et_3N (70 µL, 0.50 mmol, 2.4 equiv) and TMSOTf (80 µL, 0.43 mmol, 2.1 equiv) dropwise, after which the reaction mixture was let to warm up to room temperature. The mixture was stirred for 28 hours, after which it was diluted with DCM (4.0 mL) and quenched with water (2.0 mL). The phases were separated and the water phase was extracted with DCM (2 x 4 mL). The combined organics were dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by column chromatography (EtOAc-hexane 0:100 to 30:70) to give (*R*,*R*)-**32e** as a white solid (156 mg, 0.19 mmol, 93%).

R_f (EtOAc-hexane 10:90)= 0.71; IR (film, cm^{-1}): 1374, 1273, 1121, 987, 899, 882, 840, 706, 680; mp 88-90 °C; $[\alpha]_D$= +62.8 (*c* 1.0 DCM); ^{1}H NMR (500 MHz, $CDCl_3$): 8.11 (s, 2H), 7.92 (s, 1H), 7.89 (s, 1H), 7.79 (s, 2H), 7.78 (s, 3H), 4.38 (t, *J* = 7.4 Hz, 1H), 3.94 (t, *J* = 7.1 Hz, 1H), 2.13 (brs, 1H), 2.05–2.01 (m, 1H), 1.82–1.76 (m, 1H), 1.69–1.60 (m, 2H), –0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7, 147.1, 146.1, 132.08 (q, *J* = 33.5 Hz), 132.06 (q, *J* = 33.2 Hz), 131.8 (q, *J* = 33.4 Hz), 129.3 (app. d, *J* = 3.9 Hz), 127.8 (app. d, *J* = 3.0 Hz), 126.6 (app. d, *J* = 2.8 Hz), 123.5 (q, *J* = 272.6 Hz), 123.3 (q, *J* = 272.9 Hz), 123.2 (q, *J* = 272.8 Hz), 122.4–122.2 (m, *two signals overlapping with* ***C****F*$_3$*-quartet peaks*), 121.3 (sept, *J* = 3.8 Hz), 82.8, 65.5, 62.1, 34.4, 29.3, 1.9; HRMS (ESI$^+$): m/z calculated for $[C_{32}H_{26}N_1O_1F_{18}Si_1]^+$ = 810.1496, found 810.1513, Δ= –2.1 ppm.

8.4.4 (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)-methyl)-5-(perfluorophenyl)pyrrolidine [(*R*,*R*)-32f]

8.4.4.1 1-(*tert*-butyl) 2-methyl (2*R*,5*R*)-5-(perfluorophenyl)pyrrolidine-1,2-dicarboxylate [(*R*,*R*)-130j]



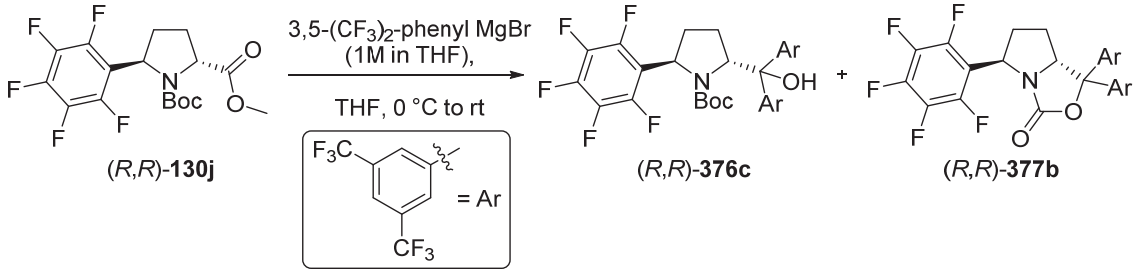
(2*R*)-**129** (*R*,*R*)-**130j**

To a stirred suspension of CuBr•SMe_2 (2.18 g, 10.5 mmol, 3.4 equiv) in Et_2O (15 mL) at –40 °C was added dropwise freshly prepared pentafluorophenyl MgBr (1M in THF, 9.5 mL, 9.87 mmol, 3.2 equiv). The mixture was stirred for 1 hour at –40 °C after which it was cooled down to –78 °C. BF_3•Et_2O (1.3 mL, 10.5 mmol, 3.4 equiv) was added, followed by (2*R*)-**129** (810 mg, 3.1 mmol, 1.0 equiv) as a solution in Et_2O (5.0 mL). The reaction mixture was stirred for 30 minutes at –78 °C, after which the reaction vessel was transferred in a cooling bath at 0 °C and stirred for 17 hours. The reaction was quenched with an aqueous solution of sat. NH_4Cl and 25% NH_4OH (1:1, 20 mL) and stirred for 30 minutes allowing the mixture to warm up to room temperature. The mixture was diluted with Et_2O (40 mL) and water (20 mL), after which the phases were separated. The water phase was extracted with Et_2O (2 x 30 mL) and the combined organic phases were dried (Na_2SO_4), filtered and the solvents were evaporated. The crude was purified by column chromatography (EtOAc-hexane 0:100 to 30:70) to give the desired product (*R*,*R*)-**130j** as a white sticky solid (490 mg, 1.24 mmol, 40%).

R_f (EtOAc-hexane 20:80)= 0.45; IR (film, cm^{-1}): 2983, 2956, 1752, 1697, 1520, 1377, 1203, 1127, 1041, 858, 751; mp 88–91 °C; $[\alpha]_D$= +48.3 (*c* 0.99 DCM); ^{1}H NMR (500 MHz, $CDCl_3$, *mixture of rotamers*): δ 5.41 (dd, *J* = 8.7 Hz, 2.8 Hz, 0.6H), 5.41 (dd, *J* = 8.7 Hz, 2.8 Hz, 0.4H), 4.54 (dd, *J* = 8.7 Hz, 2.7 Hz, 0.4H), 4.44 (dd, *J* = 8.7 Hz, 2.6 Hz, 0.6H), 3.76 (s, 1.4H), 3.75 (s, 1.6 H), 2.61–2.41 (m, 2H), 2.07–2.01 (m, 1 H), 1.99–1.93 (m, 0.4H), 1.91–1.87 (m, 0.6H), 1.37 (s, 4.8H), 1.25 (s, 4.2H); ^{13}C NMR (125 MHz, $CDCl_3$, *mixture of rotamers*): δ 173.4 (major), 173.2 (minor), 153.6 (mi-

nor), 153.4 (major), 144.7 (app, d, *J* = 247.1 Hz), 140.2 (app, d, *J* = 253.0 Hz), 137.7 (app. d, *J* = 252.0 Hz), 117.6 (minor, app. t, *J* = 13.5 Hz), 116.6 (major, app. t, *J* = 13.1 Hz), 81.0 (major), 81.0 (minor), 60.30 (major), 60.28 (minor), 52.9, 52.4 (minor), 52.3 (major), 32.0 (minor), 31.5 (major), 29.4 (major), 28.4 (minor), 28.3 (major), 28.1 (minor); HRMS (ESI$^+$): m/z calculated for $[C_{17}H_{18}N_1O_4F_5Na_1]^+$ = 418.1054, found 418.1048, Δ= 1.4 ppm.

8.4.4.2 *tert*-butyl (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-5-(perfluorophenyl)pyrrolidine-1-carboxylate [(*R*,*R*)-376c] and (5*R*,7a*R*)-1,1-bis(3,5-bis(trifluoromethyl)phenyl)-5-(perfluorophenyl)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one [(*R*,*R*)-377b]

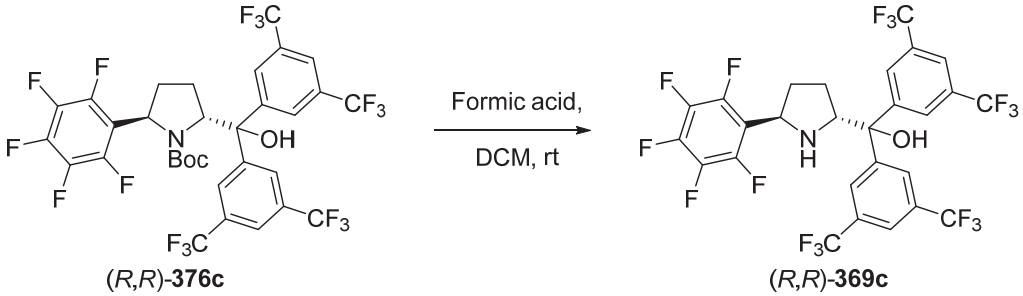


To a stirred solution of freshly prepared 3,5-$(CF_3)_2$-phenyl MgBr (1M in THF, 2.5 mL, 30.8 mmol, 4.3 equiv) at 0 °C was added dropwise (*R*,*R*)-**130j** (189 mg, 0.48 mmol, 1.0 equiv) as a solution in THF (3.0 mL). The mixture was stirred for 1 hour at 0 °C, after which it was warmed up to room temperature an stirred for 17 hours. The reaction mixture was then cooled down to –78 °C and water (2 mL) was added. The mixture was let to warm up to room temperature and sat. aq. NH_4Cl (5 mL) was added. The mixture was diluted with Et_2O (15 mL), the phases were separated and the water phase extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered and the solvents evaporated. The crude was purified by CombiFlash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give the Boc-compound (*R*,*R*)-**376c** (98.4 mg, 0.12 mmol, 26%) as a foam and the carbamate (*R*,*R*)-**377b** (133 mg, 0.19 mmol, 39 %) as a foamy solid.

Boc-compound (*R*,*R*)-**376c**:
R_f (EtOAc-hexane 10:90)= 0.50; IR (film, cm^{-1}): 2983, 1671, 1504, 1366, 1277, 1173, 1131, 982, 901, 844, 710, 681; mp 56–58 °C; $[\alpha]_D$= –18.8 (*c* 1.0 ACN); ^{1}H NMR (500 MHz, CD_3CN): δ 8.12 (s, 2H), 8.00 (s, 1H), 7.95 (s, 2H), 7.88 (s, 1H), 5.88 (brs, 1H), 5.32 (brs, 1H), 5.15 (brs, 1H), 2.41–2.31 (m, 1H), 2.21 (brs, 1H), 1.90–1.89 (brs, 1H), 1.81–1.77 (m, 1H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN): δ 155.6, 148.4, 148.0, 145.4 (app. dt, *J* = 245.5 Hz, 10.2 Hz), 140.8 (app. d, *J* = 250.9 Hz), 138.6 (app. dt, *J* = 248.4 Hz, 13.5 Hz), 132.2 (q, *J* = 33.2 Hz), 131.5 (q, *J* = 33.0 Hz), 129.0, 128.9, 124.7 (q, *J* = 271.9 Hz), 124.6 (q, *J* = 272.1 Hz), 122.9 (app. t, *J* = 3.5 Hz), 122.4, 119.4 (t, *J* = 14.8 Hz), 82.3, 81.8, 67.1, 54.9, 32.9, 28.7, 27.8; HRMS (ESI$^-$): m/z calculated for $[C_{32}H_{22}N_1O_3F_{17}]^-$ = 790.1250, found 790.1230, Δ= 2.5 ppm.

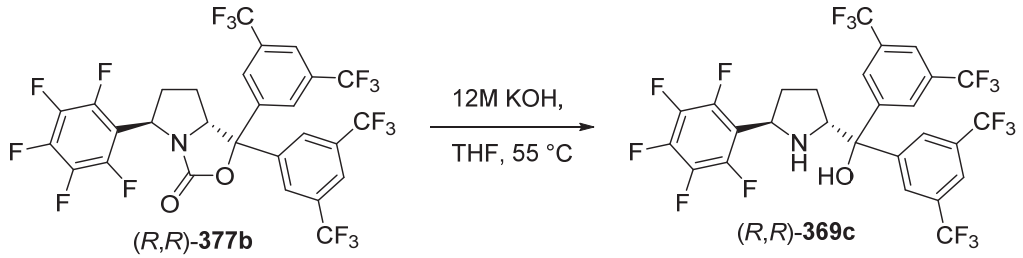
Carbamate (*R*,*R*)-**377b**:
R_f (EtOAc-hexane 10:90)= 0.31; IR (film, cm^{-1}): 1762, 1524, 1506, 1369, 1277, 1175, 1080, 1012, 972, 903, 736, 709; mp 75–77 °C; $[\alpha]_D$= +98.0 (*c* 0.96 DCM); ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.94 (s, 2H), 7.90 (s, 2H), 5.39 (t, *J* = 8.7 Hz, 1H), 5.04 (dd, *J* = 11.5 Hz, 4.7 Hz, 1H), 2.65 (dt, *J* = 13.6 Hz, 7.6 Hz, 1H), 2.14 (tdd, *J* = 13.1 Hz, 9.1 Hz, 6.2 Hz, 1H), 1.93 (app. dt, *J* = 11.9 Hz, 5.8 Hz, 1H), 1.27 (qd, *J* = 12.1 Hz, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 145.0 (app. d, *J* = 244.4 Hz), 144.1, 141.2 (app. d, *J* = 256.0 Hz), 141.1, 138.0 (app. dt, *J* = 253.4 Hz, 14.5 Hz), 133.1 (q, *J* = 34.0 Hz), 133.0 (q, *J* = 34.0 Hz), 126.4 (app. d, *J* = 2.7 Hz), 125.7 (app. d, *J* = 2.7 Hz), 123.8 (sept, *J* = 3.6 Hz), 123.2 (sept, *J* = 3.6 Hz), 122.9 (q, *J* = 273.1 Hz), 122.9 (q, *J* = 273.1 Hz), 114.8 (app. t, *J* = 12.7 Hz), 84.0, 69.0, 53.8, 33.6, 31.1; HRMS (ESI^+): m/z calculated for $[C_{28}H_{12}N_1O_2F_{17}Na_1]^+$ = 740.0494, found 740.0480, Δ= 1.9 ppm.

8.4.4.3 Bis(3,5-bis(trifluoromethyl)phenyl)((2*R*,5*R*)-5-(perfluorophenyl)pyrrolidin-2-yl)methanol [(*R*,*R*)-369c]



(*R*,*R*)-**376c** (*R*,*R*)-**369c**

To a stirred solution of (*R*,*R*)-**376c** (40.2 mg, 0.051 mmol, 1.0 equiv) in DCM (0.3 mL) was added formic acid (2.0 mL, 53.0 mmol, 1040 equiv) at room temperature. The reaction was stirred for 18 hours, after which the solvents were evaporated and the remaining formic acid neutralised with sat. aq. $NaHCO_3$ (pH set to ~7 based on pH paper). The mixture was extracted with Et_2O (3x15 mL), the combined organics washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by CombiFlash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give the product (*R*,*R*)-**369c** as a white foam (26.5 mg, 0.038 mmol, 75%).
The spectroscopic data matched those reported below.



