UNIVERSITAT DE BARCELONA

The development of new, direct andasymmetric Ni(II) catalysed carbon-carbon bond forming reactions and their application to total synthesis

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Doctoral Thesis in Organic Chemistry

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Supervised by: Professors Pedro Romea Garcia and Fèlix Urpí Tubella

"Programa de Doctorat de Química Orgànica"

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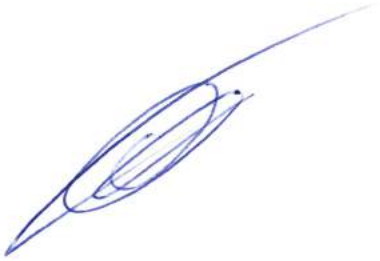

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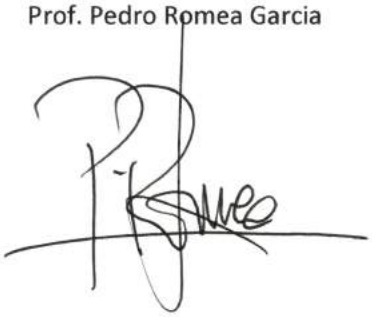

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Secció de Química Orgànica

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List of Abbreviations

3MPM – 3-methoxybenzyl (3-methoxyphenylmethyl)

4Å MS – 4 Angstrom Molecular Sieves

9-BBN – 9-Borabicyclo[3.3.1]nonane

ACN – Acetonitrile

ATH – Atom Transfer Hydrogenation

BINAP – 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl

CBS – Corey–Bakshi–Shibata Catalyst

COD – Cyclooctadiene

CSA – Camphorsulphonic Acid

DCC – *N,N'*-Dicyclohexylcarbodiimide

DCM – Dichloromethane

DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DHQ – Dihydroquinine

DHQD – Dihydroquinidine

DIAD – Diisopropyl Azodicarboxylate

DIBAL-H – Diisobutylaluminium Hydride

DiPAMP - DiPhenyAnisylMethylPhosphine

DIPEA – Diisopropyl Ethylamine

DPEN – 1,2-Diphenylethylenediamine

DIPT – Diisoproyl Tartrate

DMAP – 4-Dimethylaminopyridine

DMF – Dimethylformamide

DMP – Dess-Martin Periodinane

DMSO – Dimethylsulphoxide

DPMS – Diphenylmethylsilyl

DTBM – Di-*tert*-butylmethoxy

DTBMP – 2,6-Di-tBu-4-Me-pyridine

E – Electrophile

EDC – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

EMA – European Medicines Agency

FDA – Food and Drugs Administration (United States)

HMDS – Hexamethyldisilazide (also: bis(trimethylsilyl)amide)

HMPA – Hexamethylphosphoramide

HOBt – Hydroxybenzotriazole

HOMO – Highest Occupied Molecular Orbital

IBCF – Isobutyl Chloroformate

IBX – 2-Iodoxybenzoic Acid

IPA – Isopropyl Alcohol or Isopropanol

LDA – Lithium Diisopropylamide

LICA – Lithium Cyclohexylisopropylamide

LLB – $LaLi_3$tris(Binaphthoxide) Catalyst

LUMO – Lowest Unoccupied Molecular Orbital

Lutidine – 2,6-Lutidine

*m*CPBA – *meta*-Chloroperoxybenzoic Acid

MEM – Methoxyethoxymethyl Ether

MOM – Methoxymethyl

MXY – *meta*-Xylene

NFSI – *N*-Fluorobenzenesulfonimide

NIS – *N*-Iodosuccinimide

NMM – *N*-Methylmorpholine

NMO – 4-Methylmorpholine-4-oxide

O/N – Overnight

PCC – Pyridinium Chlorochromate

PG – Protecting Group

PHAL – Phthalazine

PNBA – *para*-Nitro Benzoic Acid

PMB – *para*-Methoxybenzyl

PPTS – Pyridinium *para*-