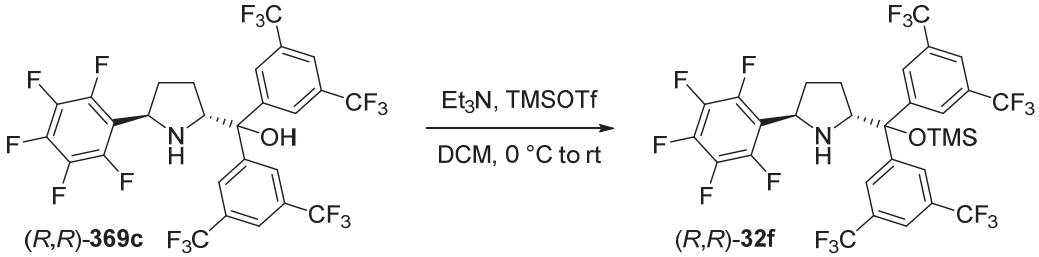
(*R*,*R*)-**377b** (*R*,*R*)-**369c**

To a stirred solution of (*R*,*R*)-**377b** (62.6 mg, 0.087 mmol, 1.0 equiv) in THF (0.45 mL) was added 12M KOH (0.3 mL, 3.6 mmol, 41 equiv) and the reaction mixture was warmed up to 55 °C. After 6 hours, 12M KOH (0.1 mL, 1.2 mmol, 14 equiv) was added to push the reaction towards completion. After total of 23 hours the reaction mixture was let to cool down to room temperature and

worked up by adding water (3 mL) and extracting with Et_2O (3 x 5 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by CombiFlash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give the product (*R*,*R*)-**369c** as a white foam (42.8 mg, 0.062 mmol, 71%).

R_f (EtOAc-hexane 10:90)= 0.47; IR (film, cm^{-1}): 2919, 1523, 1502, 1370, 1276, 1170, 1127, 1037, 1002, 899, 844, 753, 709; mp 139–141 °C; $[\alpha]_D$= +68.6 (*c* 1.0 DCM); ^1H NMR (300 MHz, CD_2Cl_2): δ 8.11 (s, 2H), 8.02 (s, 2H), 7.82 (s, 2H), 4.86 (s, 1H), 4.82 (t, *J* = 7.8 Hz, 1H), 4.75 (dd, *J* = 9.3 Hz, 6.3 Hz, 1H), 2.31 (dtd, *J* = 12.6 Hz, 7.3 Hz, 2.2 Hz, 1H), 2.04 (tt, *J* = 11.1 Hz, 8.4 Hz, 1H), 1.90 (brs, 1H), 1.87–1.64 (m, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 149.4, 146.5, 145.5 (app. d, *J* = 239.6 Hz), 140.8 (app. d, *J* = 253.7 Hz), 138.3 (app. d, *J* = 251.0 Hz), 132.5 (q, *J* = 33.3 Hz), 132.2 (q, *J* = 33.3 Hz), 126.7 (app. d, *J* = 2.8 Hz), 126.2 (app. d, *J* = 2.7 Hz), 123.8 (q, *J* = 272.7 Hz), 123.7 (q, *J* = 272.7 Hz), 122.2 (sept, *J* = 3.7 Hz), 122.0 (sept, *J* = 3.9 Hz), 117.5 (t, *J* = 15.1 Hz), 76.7, 65.5, 52.9, 33.5, 28.1; HRMS (ESI^+): m/z calculated for $[C_{27}H_{15}N_1O_1F_{17}]^+$ = 692.0882, found 692.0862, Δ= 3.0 ppm.

8.4.4.4 (2*R*,5*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-5-(perfluorophenyl)pyrrolidine [(*R*,*R*)-32f]

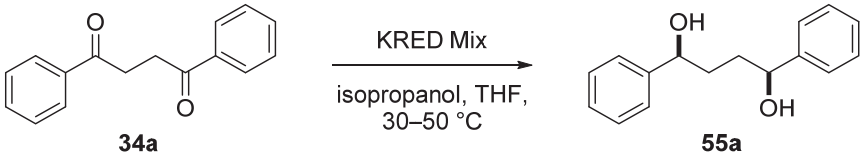


To a stirred solution of (*R*,*R*)-**369c** (24.4 mg, 0.035 mmol, 1.0 equiv) in DCM (1.0 mL) at 0 °C was added Et_3N (0.03 mL, 0.21 mmol, 6.0 equiv) and TMSOTf (0.03 mL, 0.16 mmol, 4.6 equiv) and the reaction mixture was let to warm up to room temperature. After 3 hours, the reaction mixture was cooled down to 0 °C and additional Et_3N (0.01 mL, 0.071 mmol, 2.0 equiv) and TMSOTf (0.01 mL, 0.054 mmol, 1.5 equiv) were added to drive the reaction to completion. The reaction mixture was let to warm up to rt and react for 20 hours in total. The reaction mixture was then diluted with DCM (5 mL) and quenched with water (3 mL). The phases were separated and the water phase was extracted with DCM (2 x 5 mL). The combined organics were dried with Na_2SO_4, filtered and the solvents were evaporated. The crude was purified by CombiFlash chromatography (EtOAc-hexane gradient 0:100 to 100:0). The product (*R*,*R*)-**32f** was a sticky white foam (18.0 mg, 0.024 mmol, 67%).

R_f (EtOAc-hexane 10:90)= 0.73; IR (film, cm^{-1}): 2961, 1522, 1502, 1371, 1275, 1172, 1125, 840, 709, 680; $[\alpha]_D$= +55.9 (*c* 1.0 DCM); ^1H NMR (300 MHz, CD_2Cl_2): δ 8.05 (s, 2H), 7.91 (s, 1H), 7.89 (s, 1H), 7.82 (s, 2H), 4.49 (dd, *J* = 7.9 Hz, 6.2 Hz, 1H), 4.24 (t, *J* = 7.5 Hz, 1H), 2.21 (brs, 1H), 1.88–1.80 (m, 3H), 1.67–1.55 (m, 1H), –0.04

(s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 148.4, 146.7, 145.5 (app. d, *J* = 246.8 Hz), 140.6 (app. d, *J* = 252.2 Hz), 138.2 (app. d, *J* = 251.8 Hz), 132.0 (q, *J* = 33.4 Hz), 131.6 (q, *J* = 33.3 Hz), 129.4, 128.3, 123.8 (q, *J* = 272.7 Hz), 123.7 (q, *J* = 272.7 Hz), 122.5–122.4 (m, *two overlapping signals*), 118.0 (t, *J* = 15.1 Hz), 82.7, 65.5, 53.5 (*overlaps with the NMR solvent signals*), 32.8, 29.3, 1.9; HRMS (ESI$^+$): m/z calculated for $[C_{30}H_{23}N_1O_1F_{17}Si_1]^+$ = 764.1272, found 764.1283, Δ= –1.4 ppm.

8.5 Enzymatic diketone reduction studies

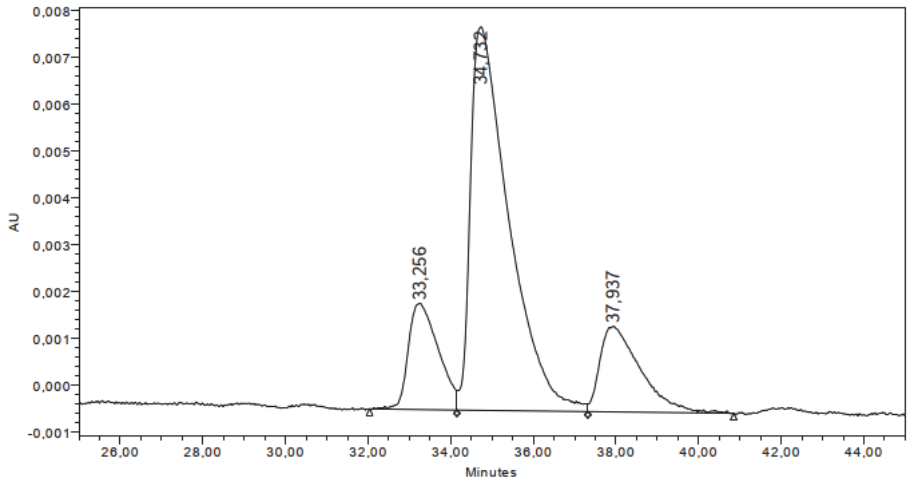


34a **55a**

The general procedure[248] was followed with the following modifications: Cofactor–buffer-mixes* KRED Mix N (302 mg) and KRED Mix P (604 mg) were dissolved in deionised water (6.0 mL and 20.0 mL, respectively). The commercial KRED screening pack of 24 enzymes by Codexis was used.

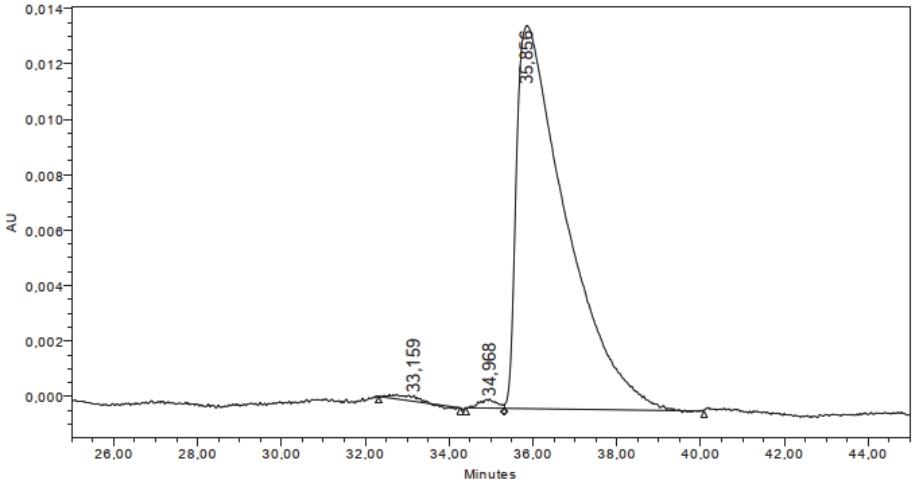
A solution of diketone **34a** (~10 mg) in isopropanol-THF (9:1, 0.1 mL) was added to a solution of enzyme (~10 mg) in KRED Mix solution (0.9 mL). The reaction mixtures were stirred 18 hours at 30 °C. To drive the reactions to completion, the temperature was raised to 40 °C. After 24 hours, isopropanol (0.3 mL) and $NADP^+$ (~1 mg) were added to the reactions, which utilised these compounds in the reduction cycle, and NAD^+ (~1 mg) to the rest. The temperature was raised to 50 °C, and the reactions were let to proceed for additional 14 hours. The reactions, which showed the formation of the product based on TLC, were worked up by adding EtOAc (1.5 mL) and washed with sat. aq. NaCl (0.3 mL). The organic phases were separated by centrifuging, dried with Na_2SO_4 and filtered. The samples were analysed by chiral HPLC (CHIRALPAK IB, isopropanol-hexane 3:97, 1 mL/min, 254 nm, 10 µl inj.). The results were compared with a sample consisting of (±)-**55a** and *meso*-**55a**, synthesised from the parent diketone **34a** by borane reduction.

* When dissolved in water, KRED Mix N contains 263 mM Na_3PO_4, 1.7 mM $MgSO_4$, 1.1 mM $NADP^+$, 1.1 mM NAD^+, 80 mM D-glucose and 4.3 U/mL glucose dehydrogenase at pH 7.0 and KRED Mix P contains 128 mM Na_3PO_4, 1.7 mM $MgSO_4$ and 1.1 mM $NADP^+$ at pH 7.0.



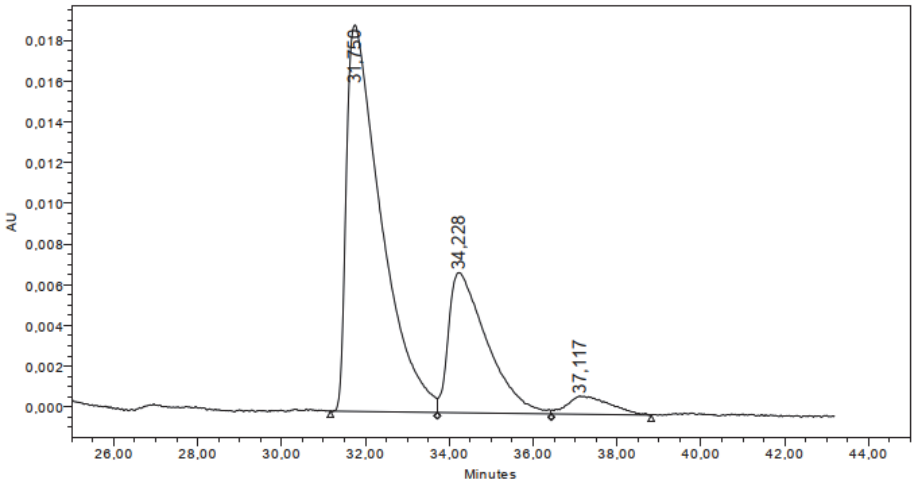
	RT	Area	% Area	Height
1	33,256	114535	14,93	2271
2	34,732	528210	68,86	8187
3	37,937	124331	16,21	1825

Figure 10: An HPLC chromatogram of a mixture of (±)-**55a** and *meso*-**55a**.



	RT	Area	% Area	Height
1	33,159	9651	0,84	210
2	34,968	9264	0,80	322
3	35,856	1136895	98,36	13797

Figure 11: An HPLC chromatogram from a reduction reaction conducted with enzyme P1-B02.

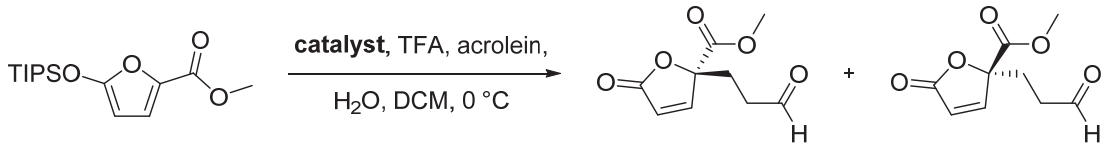


	RT	Area	% Area	Height
1	31,750	1090169	68,50	18967
2	34,228	438712	27,56	6883
3	37,117	62714	3,94	885

Figure 12: An HPLC chromatogram from a reduction reaction conducted with enzyme P2-D03.

8.6 Mukaiyama–Michael reaction screening studies

8.6.1 Catalyst screenings

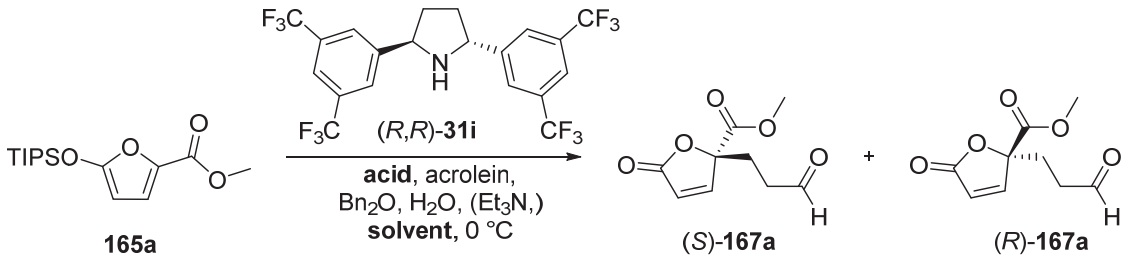


165a (*S*)-**167a** (*R*)-**167a**

General procedure: A **catalyst** (0.2 equiv), TFA (0.2 equiv), H_2O (2.0 equiv), DCM (0.17 M) and acrolein (5.0 equiv) were mixed in a 4 mL vial and cooled down to 0 °C. After ~10 minutes, silyloxyfuran **165a** (1.0 equiv) was added. After the specified time, a sample was taken from the reaction mixture, diluted with 1 mL of DCM, washed with sat. aq. $NaHCO_3$ and the phases were separated. The organic phase was analysed with chiral GC (B-DM column, 150 °C, isotherm). Another sample (~50 µl) was also taken and diluted with $CDCl_3$.

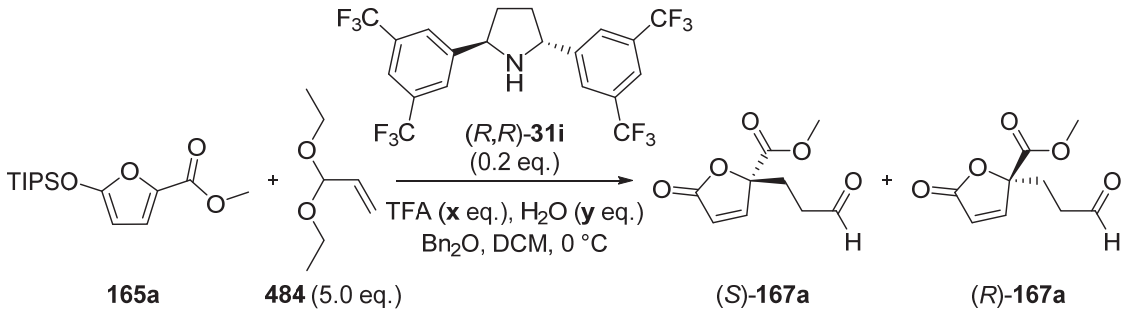
The SM:product-ratios were determined from ^1H NMR spectra by comparing the integral of the double bond proton of starting material **165a** (1H, 7.09 ppm) with the integral of the double bond proton of the product **167a** (1H, 6.17 ppm). When applicable, the conversion was determined from ^1H NMR spectra by comparing the integral of the benzylic protons of dibenzyl ether (0.42 mM, 4H, 4.56 ppm) with the integral of the double bond proton of **167a** (1H, 6.17 ppm).

8.6.2 Screening of acids, conditions and solvents



General procedure: The catalyst (*R*,*R*)-**31i** (0.2 equiv), **acid** (0.2 equiv), H_2O (2.0 equiv), **solvent** (0.17 M), (Et_3N, 0.04 equiv *or* 0.09 equiv *when used*) dibenzyl ether (0.42 mM) and acrolein (5.0 equiv) were mixed in a 4 mL vial and the mixture was cooled down to 0 °C with stirring. After ~10 min, silyloxyfuran **165a** (1.0 equiv) was added. After the specified time, a ~50 µL sample was taken from the reaction mixture and diluted with $CDCl_3$. The conversion was determined from ^1H NMR spectra by comparing the integral of the benzylic protons of dibenzyl ether (4H, 4.56 ppm) with the integral of the double bond proton of **167a** (1H, 6.17 ppm). The enantiomeric ratios were determined as described in subsection 8.6.1.

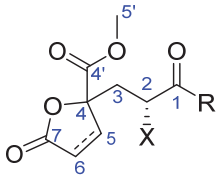
8.6.3 Initial studies with the acrolein substitute diethyl acetal acrolein



General procedure: The catalyst (*R*,*R*)-**31i** (0.2 equiv), TFA (0.2/0.5 equiv), H_2O (2.0/4.0/6.0/7.5 equiv), DCM (0.17 M), dibenzyl ether (0.42 mM) and diethyl acetal acrolein (5.0 equiv) were mixed in a 4 mL vial and the mixture was cooled down to 0 °C with stirring. After ~10 min, silyloxyfuran **165a** (1.0 equiv) was added. After the specified time, a ~50 µL sample was taken from the reaction mixture and diluted with $CDCl_3$. The conversion was determined from ^1H NMR spectra as described in subsection 8.6.2. The enantiomeric ratios were determined as described in subsection 8.6.1.

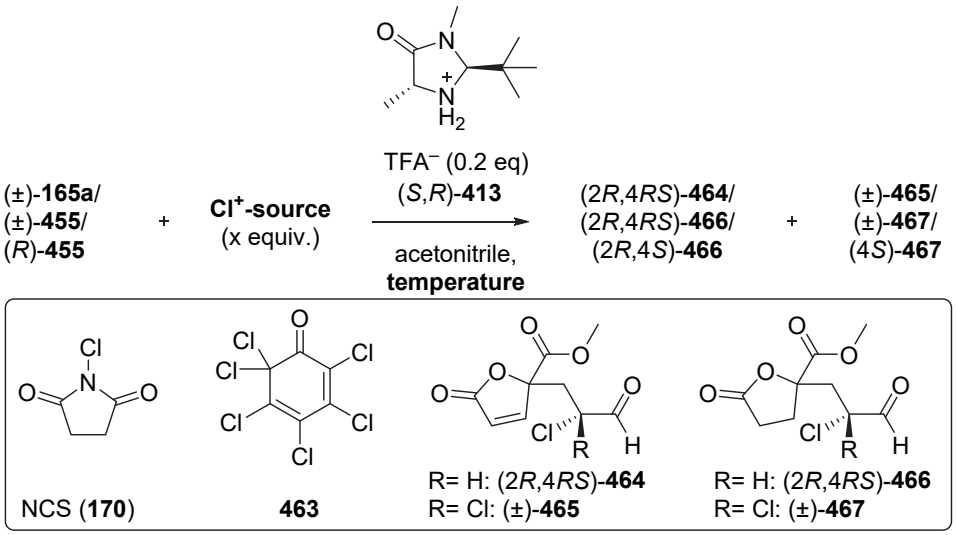
8.7 α-Chlorination screening studies

Non-IUPAC nomenclature notice: compounds were short-named according to below numbering when diastereomeric mixtures were used.



(2*R*,4*RS*)-**462**
or (*R*,*RS*)-**462**,
the first letter describing the C2-stereocenter
and the second one the C4-stereocenter

8.7.1 General procedure for the α-chlorinations

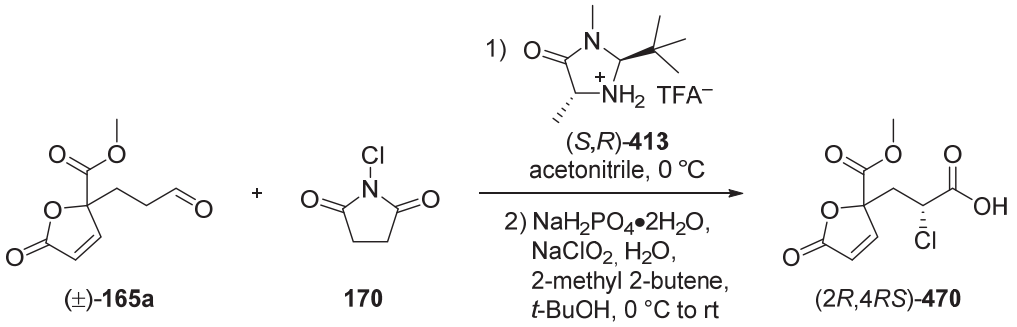


To a stirred solution of Cl^+-source (1.0–1.2 equiv) and TFA-salt of (*S*,*R*)-**413** (0.20 equiv) in acetonitrile (0.25 M) at set temperature (–27 °C/0 °C/rt) was added the aldehyde (**165a** or **455**, 1.0 equiv). After the specified time, a small sample was withdrawn from the reaction mixture, diluted with CD_3CN and a ^1H NMR spectrum recorded to find the disappearance of the starting material (triplet (J = 0.93 Hz) of **165a** in CD_3CN at 9.61 ppm and triplet (J = 1.2 Hz) of **455** in CD_3CN at 9.66 ppm).

When applicable, 1,2,4,5-tetramethylbenzene was used as an internal standard (either 0.22 mM or 0.25 mM in acetonitrile). The conversions were determined from ^1H NMR spectra of reaction mixture samples by comparing the integrals of the aromatic C–H-protons (s, 2H, 6.88 ppm) with the sum of integrals of the diastereomeric aldehyde **466** protons (d, 1H, 9.43 ppm; d, 1H, 9.41 ppm). The conversion of dichlorocompound **467** (s, 1H, 9.27 ppm) was determined in the similar manner.

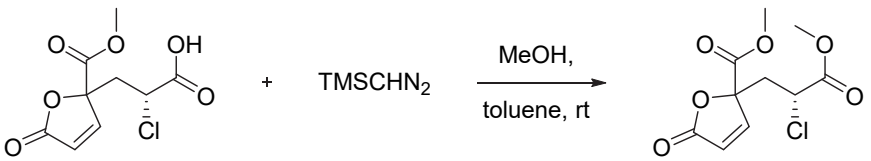
The *dr* were determined from the ^1H NMR spectra by integrating the aldehyde proton signals separately. For aldehyde **464**, the product aldehyde peaks were visible at 9.40 ppm (d, J = 1.0 Hz, 1H) and 9.38 ppm (d, J = 1.4 Hz, 1H).

8.7.2 Methyl 2-((*R*)-2-chloro-3-methoxy-3-oxopropyl)-5-oxo-2,5-dihydrofuran-2-carboxylate [(2*R*,4*RS*)-471]



(±)-**165a** **170** (2*R*,4*RS*)-**470**

To a dissolved solution of (±)-**165a** (0.103 g, 0.521 mmol, 1.0 eq) was added TFA-salt of imidazolidinone (*S*,*R*)-**413** (0.031 g, 0.108 mmol, 0.21 equiv) and *N*-chlorosuccinimide (0.080 g, 0.596 mmol, 1.1 equiv) at 0 °C and stirred for 3 hours. To the reaction mixture was added *t*-BuOH (4.0 mL), 2-methyl 2-butene (0.4 mL, 3.59 mmol, 6.9 equiv) and NaH_2PO_4 dihydrate (0.166 g, 1.06 mmol, 2.0 equiv) dissolved in water (1.7 mL), after which $NaClO_2$ (0.232 g, 2.05 mmol, 4.0 equiv) dissolved in water (1.7 mL) was added dropwise. After the addition of $NaClO_2$-solution, the reaction mixture was let to warm up to rt and stir for one hour. The reaction mixture was worked up by adding sat. aq. NaCl (4.0 mL) and extracting with EtOAc (4.0 mL). The organic phase was dried with Na_2SO_4, filtered and the solvents evaporated. The crude acid (2*R*,4*RS*)-**470** was used in the next step without further purification.



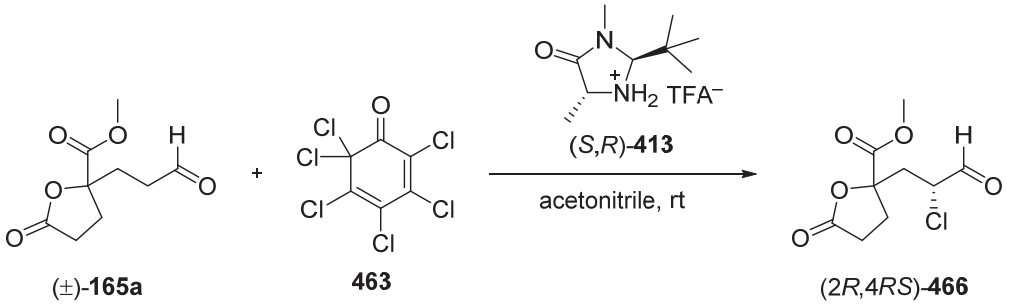
(2*R*,4*RS*)-**470** (2*R*,4*RS*)-**471**

To a solution of crude acid (2*R*,4*RS*)-**470** in methanol (3.0 mL) and toluene (10 mL) was added $TMSCHN_2$ (2.0 M in Et_2O, 0.49 mL, 0.980 mmol, 1.9 equiv) until the yellow colour persisted. The solution was stirred for 2.5 hours, after which more $TMSCHN_2$ (0.25 mL, 0.500 mmol, 1.0 equiv) was added to drive the reaction towards completion. After 1.5 hours, the reaction was quenched with AcOH, until the yellow colour disappeared. The mixture was worked up by adding water (10 mL) and extracting with EtOAc (2 x 5 mL). The combined organics were dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by column chromatography (EtOAc-hexane 20:80 to 40:60) to give (2*R*,4*RS*)-**471** along with few impurities (35.0 mg, 0.133 mmol, 26%).

^{1}H NMR (400 MHz, $CDCl_3$, *mixture of diastereomers*): δ 7.50 (d, *J* = 5.6 Hz, 0.5H), 7.44 (d, *J* = 5.6 Hz, 0.5H), 6.21 (d, *J* = 5.6 Hz, 0.5H), 6.16 (d, *J* = 5.6 Hz, 0.5H), 4.47 (dd, *J* = 7.3 Hz, 6.4 Hz, 0.5H), 4.25 (dd, *J* = 6.7 Hz, 6.5 Hz, 0.5H), 3.80 (s, 1.5H), 3.779 (s, 3H), 3.776 (s, 1.5H), 3.07 (dd, *J* = 15.3 Hz, 6.3 Hz, 0.5H), 2.87 (dd, *J* = 14.9 Hz, 7.2 Hz, 0.5H), 2.70 (dd, *J* = 14.9 Hz, 6.4 Hz, 0.5H), 2.67 (dd, *J* = 15.2 Hz, 6.8

Hz, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$, *mixture of diastereomers*): δ 170.7, 170.5, 169.1, 168.9, 167.2, 167.1, 153.9, 153.8, 122.5, 122.3, 87.3, 87.1, 53.83, 53.82, 53.5 (*two overlapping signals*), 51.3, 50.9, 40.1, 40.0.

8.7.3 Methyl 2-((*R*)-2-chloro-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(2*R*,4*RS*)-466]

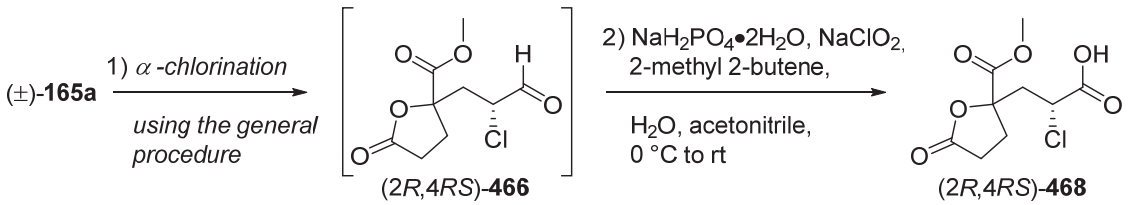


An isolated example of chloroaldehyde (2*R*,4*RS*)-**466** was obtained using the general procedure for the α-chlorinations with the following changes: To a stirred solution of **463** (254 mg, 0.836 mmol, 1.1 equiv) and TFA-salt of (*S*,*R*)-**413** (44.2 mg, 0.155 mmol, 0.20 equiv) in acetonitrile (0.80 mL) at rt was added the aldehyde (±)-**165a** (152 mg, 0.757 mmol, 1.0 equiv). After 1 hour, the reaction mixture was directly purified by column chromatography (Et_2O:EtOAc gradient from 100:0 to 0:100) to give the product as oil with few impurities (175 mg, 0.744 mmol, 98%).

Characterisation data for diastereomeric mixture of chloroaldehyde (2*R*,4*RS*)-**466**.

^{1}H NMR (300 MHz, $CDCl_3$, *mixture of diastereomers*): δ 9.51 (d, *J* = 0.87 Hz, 0.6H), 9.46 (d, *J* = 1.6 Hz, 0.4H), 4.52 (ddd, *J* = 8.5 Hz, 4.7 Hz, 0.82 Hz, 0.6H), 4.41 (td, *J* = 6.2 Hz, 1.5 Hz, 0.4H), 3.83 (s, 2H), 3.81 (s, 1H), 3.04 (dd, *J* = 15.2 Hz, 6.6 Hz, 0.4H), 2.67–2.49 (m, 4.2H, *overlapping signals*), 2.42–2.26 (m, 1.4H, *overlapping signals*); ^{13}C NMR (75 MHz, CD_3CN, *major diastereomer peaks*): δ 194.5, 176.4, 172.4, 84.4, 59.7, 53.7, 39.9, 33.3, 28.2; (*minor diastereomer peaks*): δ 194.9, 176.5, 172.3, 84.8, 60.0, 53.8, 39.6, 32.8, 28.1; HRMS (ESI$^+$): m/z calculated for $[C_9H_{11}O_5Cl_1C_1H_3O_1H_1Na_1]^+$ = 289.0449, found 289.0451, Δ= –0.55 ppm.

8.7.4 (2*R*)-2-chloro-3-(2-(methoxycarbonyl)-5-oxotetrahydrofuran-2-yl)propanoic acid [(2*R*,4*RS*)-468]



The general procedure for the α-chlorinations with the following changes was used: To a stirred solution of 4**63** (154 mg, 0.507 mmol, 1.1 equiv) and TFA-salt of (*S*,*R*)-**413** (27.1 mg, 95 μmol, 0.20 equiv) in acetonitrile (2.5 mL) at 0 °C was

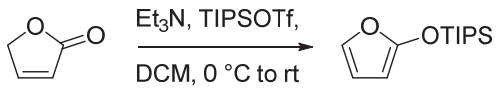
added the aldehyde (±)-**165a** (92.5 mg, 0.462 mmol, 1.0 equiv). After the consumption of the starting material, 2-methyl 2-butene (0.20 mL, 1.51 mmol, 3.3 equiv) and NaH_2PO_4 dihydrate (37.0 mg, 0.235 mmol, 0.50 equiv), dissolved in water (0.72 mL), were added to the same reaction vessel, after which $NaClO_2$ (104 mg, 1.14 mmol, 2.5 equiv), dissolved in water (0.24 mL), was added dropwise. The reaction was let to warm up to rt. After 1 hour, ACN (0.7 mL), 2-methyl 2-butene (0.20 mL, 1.51 mmol, 3.3 equiv) and $NaClO_2$ (115 mg, 1.26 mmol, 2.7 equiv), dissolved in water (0.72 mL), were added at 0 °C to drive the reaction to completion. The reaction was let to warm up to rt. After 11 hours, the mixture was worked up by adding sat. aq. NaCl (4.0 mL) and extracting with EtOAc (4 x 4 mL). The combined organics were dried (Na_2SO_4), filtered and solvents evaporated. The crude was purified by column chromatography (DCM-MeOH gradient from 100:0 to 50:50), which gave the product (2*R*,4*RS*)-**468** with few impurities (14.0 mg, 55.9 µmol, 12%).

The crude obtained from the water phase after the above work up was concentrated, the residue dissolved in acetone and filtered through cotton. After the solvents were evaporated, the crude was purified by column chromatography in the above manner to give the product with few impurities (74.7 mg, 0.298 mmol, 65%), the combined total yield being 88.7 mg (0.354 mmol, 77%).

^{1}H NMR (400 MHz, CD_3OD, *mixture of diastereomers*): δ 4.39 (dd, *J* = 8.7 Hz, 5.1 Hz, 0.6H), 4.36 (dd, *J* = 7.2 Hz, 6.1 Hz, 0.4H), 3.80 (s, 1.9H), 3.79 (s, 1.1H), 2.91 (dd, *J* = 15.0 Hz, 7.2 Hz, 0.4H), 2.73–2.68 (m, 1H), 2.67–2.60 (m, 2H), 2.58–2.44 (m, 1.8H), 2.37 (ddd, *J* = 13.0 Hz, 9.9 Hz, 8.5 Hz, 0.8H); ^{13}C NMR (100 MHz, CD_3OD, *major diastereomer peaks*): δ 178.1, 174.9, 173.3, 85.7, 57.3, 53.5, 44.0, 33.6, 28.42; (*minor diastereomer peaks*): δ 178.3, 174.7, 172.8, 86.3, 56.6, 53.6, 43.5, 32.5, 28.44.

8.8 The total synthesis route

8.8.1 (Furan-2-yloxy)triisopropylsilane (410a)



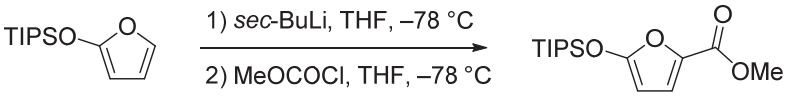
409 **410a**

To a stirred solution of **409** (2.11 g, 25.1 mmol, 1.0 equiv) in DCM (20 mL) at 0 °C was added Et_3N (7.0 mL, 50.2 mmol, 2.0 equiv), followed by dropwise addition of TIPSOTf (7.8 mL, 28.8 mmol, 1.2 equiv). The cooling bath was removed and the reaction mixture was allowed to warm to rt. After 2.5 h, water (20 mL) was added. The phases were separated, and the aqueous phase was extracted with DCM (5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography

using deactivated silica (pentane) giving the desired product **410a** as a colourless oil (5.84 g, 24.3 mmol, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (dd, *J* = 2.1 Hz, 1.1 Hz, 1H), 6.20 (dd, *J* = 3.0 Hz, 2.3 Hz, 1H), 5.12 (dd, *J* = 3.1 Hz, 0.98 Hz, 1H), 1.34–1.19 (m, 3H), 1.10 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 132.0, 111.2, 83.6, 17.7, 12.4.
The spectral data matched that of reported in literature.[36]

8.8.2 Methyl 5-((triisopropylsilyl)oxy)furan-2-carboxylate (165a)

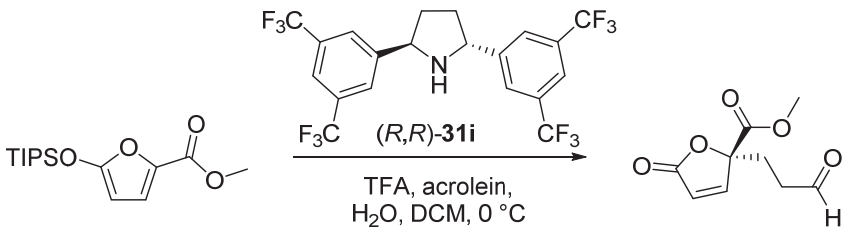


410a **165a**

To a stirred solution of **410a** (5.8 g, 24.3 mmol, 1.0 equiv) in THF (60 mL) at –78 °C was added *sec*-BuLi (1.3 M, 19.7 mL, 25.6 mmol, 1.1 equiv) dropwise (*CAUTION: sec-BuLi is pyroforic, air and moisture sensitive reagent*). After 1 hour, a solution of MeOCOCl (1.98 mL, 25.6 mmol, 1.1 equiv) in THF (2 mL) was added dropwise *via* cannula. After 1 hour, the reaction mixture was allowed to warm to rt and then concentrated. The residue was dissolved in EtOAc (100 mL) and filtered through a glass sintered funnel. The filtrate was washed with water (40 mL+30 mL), and the aqueous phases were back-extracted with EtOAc (2 x 40 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by Kugelrohr distillation in vacuum ($1.0 \bullet 10^{-1}$ mbar, 170 °C) to give ester **165a** as a yellow oil (2.17 g, 7.26 mmol, 30%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, *J* = 3.5 Hz, 1H), 5.30 (d, *J* = 3.5 Hz, 1H), 3.82 (s, 3H), 1.36–1.23 (m, 3H), 1.11 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 159.0, 133.9, 121.8, 87.6, 51.5, 17.6, 12.4.
The spectral data matched those reported in literature.[190]

8.8.3 Methyl (*R*)-5-oxo-2-(3-oxopropyl)-2,5-dihydrofuran-2-carboxylate [(*R*)–167a]



165a (*R*)-**167a**

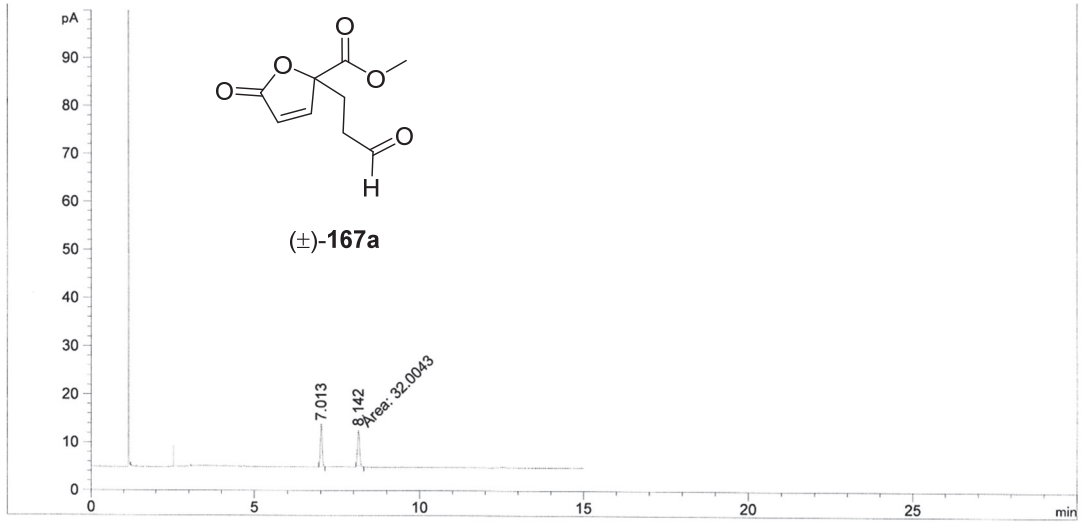
To a solution of catalyst (*R*,*R*)-**31i** (0.731 g, 1.48 mmol, 0.20 equiv), TFA (0.11 mL, 1.42 mmol, 0.20 equiv), H_2O (0.26 mL, 14.4 mmol, 2.0 equiv) in DCM (20 mL) at 0 °C was added acrolein (2.7 mL, 36.4 mmol, 5.0 equiv). A solution of **165a** (2.17 g, 7.26 mmol, 1.0 equiv) in DCM (15 mL) was added. After 26 h, sat. aq. $KHSO_4$ (10 mL) was added. The phases were separated and the aqueous phase was ex-

tracted with DCM (5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (EtOAc-hexane 40:60 to 0:100) to give (*R*)-**167a** as a yellow oil (0.676 g, 3.41 mmol, 47%, *er* 94:6). The enantiomeric ratio was determined by GC (SUPELCO Astec CHIRALDEX B-DM column, 150 °C isothermic); (*S*)-enantiomer: τ= 6.9 min, (*R*)-enantiomer: τ= 8.0 min (see the following page).

R_f (EtOAc-hexane 50:50)= 0.25; IR (film, cm^{-1}): 2957, 1739, 1438, 1279, 1103, 1002, 821; $[\alpha]_D$= +118.0 (*c* 0.99 DCM); ^1H NMR (300 MHz, $CDCl_3$): δ 9.75 (brs, 1H), 7.41 (d, *J* = 5.6 Hz, 1H), 6.17 (d, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 2.62–2.48 (m, 3H), 2.35–2.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 171.1, 167.8, 154.4, 122.5, 88.7, 53.7, 37.8, 27.6; HRMS (ESI^+): m/z calculated for $[C_9H_{10}O_5Na_1]^+$ = 221.0420, found 221.0425, Δ= –2.3 ppm.

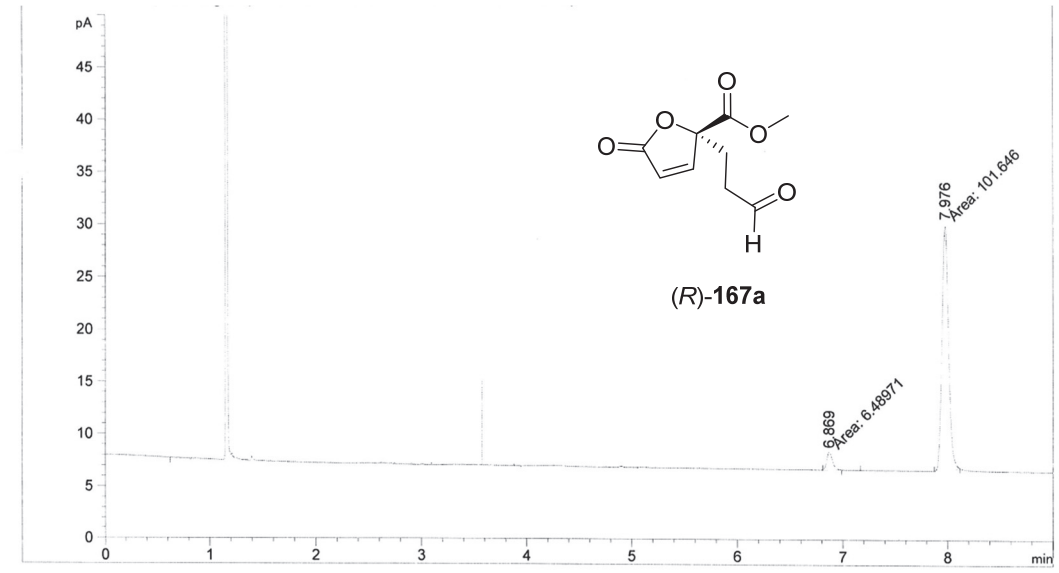
A racemic batch was synthesised in the same manner in 71% yield, using dibenzylamine as the secondary amine catalyst. The spectral data matched those of an enantioenriched sample.

GC chromatograms of racemic (±)-**167a** and (*R*)-**167a**, the latter prepared with catalyst (*R,R*)-**31i**:



(±)-**167a**

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.013	BB	0.0615	34.24785	8.79046	51.69321
2	8.142	MM	0.0716	32.00427	7.45477	48.30679
Totals :				66.25212	16.24523	



(*R*)-**167a**

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.869	MM	0.0631	6.48971	1.71354	6.00144
2	7.976	MM	0.0722	101.64609	23.45500	93.99856
Totals :				108.13579	25.16854	

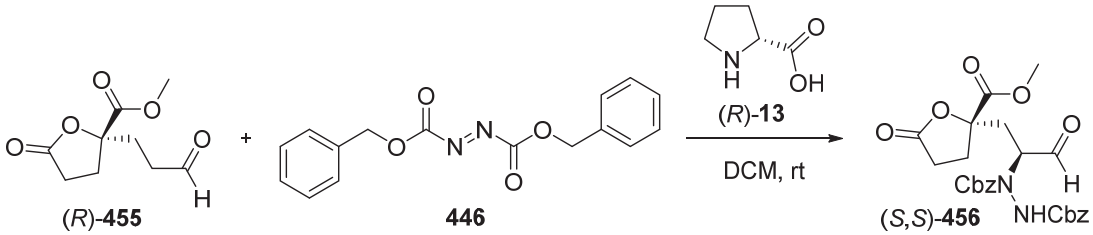
8.8.4 Methyl (*R*)-5-oxo-2-(3-oxopropyl)tetrahydrofuran-2-carboxylate [(*R*)–455]

Pd/C (5% w/w Pd in charcoal, 71 mg, 11 w-%) was mixed with aldehyde (*R*)-**167a** (0.676 g, 3.41 mmol, 1.0 equiv) in EtOAc (6.0 mL) under argon. After the atmosphere was changed to hydrogen (*via* three vacuum/hydrogen flush cycles), the mixture was vigorously stirred for 4 h. The flask was purged with argon, and the reaction mixture was filtered through a pad of Celite and the pad was rinsed with EtOAc. The filtrate was concentrated and the residue was purified by flash column chromatography (EtOAc-hexane 50:50 to 75:25) to give aldehyde (*R*)-**455** as a clear oil (0.597 g, 2.93 mmol, 86%).

R_f (EtOAc-hexane 50:50)= 0.28; IR (film, cm^{-1}): 2958, 2848, 1782, 1737, 1719, 1439, 1267, 1166, 1092, 979; $[\alpha]_D$= +8.1 (*c* 0.96 DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (brs, 1H), 3.81 (s, 3H), 2.77–2.39 (m, 6H), 2.24–2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 175.4, 171.5, 85.5, 53.3, 38.8, 32.1, 29.8, 28.0; HRMS (ESI^+): m/z calculated for $[C_9H_{12}O_5Na_1]^+$ = 223.0577, found 223.0581, Δ= –1.8 ppm.

A racemic batch was synthesised in the same manner using (±)-**167a** as starting material in 76% yield and the spectral data matched those of an enantioenriched sample.

8.8.5 Dibenzyl 1-((*S*)-1-((*S*)-2-(methoxycarbonyl)-5-oxotetrahydrofuran-2-yl)-3-oxopropan-2-yl)hydrazine-1,2-dicarboxylate [(*S*,*S*)-456]

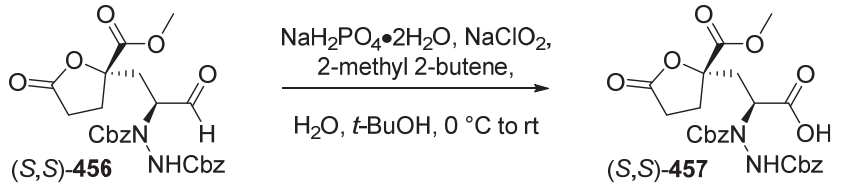


A mixture of aldehyde (*R*)-**455** (312 mg, 1.56 mmol, 1.0 equiv) and (*R*)-proline ((*R*)-**13**, 36.0 mg, 0.313 mmol, 0.20 equiv) in DCM (12 mL) at rt was stirred for 10 min. Dibenzylazodicarboxylate (**446**, 543 mg, 1.64 mmol, 1.1 equiv) was then added in one portion. After 6.5 h, aq. NH_4Cl (sat., 25 mL) was added and the resulting mixture was extracted with DCM (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (DCM-MeOH gradient from 99:1 to 95:5) to give aldehyde (*S*,*S*)-**456** as a viscous foam (659 mg, 1.32 mmol, 85%).

R_f (DCM-MeOH 98:2)= 0.26; IR (film, cm^{-1}): 3311, 2955, 1789, 1717, 1455, 1406, 1211, 1170, 1045, 982, 742, 696; $[\alpha]_D$= –2.1 (*c* 0.99 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, *mixture of rotamers*): δ 9.89–9.59 (m, 1H), 7.31 (brs, 10H), 7.03–6.78 (m, 1H), 5.17–5.12 (m, 4H), 4.73–4.37 (m, 1H), 3.80–3.42 (m, 3H), 2.80–2.09 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, *mixture of rotamers*): δ 198.8/198.1, 175.2, 171.1, 155.9, 155.0, 135.5, 135.4, 128.7, 128.7, 128.4, 128.3, 127.7, 84.8, 68.9, 68.2, 65.5, 53.5, 33.5, 33.1, 27.3 (*phenyl-carbons could not be assigned separately due to overlap of the aromatic carbons*); HRMS (ESI^+): m/z calculated for $[C_{25}H_{26}N_2O_9C_1H_3O_1H_1Na_1]^+$ = 553.1793, found, 553.1821 Δ= –5.1 ppm.

The corresponding diastereomeric mixture was synthesised in the above manner using (±)-**455** as starting material in 76% yield. The spectral data resembled those of diastereoenriched sample. In both cases, the *dr* could not be determined from the ^1H spectra due to rotamers.

8.8.6 (*S*)-2-(1,2-bis((benzyloxy)carbonyl)hydrazineyl)-3-((*S*)-2-(methoxycarbonyl)-5-oxotetrahydrofuran-2-yl)propanoic acid [(*S*,*S*)-457]

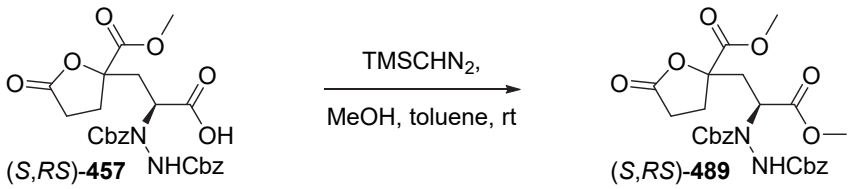


To a stirred solution of aldehyde (*S*,*S*)-**456** (628 mg, 1.26 mmol, 1.0 equiv) and 2-methyl 2-butene (0.93 mL, 8.82 mmol, 7.0 equiv) in *t*-BuOH (23 mL) at rt was added a solution of $NaH_2PO_4 \bullet 2H_2O$ (398 mg, 2.55 mmol, 2.0 equiv) in water (2.2 mL). The resulting heterogeneous mixture was cooled to 0 °C. Then, a solution of $NaClO_2$ (571 mg, 5.1 mmol, 4.0 equiv) in water (2.2 mL) was added dropwise. The cooling bath was removed and the reaction mixture was allowed to warm to rt. After 5 hours, brine (35 mL) was added and the solution extracted with EtOAc (2 x 20 mL). After the solvents were evaporated, the crude was purified by column chromatography (DCM-MeOH gradient from 98:2 to 80:20). The product was an off-white solid (399 mg, 0.776 mmol, 62%).

R_f (DCM-MeOH 92:8)= 0.23; IR (film, cm^{-1}): 3275, 2920, 1788, 1715, 1498, 1454, 1404, 1212, 1168, 1043, 983, 817, 739, 579; mp 50–52 °C; $[\alpha]_D$= –2.5 (*c* 1.0 DCM); ^1H NMR (400 MHz, CD_3OD, *mixture of rotamers*): δ 7.36–7.29 (m, 11H), 5.17–5.07 (m, 4H), 4.91–4.81 (m, 1H, *overlaps with the signal of water*), 3.74 (brs, 1.9H), 3.66 (brs, 1.1H), 2.81–2.68 (m, 1H), 2.52–2.44 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD, *mixture of rotamers, which are assigned as pairs and denoted with "/"*): δ 178.3/178.1, 174.3, 173.1, 159.0, 157.4, 137.5, 137.3, 129.5, 129.2, 128.9/128.7, 86.5, 69.7/69.3, 68.6, 59.2, 53.55/53.46, 36.7, 32.4/31.5, 28.7/28.6; HRMS (ESI^+): m/z calculated for $[C_{25}H_{26}N_2O_{10}Na_1]^+$ = 537.1480, found 537.1469, Δ= –2.0 ppm.

The corresponding diastereomeric mixture was synthesised in the above manner using (2*S*,4*RS*)-**456** as starting material in 90% yield. The spectral data resembled those of diastereoenriched sample. In both cases, the *dr* could not be determined from the ^{1}H spectra due to rotamers.

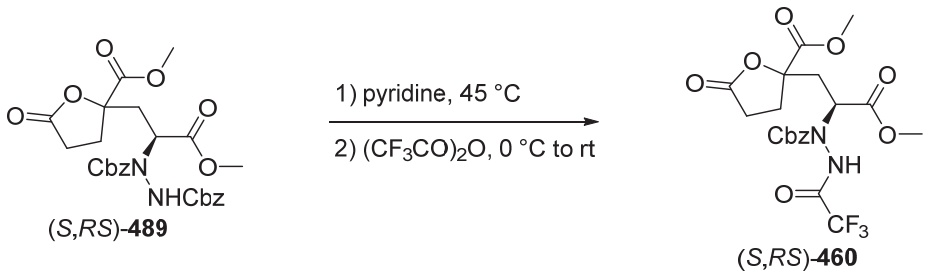
8.8.7 Dibenzyl 1-((2*S*)-1-methoxy-3-(2-(methoxycarbonyl)-5-oxotetrahydrofuran-2-yl)-1-oxopropan-2-yl)hydrazine-1,2-dicarboxylate [(*S*,*RS*)-489]



To a stirred solution of acid (*S*,*RS*)-**457** (0.818 g, 1.59 mmol, 1.0 equiv), methanol (14.0 mL) and toluene (7.0 mL) was added $TMSCHN_2$ (2.0 M in Et_2O, 1.7 mL, 3.40 mmol, 2.1 equiv) dropwise. After 3 hours, the reaction was quenched with few drops of AcOH, until the yellow colour completely disappeared. The volatiles were evaporated and the crude was purified by column chromatography (DCM-MeOH gradient from 100:0 to 80:20) to give the product (474 mg, 0.897 mmol, 56%).

R_f (DCM-MeOH 99:1)= 0.28; ^{1}H NMR (300 MHz, $CDCl_3$, *mixture of rotamers and diastereomers*): δ 7.33 (brs, 10H), 6.79 (brs, 1H), 5.14 (brs, 5H), 3.81 (brs, 2.3H), 3.74 (brs, 0.7H), 3.68 (brs, 3H), 2.81 (brs, 0.6H), 2.69 (brs, 0.4H), 2.45 (brs, 2H), 2.39 (brs, 2H), 2.19 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, *mixture of rotamers and diastereomers, which were assigned as pairs/groups of chemical shifts, denoted with "/"*): δ 172.9/172.5, 171.51, 170.8, 156.5, 155.0, 135.7/135.3, 128.7, 128.3, 128.0, 83.1, 69.0/68.6, 68.3/68.0, 58.8, 53.4/53.3, 52.0/51.9, 34.9, 32.3/31.8, 28.5; HRMS (ESI$^+$): m/z calculated for $[C_{26}H_{28}O_{10}N_2K_1]^+$ = 567.1376, found 567.1366, Δ= 1.7 ppm.

8.8.8 Benzyl 1-((2*S*)-1-methoxy-3-(2-(methoxycarbonyl)-5-oxotetrahydrofuran-2-yl)-1-oxopropan-2-yl)-2-(2,2,2-trifluoroacetyl)hydrazine-1-carboxylate [(*S*,*RS*)-460]

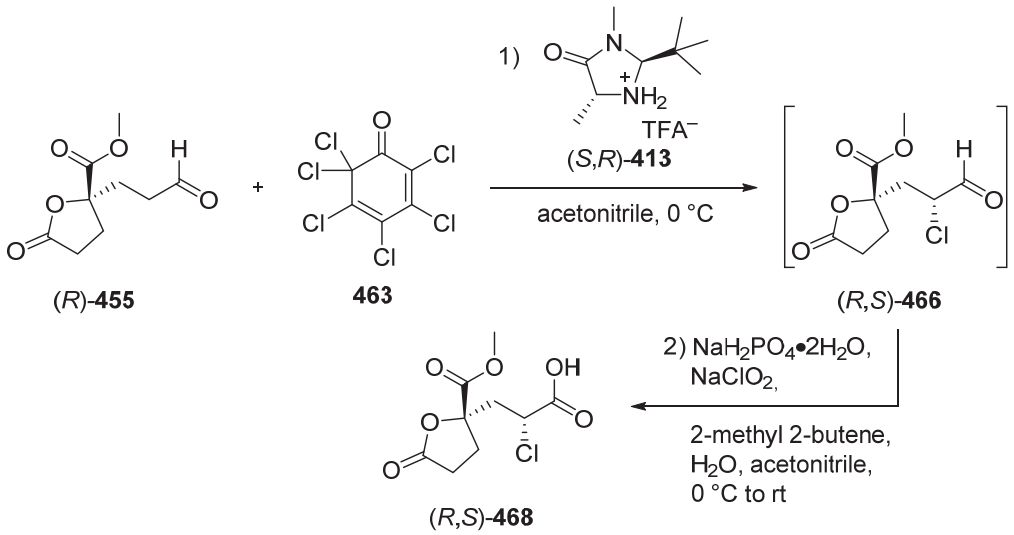


Stirred solution of diester (*S*,*RS*)-**489** (0.115 mg, 0.218, 1.0 equiv) in pyridine (2.0 mL) was heated up to 45 °C. After 16 hours, the reaction mixture was cooled down to 0 °C and TFA-anhydride (0.17 mL, 1.21 mmol, 5.6 equiv) was added

dropwise, after which the reaction mixture was let to warm up to rt. After 48 hours, the volatiles were evaporated and the crude purified by column chromatography (EtOAc-hexane 80:20 to 30:70) to give the product with few impurities (62.3 mg, 0.127 mmol, 58%).

R_f (EtOAc-Hex 30:70)= 0.20; ^{1}H NMR (400 MHz, $CDCl_3$, *mixture of rotamers and diastereomers, which were assigned as pairs/groups of chemical shifts, denoted with "/"*): δ 9.18 (brs, 1H), 7.37–7.23 (m, 5H, *overlaps with residual $CHCl_3$*), 5.27–5.11 (m, 3H, *overlapping benzylic and a-proton signals*), 3.86/3.80 (s, 3H), 3.69/3.66 (s, 3H), 2.98–2.79 (m, 1H), 2.68–2.53 (m, 1H), 2.52–2.40 (m, 2H), 2.38–2.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, *mixture of rotamers and diastereomers, which were assigned as pairs/groups of chemical shifts, denoted with "/"*): δ 172.62/172.52/172.46, 171.4/168.8, 170.6/170.1, 157.9, 153.6, 134.7, 128.8, 128.5, 128.1, 115.4 (q, *J* = 288.1 Hz)/115.0 (q, *J* = 271.6 Hz), 83.6/83.4/83.3, 69.6/68.6, 59.2/54.71, 53.9/53.6, 52.2/52.1, 35.6/35.0, 31.96/31.93, 28.54/28.44/28.39; HRMS (ESI$^+$): m/z calculated for $[C_{20}H_{21}O_9N_2F_3Na_1]^+$ = 513.1091, found 513.1082, Δ= 1.8 ppm.

8.8.9 Methyl (*S*)-2-((*R*)-2-chloro-3-methoxy-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(*R*,*S*)-469a]

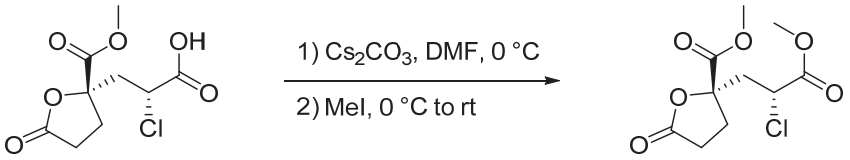


Catalyst (*S*,*R*)-**413** (TFA salt of (2*S*,5*R*)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one, 74.3 mg, 0.261 mmol, 0.20 equiv) and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (**463**, 394 mg, 1.30 mmol, 1.1 equiv) were dissolved in acetonitrile (0.8 mL). The resulting clear solution was cooled down to 0 °C with stirring. A solution of aldehyde (*R*)-**455** (247 mg, 1.23 mmol, 1.0 equiv) in acetonitrile (0.7 mL) was added dropwise *via* syringe. After 5 h, a ^{1}H NMR sample from an aliquot taken from the reaction mixture showed that the reaction was complete, *dr* of (*R*,*S*)-**466** being ~85:15.

2-methyl 2-butene (0.65 mL, 5.83 mmol, 4.7 equiv), acetonitrile (2.0 mL) and NaH_2PO_4•$2H_2O$ (129 mg, 0.82 mmol, 0.7 equiv) in water (0.8 mL) were then added to the reaction mixture, after which a solution of $NaClO_2$ (343 mg, 3.03

mmol, 2.5 equiv) in water (1.8 mL) was added dropwise. After the completion of the addition, the reaction mixture was allowed to warm to rt. After 1.5 h, more $NaClO_2$ (17.4 mg, 0.154 mmol, 0.1 equiv) was added. After 1 h, solid Na_2SO_3 (0.250 g) was added. EtOAc (20 mL) and few drops of 2 M aq. HCl were added and the phases were separated. The aqueous phase was extracted with EtOAc (10 mL), mixed with brine (10 mL) and 2 M aq. HCl was added to set the pH ~3 based on pH paper and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to give the crude acid (*R*,*S*)-**468** which was used in the next reaction without further purification.

The aqueous phase was also concentrated. The crude (m= 208 mg) was analysed by NMR, which suggested that this crude also contained some of the desired crude acid (*R*,*S*)-**468**. This was used in the next step without further purification.



(*R*,*S*)-**468** (*R*,*S*)-**469a**

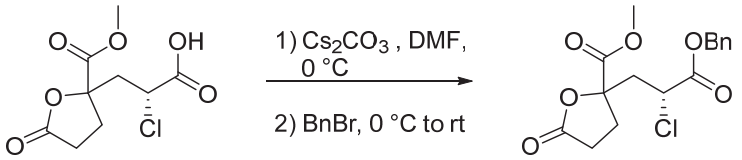
The crude acid (*R*,*S*)-**468** obtained before from the organic phase was dissolved in DMF (3.5 mL) at 0 °C, after which Cs_2CO_3 (416 mg, 1.27 mmol, 1.0 equiv) was added. After 30 min, MeI (0.17 mL, 2.71 mmol, 2.2 equiv) was added and the reaction mixture was allowed to warm to rt. After 17 h, EtOAc (20 mL) and brine (10 mL) were added. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with brine (10 mL) and dried with Na_2SO_4. After the filtration and evaporation of the solvents, the crude was prepurified by column chromatography and repurified by CombiFlash (EtOAc-hexane gradient from 0:100 to 100:0) to give ester (*R*,*S*)-**469a** as a yellow oil (92.0 mg, 0.348 mmol, *dr* 88:12).

The crude (*R*,*S*)-**468** from the aqueous phase obtained after the chlorination was also subjected to the methylation reaction in the same manner to give, after purification, diester (*R*,*S*)-**469a** (139 mg, 0.527 mmol, *dr* 87:13). After combining the products, the total yield was 231 mg (0.874 mmol, 71%, *dr* ~87:13).

R_f (EtOAc-hexane 50:50)= 0.43; IR (film, cm^{-1}): 2957, 1788, 1738, 1437, 1270, 1162, 1071, 990, 933, 868, 812, 731; $[\alpha]_D$= +17.3 (*c* 0.97 DCM); ^1H NMR (300 MHz, $CDCl_3$): δ 4.49 (dd, *J* = 7.4 Hz, 6.4 Hz, 1H), 3.82 (s, 2.7H), 3.79 (s, 2.5H), 3.78 (s, 0.4H), 3.78 (s, 0.4H), 3.00 (dd, *J* = 15.1 Hz, 7.8 Hz, 0.1H), 2.80 (dd, *J* = 14.9 Hz, 7.5 Hz, 1H), 2.66–2.47 (m, 4H), 2.40–2.32 (m, 0.2H), 2.29–2.19 (m, 0.9H); ^{13}C NMR (75 MHz, $CDCl_3$, *major diastereomer*): δ 174.6, 171.1, 169.4, 83.5, 53.5, 53.4, 51.8, 42.5, 33.0, 27.5; ^{13}C NMR (75 MHz, $CDCl_3$, *minor diastereomer*): δ 174.8, 170.9, 169.4, 83.8, 53.5, 53.4, 51.5, 41.7, 31.7, 27.7; HRMS (ESI^+): m/z calculated for $[C_{10}H_{13}O_6Cl_1Na_1]^+$ = 287.0293, found 287.0284, Δ= 3.1 ppm.

The corresponding diastereomeric mixture was synthesised in the above manner using (±)-**468** as starting material in 85% yield. The spectral data resembled those of diastereoenriched sample.

8.8.10 Methyl 2-((*R*)-3-(benzyloxy)-2-chloro-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(*R,RS*)-469b]

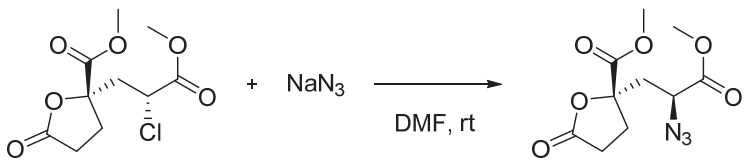


(*R,RS*)-**468** (*R,RS*)-**469b**

To a stirred solution of crude (*R,RS*)-**468** (0.252 g, 1.01 mmol, 1.0 equiv, *theoretical amount based on the amount of starting material aldehyde* (±)-***455*** *used in the first step*) in DMF (4.0 mL) was added Cs_2CO_3 (0.341 g, 1.03 mmol, 1.0 equiv) at 0 °C. After 0.5 hour, BnBr (0.15 mL, 1.24 mmol, 1.2 equiv) was added and the reaction mixture was let to warm up to rt. After 15 hours, the reaction was worked up by adding water (10 mL), brine (2 mL) and EtOAc (15 mL). The phases were separated and the water phase was extracted with EtOAc (2 x 10 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered and the solvents were evaporated. The crude was purified by column chromatography to yield (*R,RS*)-**469b** as a mixture of diastereomers and few impurities (0.190 g, 0.558 mmol, 55%, *dr* ~60:40).

^{1}H NMR (400 MHz, $CDCl_3$, *mixture of diastereomers, major diastereomer*): δ 7.38–7.34 (m, 5H), 5.20 (s, 1.1H), 4.54 (dd, *J* = 7.5 Hz, 6.4 Hz, 0.55H), 3.77 (s, 1.8H), 2.82 (dd, *J* = 14.9 Hz, 7.6 Hz, 0.6H), 2.65–2.47 (m, 4H), 2.22 (dt, *J* = 13.0 Hz, 9.4 Hz, 0.6H); (*resolved minor diastereomer peaks*): δ 5.22/5.17 (AB-quartet, J_{AB} = 12.2 Hz, 0.9H), 4.52 (dd, *J* = 7.7 Hz, 5.5 Hz, 0.45H), 3.74 (s, 1.2H), 3.02 (dd, *J* = 15.1 Hz, 7.7 Hz, 0.4H), 2.33 (dt, *J* = 13.2 Hz, 9.8 Hz, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$, *mixture of diastereomers, major diastereomer*): δ 174.6, 171.1, 168.8, 134.89, 128.76, 128.72, 128.6, 83.5, 68.3, 53.39, 52.0, 42.4, 33.1, 27.5; (*minor diastereomer*): δ 174.9, 170.9, 168.7, 134.86, 128.76, 128.72, 128.5, 83.8, 68.2, 53.37, 51.6, 41.6, 31.6, 27.7; HRMS (ESI$^+$): m/z calculated for $[C_{16}H_{17}O_6Cl_1Na_1]^+$ = 363.0606, found 363.0591, Δ= 4.1 ppm.

8.8.11 Methyl (*S*)-2-((*S*)-2-azido-3-methoxy-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(*S,S*)-481a]



(*R,S*)-**469a** (*S,S*)-**481a**

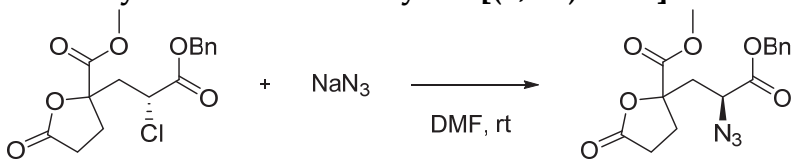
To a stirred slurry of NaN_3 (309 mg, 4.71 mmol, 5.4 equiv) in DMF (3 mL) was added a solution of diester (*R*,*S*)-**469a** (231 mg, 0.874 mmol, 1.0 equiv) in DMF (2.5 mL) dropwise. After 15 h, H_2O (20 mL) and EtOAc (20 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (2x10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (gradient EtOAc-hexane 0:100 to 100:0) to give azide (*S*,*S*)-**481a** as a colourless oil (199 mg, 0.734 mmol, 84%, *dr* 84:16).

R_f (EtOAc-hexane 50:50)= 0.29; IR (film, cm^{-1}): 2957, 2113, 1787, 1737, 1437, 1165, 1071, 988, 942, 811, 731, 666, 556; $[\alpha]_D$= –35.7 (*c* 1.0 DCM); ^{1}H NMR (300 MHz, $CDCl_3$, *major diastereomer*): δ 4.12 (dd, *J* = 7.3 Hz, 5.4 Hz, 0.8H), 3.81 (s, 3H), 3.81 (s, 3H), 2.72 (dd, *J* = 14.9 Hz, 5.4 Hz, 1H), 2.65–2.55 (m, 2H), 2.54–2.45 (m, 1H), 2.40–2.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *major diastereomer* δ 174.9, 171.2, 170.0, 83.6, 58.0, 53.4, 53.2, 37.8, 31.8, 27.7; ^{13}C NMR (75 MHz, $CDCl_3$): *minor diastereomer* δ 174.7, 171.4, 170.1, 83.4, 58.2, 53.3, 53.1, 39.1, 33.1, 27.7; HRMS (ESI^+): m/z calculated for $[C_{10}H_{13}O_6N_3N_1H_4]^+$ = 289.1143, found 289.1126, Δ= 5.9 ppm.

A characteristic signal of the minor diastereomer in ^{1}H spectrum at δ 4.22 (dd, *J* = 10.5 Hz, 3.7 Hz, 0.2H) was used in the determination of *dr*.

The corresponding diastereomeric mixture was synthesised in the above manner using (2*R*,4*RS*)-**469a** as starting material in 85% yield. The spectral data resembled those of diastereoenriched sample.

8.8.11.1 Methyl 2-((*S*)-2-azido-3-(benzyloxy)-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(*S*,*RS*)-481b]



(*R*,*RS*)-**469b** (*S*,*RS*)-**481b**

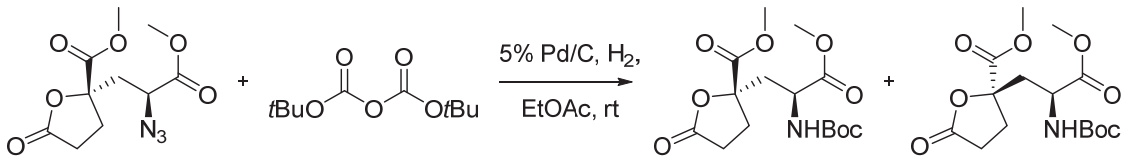
To a stirred slurry of NaN_3 (111 mg, 1.69 mmol, 5.5 equiv) in DMF at rt (1 mL) was added a solution of diester (*R*,*RS*)-**469b** (104 mg, 0.306 mmol, 1.0 equiv) in DMF (2.0 mL) dropwise. After 5 h, H_2O (15 mL) and EtOAc (15 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (2x15 mL). The combined organic layers were washed with H_2O (15 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography to give azide (*S*,*RS*)-**481b** with few impurities as an oil (92.0 mg, 0.265 mmol, 87%, 60:40 *dr*).

^{1}H NMR (400 MHz, $CDCl_3$, *mixture of diastereomers, major*): δ 7.38–7.35 (m, 5H), 5.25/5.20 (AB-quartet, J_{AB} = 12.1 Hz, 1.2H), 4.15 (dd, *J* = 7.5 Hz, 5.1 Hz, 0.6H), 3.78 (s, 1.8H), 2.71 (dd, *J* = 15.9 Hz, 5.1 Hz, 0.6H), 2.61–2.56 (m, 2.4H), 2.52–2.45 (m, 1H), 2.37–2.22 (m, 2H); (*resolved minor diastereomer peaks*): δ 5.22 (s, 0.8H),

4.26 (dd, *J* = 10.6 Hz, 3.8 Hz, 0.4H), 3.80 (s, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$, *major diastereomer*): δ 175.0, 171.2, 169.4, 134.83, 128.84, 128.8, 128.68, 83.7, 68.22, 58.0, 53.4, 37.7, 31.8, 27.69; (*minor diastereomer*): δ 174.8, 171.4, 169.5, 134.82, 138.9, 128.85, 128.67, 83.3, 68.17, 58.2, 53.3, 39.0, 33.2, 27.72; HRMS (ESI$^+$): m/z calculated for $[C_{16}H_{17}O_6N_3Na_1]^+$ = 370.1010, found 370.1028, Δ= –5.0 ppm.

The *dr* was estimated from ^{1}H spectrum by integrating the chemical shifts at 4.26 ppm (*minor*) and 4.15 ppm (*major*).

8.8.12 Methyl (*S*)-2-((*S*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-5-oxotetrahydrofuran-2-carboxylate [(*S*,*S*)-482a]



(*S*,*S*)-**481a** **490** (*S*,*S*)-**482a** (*S*,*R*)-**482a** (i.e. 4-*epi*-**482a**)

To a mixture of Boc_2O (**490**, 0.662 g, 2.94 mmol, 3.0 equiv) and Pd/C (5% w/w Pd in charcoal, 60 mg, 20 w-%) was added a solution of azide (*S*,*S*)-**481a** (269 mg, 0.993 mmol, 1.0 equiv) in EtOAc (8.0 mL). The heterogeneous mixture was stirred vigorously and the flask was flushed first with argon (*via* three vacuum/Ar cycles) and then with hydrogen. After 15 h, the flask was purged with argon, and the reaction mixture was filtered through Celite, rinsed with EtOAc (2 x 10 mL). The filtrate was concentrated and the residue was first prepurified by column chromatography and then repurified by CombiFlash (gradient EtOAc-hexane 0:100 to 100:0) to give the pure diastereomer (*S*,*S*)-**482a** as a white foamy semisolid (254 mg, 0.734 mmol, 74%). In addition, 4-*epi*-**482a** was also isolated as a white solid (32.4 mg, 0.094 mmol, 9%, *dr* ~86:14).

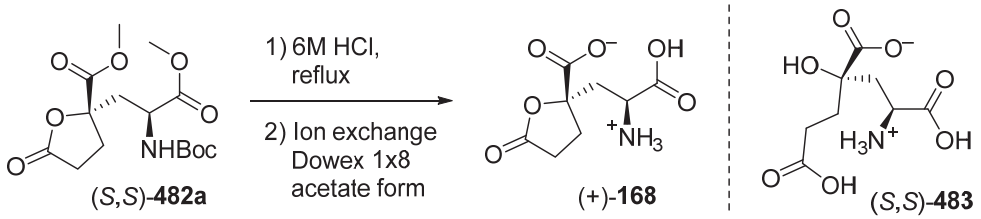
(*S*,*S*)-**482a**:
R_f (EtOAc-hexane 60:40)= 0.39; IR (film, cm^{-1}): 3373, 2978, 2956, 1789, 1740, 1709, 1501, 1438, 1392, 1366, 1246, 1158, 1070, 1023, 915, 729; $[\alpha]_D$= +51.9 (*c* 0.68 DCM); ^{1}H NMR (500 MHz, $CDCl_3$, *mixture of rotamers*): δ 5.24 (d, *J* = 6.2 Hz, 0.9H), 5.02 (brs, 0.1H), 4.45–4.42 (m, 0.9H), 4.27 (brs, 0.1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.80 (dd, *J* = 14.8 Hz, 5.7 Hz, 1H), 2.60–2.47 (m, 2H), 2.41 (ddd, *J* = 13.6 Hz, 8.1 Hz, 5.7 Hz, 1H), 2.32 (dd, *J* = 14.8 Hz, 5.6 Hz, 1H), 2.23 (dt, *J* = 13.3 Hz, 9.3 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 171.7, 171.6, 155.0, 83.9, 80.3, 53.2, 52.9, 50.3, 39.0, 32.5, 28.3, 27.5; HRMS (ESI$^+$): m/z calculated for $[C_{15}H_{23}O_8N_1Na_1]^+$ = 368.1316, found 368.1302, Δ= 3.8 ppm.

(*S*,*R*)-**482a** (4-*epi*-**482a**):
R_f (EtOAc-hexane 60:40)= 0.31; IR (film, cm^{-1}): 3356, 2967, 1782, 1748, 1691, 1522, 1222, 1159, 1091, 1048, 1024, 862; mp 116–117 °C; $[\alpha]_D$= +11.3 (*c* 0.95 DCM); ^{1}H NMR (500 MHz, $CDCl_3$, *mixture of rotamers and diastereomers*): δ 5.00 (d, *J* = 6.9

Hz, 0.85H), 4.61 (brs, 0.16H), 4.47 (brs, 1H, *overlaps with a signal of the other diastereomer*), 4.36 (brs, 0.17H), 3.80 (s, 3H), 3.74 (s, 3H), 2.64–2.55 (m, 3H), 2.49–2.41 (m, 1H), 2.37–2.22 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 172.1, 171.9, 155.2, 84.1, 80.5, 53.3, 52.8, 50.3, 39.1, 32.4, 28.4, 27.8; HRMS (ESI$^+$): m/z calculated for $[C_{15}H_{23}O_8N_1Na_1]^+$ = 368.1316, found 368.1302, Δ= –3.5 ppm.

When (2*S*,4*RS*)-**481a** was used as a starting material in a reaction done in the above manner, diastereomerically pure (*S*,*S*)-**482a** was isolated with 16% yield along with a diastereomer mixture of (*S*,*S*)-**482a** and 4-*epi*-**482a** in 59% yield (~55:45 *dr*). The spectral data resembled those reported above.

8.8.13 (+)-Lycoperdic acid [(+)-168]



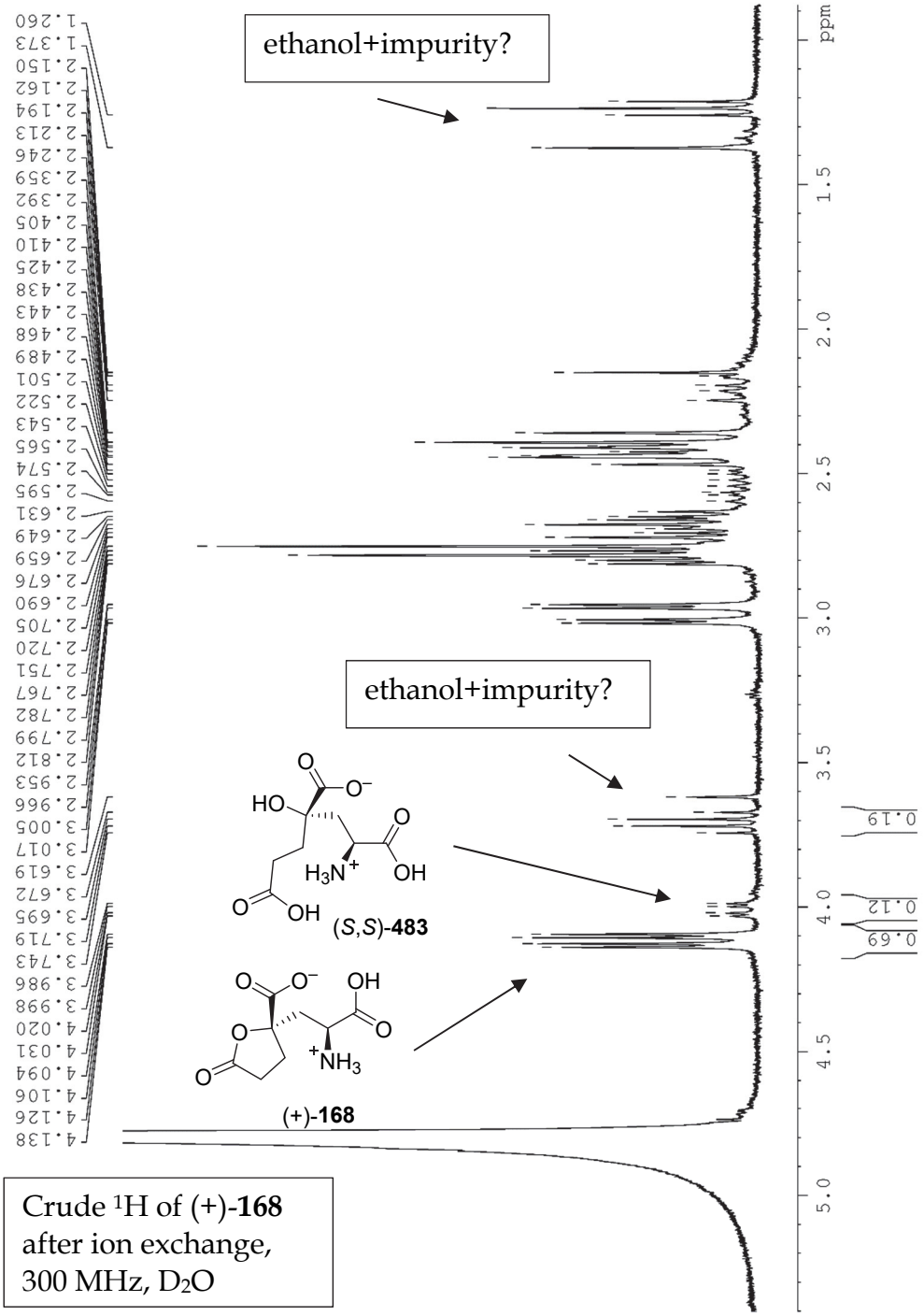
A mixture of diester (*S*,*S*)-**482a** (50.1 mg, 0.145 mmol, 1.0 equiv) and 6 M HCl (4.0 mL, 24.0 mmol, 170 equiv) was heated to reflux and refluxed for 3 h. After cooling to rt, the reaction mixture was concentrated and the residue was dissolved in a minimum amount of H_2O and eluted through a Dowex ion exchange resin (freshly converted to acetate form from chloride form) with 2 M AcOH. Fractions staining positive with ninhydrin stain were combined and concentrated to give crude (+)-**168** (22.4 mg, assumed purity ~75–80%, mixture of the hydroxy acid (*S*,*S*)-**483** and few other impurities, see spectrum below). Analytically pure samples of (+)-**168** were recrystallised from water twice to give a white solid (8.7 mg, 0.040 mmol, 28%).

$[\alpha]_D$= +10.7 (*c* 0.27 in H_2O) (lit.[212] +14.2 (*c* 0.46 in H_2O), lit.[109] +14.9 (*c* 0.47 in H_2O)). ^{1}H NMR (500 MHz, D_2O): δ 3.93 (dd, *J* = 10.2 Hz, 3.3 Hz, 1H), 2.84 (dd, *J* = 15.6 Hz, 3.3 Hz, 1H), 2.70–2.60 (m, 2H), 2.54 (ddd, *J* = 13.3 Hz, 8.5 Hz, 4.9 Hz, 1H), 2.28 (dt, *J* = 13.2 Hz, 9.6 Hz, 1H), 2.26 (dd, *J* = 15.6 Hz, 10.2 Hz, 1H); ^{13}C NMR (125 MHz, D_2O): δ 180.6, 176.2, 172.9, 88.7, 52.4, 38.6, 33.1, 28.5.

Note: To avoid disturbing the chemical shifts by any reference compounds, the ^{1}H and ^{13}C spectra were calibrated by matching the signal of the amino acid α-proton and carbon to 3.93 ppm and 88.65 ppm respectively, which are the values reported by Yoshifuji *et al.*[212] for these signals. The spectral data and the sign of the optical rotation matched those reported in the literature.[17]

When a 50:50 diastereomeric mixture of (2*S*,4*RS*)-**482a** was used as a starting material, the deprotection was conducted by saponifying (2*S*,4*RS*)-**482a** with aqueous solution of NaOH in MeOH at rt, followed by acidic de-Bocing with aqueous HCl at rt. The crude was ion-exchanged in the above manner to give a

50:50 mixture of (+)-**168** and 4-*epi*-**168** in 53% yield. The spectral data resembled those reported above.



8.9 X-ray data

8.9.1 Diketone 34g

Crystal data	**34g**
Empirical formula	$C_{16}H_{12}F_2O_2$
Formula weight	274.26
Temperature (K)	120
Crystal system, space group	Monoclinic, $P2_1/c$
a, b, c (Å)	15.1545(6), 5.7263(2), 7.1385(3)
α, β, γ	90, 90.616(4), 90
V (Å^3)	619.44(4)
Z	2
μ (mm^{-1})	0.12
Crystal size (mm^3)	0.49 x 0.37 x 0.29
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Analytical, CrysAlisPro 1.171.36.32 (Rigaku Oxford Diffraction, 2013) Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by Clark and Reid.[249] Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.959, 0.974
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	3173, 1981, 1689
R_{int}	0.017
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.751
Refinement	
$R\,[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.041, 0.117, 1.06
No. reflections	1981
No. of parameters	91
No. of restraints	0
H-atom treatment	H-atom parameters were constrained.
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.41, –0.23

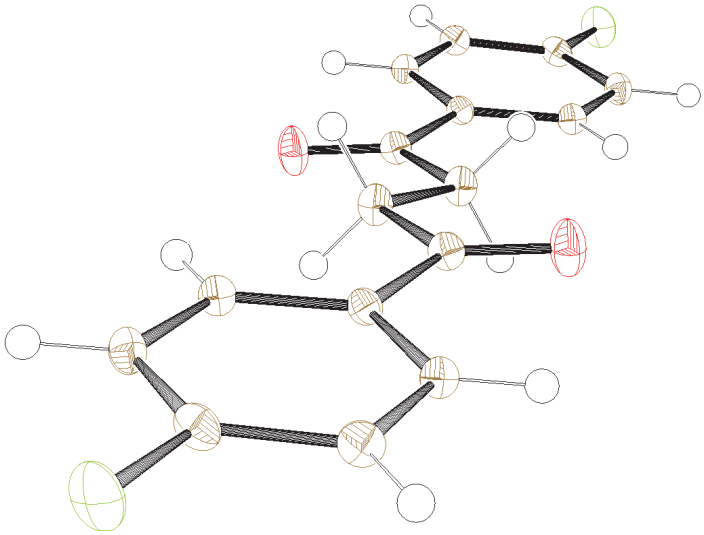


Figure 13: ORTEP-figure of the crystal structure of **34g**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of **34g**-solution in DCM-hexane. The thermal displacement parameters are shown at 50% probability level.

8.9.2 Diketone 34b

Crystal data	**34b**
Empirical formula	$C_{20}H_{10}F_{12}O_2$
Formula weight	510.28
Temperature (K)	120
Crystal system, space group	Monoclinic, $P2_1/c$
a, b, c (Å)	4.7647(2), 14.0363(6), 14.4856(6)
α, β, γ	90, 95.244(4), 90
V (Å^3)	964.72(7)
Z	2
μ (mm^{-1})	0.19
Crystal size (mm^3)	0.55 x 0.21 x 0.16
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Multi-scan, CrysAlisPro 1.171.39.46 (Rigaku Oxford Diffraction, 2018) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.621, 1.00
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	3869, 2402, 2008
R_{int}	0.021
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.702
Refinement	
$R\,[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.118, 1.04
No. reflections	2402
No. of parameters	181
No. of restraints	3
H-atom treatment	H-atom parameters were constrained.
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.34, –0.33
Disorder	Disorder present in one of the CF_3-groups in the asymmetric unit cell: F4, F5, F6, F7, F8, F9 disordered over one sites with occupancies 0.3, 0.7, 0.3, 0.7, 0.3, 0.7

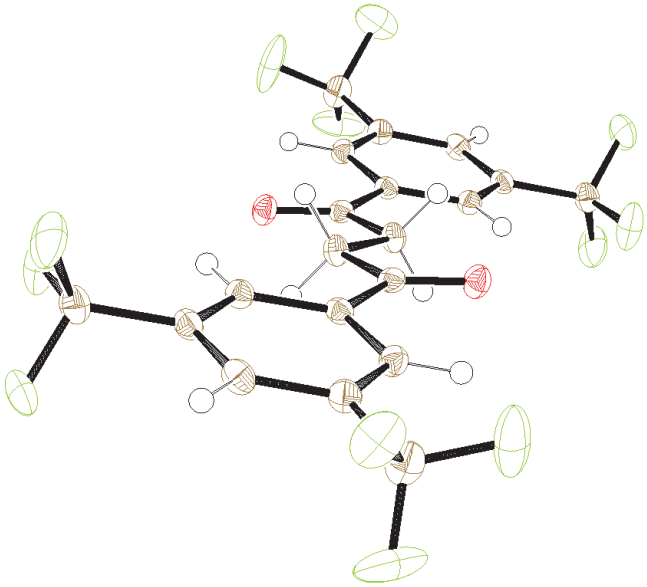


Figure 14: ORTEP-figure of the crystal structure of **34b**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of **34b**-solution in $CDCl_3$. The thermal displacement parameters are shown at 50% probability level without the disordered CF_3-parts.

8.9.3 Diketone 34d

Crystal data	**34d**
Empirical formula	$C_{16}H_{12}N_2O_6$
Formula weight	328.28
Temperature (K)	122
Crystal system, space group	Monoclinic, $P2_1/n$
a, b, c (Å)	6.9826(3), 18.8845(7), 11.3334(5)
α, β, γ	90, 103.530(4), 90
V (Å^3)	1452.98(11)
Z	4
μ (mm^{-1})	0.12
Crystal size (mm^3)	0.24 x 0.091 x 0.067
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Multi-scan, CrysAlisPro 1.171.36.32 (Rigaku Oxford Diffraction, 2013) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.926, 1.00
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10673, 3783, 3107
R_{int}	0.024
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.701
Refinement	
$R\,[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.105, 1.05
No. reflections	3783
No. of parameters	217
No. of restraints	0
H-atom treatment	H-atom parameters were constrained.
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.35, –0.21

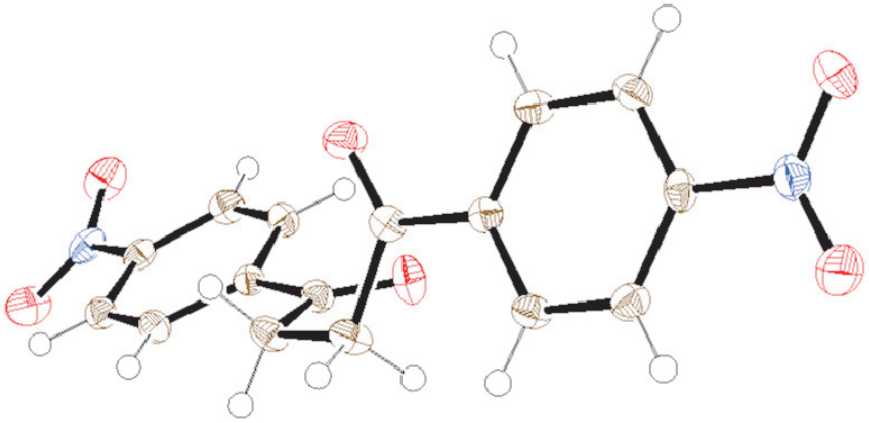


Figure 15: ORTEP-figure of the crystal structure of **34d**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of **34d**-solution in DCM-hexane. The thermal displacement parameters are shown at 50% probability level.

8.9.4 Diol (*R*,*R*)-55g

Crystal data	**(*R*,*R*)-55g**
Empirical formula	$C_{16}H_{16}F_2O_2$
Formula weight	278.29
Temperature (K)	120
Crystal system, space group	Monoclinic, $P2_1$
a, b, c (Å)	10.5408(4), 4.9924(2), 13.2984(4)
α, β, γ	90, 95.428(3), 90
V (Å^3)	696.68(4)
Z	2
μ (mm^{-1})	0.10
Crystal size (mm^3)	0.44 x 0.27 x 0.20
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Gaussian, CrysAlisPro 1.171.36.32 (Rigaku Oxford Diffraction, 2013) Numerical absorption correction based on Gaussian integration over a multifaceted crystal model. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.983, 0.966
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	6480, 4474, 4189
R_{int}	0.017
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.754
Refinement	
$R\ [F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.043, 0.110, 1.08
No. reflections	4474
No. of parameters	305
No. of restraints	1
H-atom treatment	Mixed
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.27, –0.15
Absolute structure	Flack x determined using 1633 quotients [(I+)–(I–)]/[(I+)+(I–)].[250]
Absolute structure parameter	–0.1(3)
Disorder	Disorder present in both of the aryl groups: C1, C2, C3, C5, C6, C7, C8, C9, C10, C11, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, F1, F2, F3, F4, H2A, H3, H5, H6, H8, H9, H10, H11, H17, H18, H20, H21, H22, H23, H25, H26 disordered over one sites with occupancies 0.6, 0.6, 0.6, 0.6, 0.6, 0.4, 0.4, 0.4, 0.4, 0.4, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.6, 0.4, 0.5, 0.5, 0.6, 0.6, 0.6, 0.6, 0.4, 0.4, 0.4, 0.4, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5

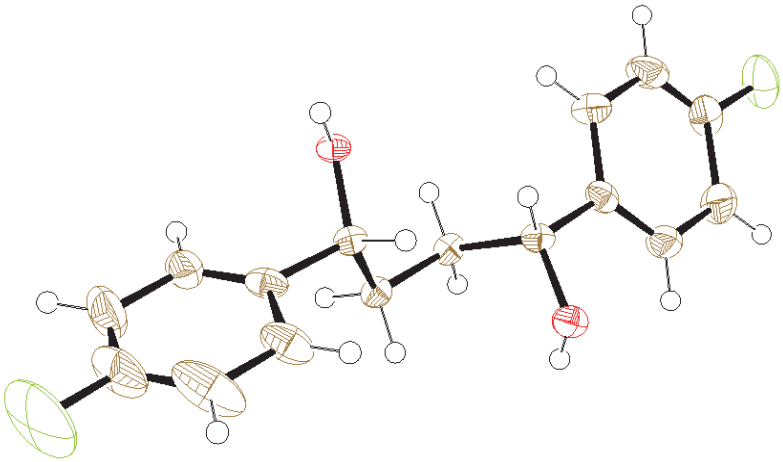


Figure 16: ORTEP-figure of the crystal structure of (*R*,*R*)-**55g**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of (*R*,*R*)-**55g**-solution in DCM-hexane. The thermal displacement parameters are shown at 50% probability level without the disordered aryl parts.

8.9.5 Diol (*R*,*R*)-55d

Crystal data	(*R*,*R*)-**55d**
Empirical formula	$C_{16}H_{16}N_2O_6$
Formula weight	332.31
Temperature (K)	127
Crystal system, space group	Triclinic, P1
a, b, c (Å)	7.1027(4), 7.5216(5), 8.1365(5)
α, β, γ	72.575(6), 65.975(6), 83.246(5)
V (Å^3)	378.80(5)
Z	1
μ (mm^{-1})	0.96
Crystal size (mm^3)	0.17 x 0.12 x 0.067
Data collection	
Diffractometer	SuperNova, Dual, Cu at home/near, Atlas
Radiation	CuKα (λ = 1.54184)
Absorption correction	Multi-scan, CrysAlisPro 1.171.39.46 (Rigaku Oxford Diffraction, 2018) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.777, 1.00
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	16528, 3016, 2933
R_{int}	0.022
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.632
Refinement	
$R\ [F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.035, 0.099, 1.05
No. reflections	3016
No. of parameters	225
No. of restraints	3
H-atom treatment	Mixed
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.37, –0.17
Absolute structure	Flack x determined using 1337 quotients [(I+)–(I–)]/[(I+)+(I–)].[250]
Absolute structure parameter	0.00(8)

Figure 17: ORTEP-figure of the crystal structure of (*R*,*R*)-**55d**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of (*R*,*R*)-**55d**-solution in DCM-hexane. The thermal displacement parameters are shown at 50% probability level.

8.9.6 Diol *meso*-55f

Crystal data	*meso*-**55f**
Empirical formula	$C_{20}H_{14}F_6O_1$
Formula weight	514.31
Temperature (K)	120
Crystal system, space group	Monoclinic, $P2_1/c$
a, b, c (Å)	8.5759(4), 27.4009(15), 9.0423(4)
α, β, γ	90, 93.414(4), 90
V (Å^3)	2121.05(17)
Z	4
μ (mm^{-1})	0.17
Crystal size (mm^3)	0.15 x 0.10 x 0.10
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Multi-scan, CrysAlisPro 1.171.36.32 (Rigaku Oxford Diffraction, 2013) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.988, 1.00
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	15339, 5484, 4360
R_{int}	0.027
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.702
Refinement	
$R\ [F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.050, 0.120, 1.03
No. reflections	5484
No. of parameters	366
No. of restraints	15
H-atom treatment	Mixed
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.37, –0.30
Disorder	Disorder present in two of the CF_3-groups in the asymmetric unit cell: F1, F2, F3, F4, F5, F6, F11, F12, F13, F14, F15, F16 disordered over one sites with occupancies 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.33, 0.67, 0.67, 0.33

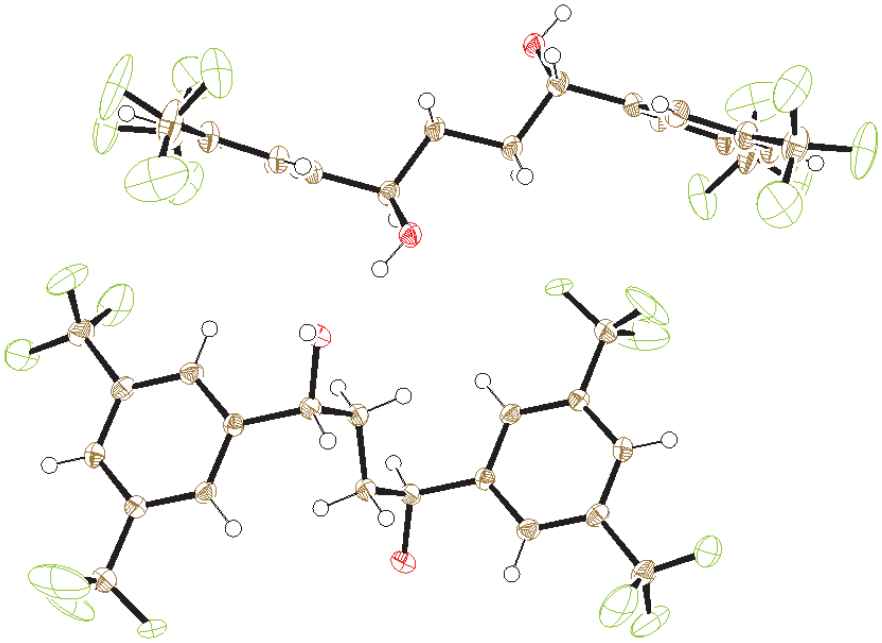


Figure 18: ORTEP-figure of the crystal structure of *meso*-**55f**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of *meso*-**55f** - solution in DCM-hexane. The thermal displacement parameters are shown at 50% probability level.

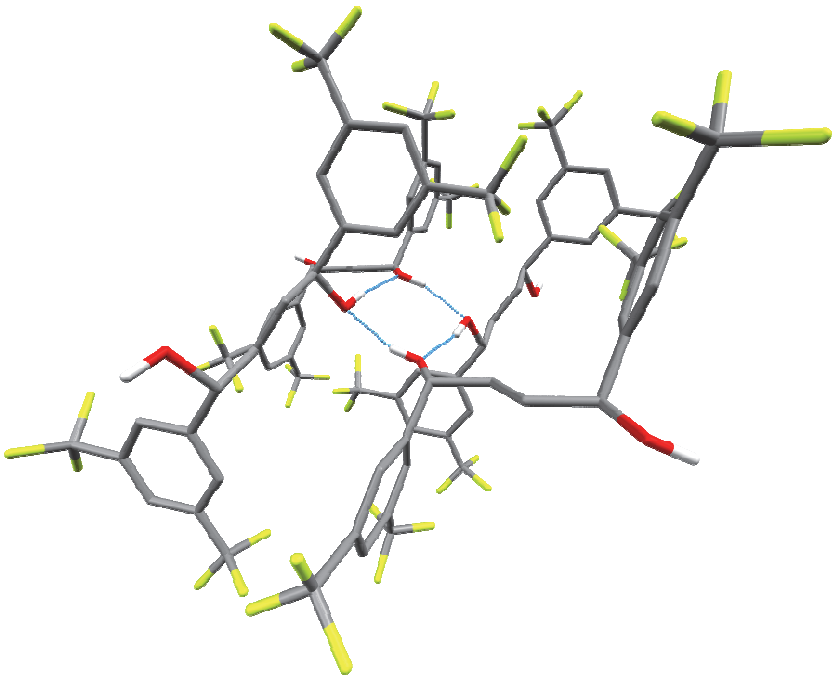


Figure 19: Intramolecular hydrogen bonding between OH-groups in *meso*-**55f**.

8.9.7 Catalyst (*R*,*R*)-31i

Crystal data	(*R*,*R*)-**31i**
CCDC deposition number/ CSD-REF	1972521/MULBED[57,167]
Empirical formula	$C_{20}H_{13}N_1F_{12}$
Formula weight	495.31
Temperature (K)	120
Crystal system, space group	Triclinic, P1
a, b, c (Å)	5.0139(5), 8.1304(10), 12.3245(8)
α, β, γ	107.908(9), 93.472(6), 93.514(9)
V (Å^3)	475.50(8)
Z	1
μ (mm^{-1})	0.184
Crystal size (mm^3)	0.20 x 0.07 x 0.03
Data collection	
Diffractometer	SuperNova, Single source at offset, Eos
Radiation	MoKα (λ = 0.71073)
Absorption correction	Gaussian, CrysAlisPro 1.171.39.46 (Rigaku Oxford Diffraction, 2018) Numerical absorption correction based on Gaussian integration over a multifaceted crystal model. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.724, 1.00
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7384, 5028, 4043
R_{int}	0.032
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.600
Refinement	
$R\ [F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.097, 0.31, 1.04
No. reflections	5028
No. of parameters	410
No. of restraints	180
H-atom treatment	Mixed
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.76, –0.52
Absolute structure	Flack x determined using 1411 quotients [(I+)–(I–)]/[(I+)+(I–)].[250]
Absolute structure parameter	0.0(4)
Disorder	Disorder present in two of the CF_3-groups: F4, F5, F6, F7, F8, F9, F10, F11, F12, F16, F17, F18, F19, F20, F21, F22, F23, F24 disordered over one sites with occupancies 0.45, 0.35, 0.25, 0.25, 0.4, 0.3, 0.25, 0.4, 0.35, 0.3, 0.4, 0.3, 0.3, 0.35, 0.35, 0.3, 0.4, 0.3

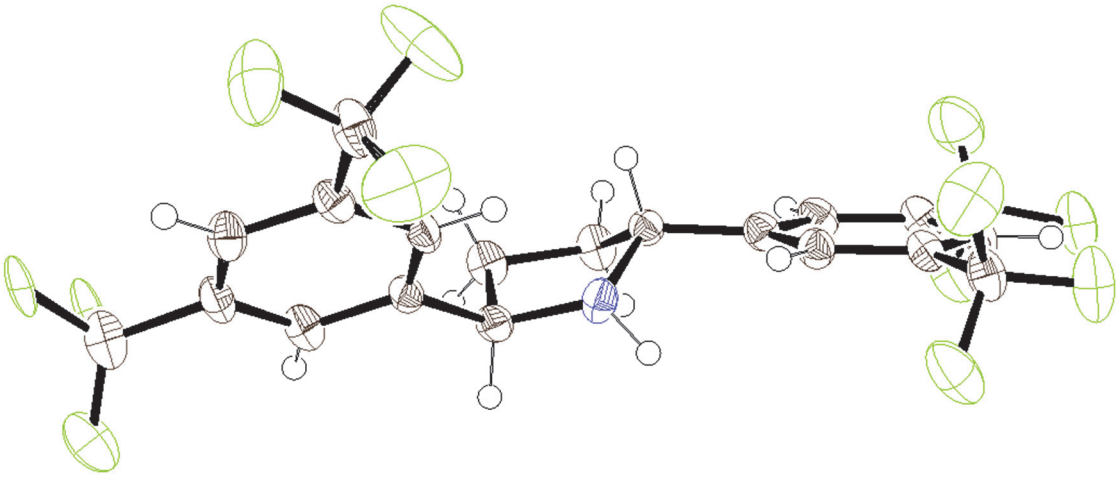


Figure 20: ORTEP-figure of the crystal structure of (*R*,*R*)-**31i**. Single crystal of the compound used in X-ray diffraction was obtained by slow evaporation of (*R*,*R*)-**31i**-solution in $CDCl_3$. The thermal displacement parameters are shown at 50% probability level without the disordered CF_3-parts.

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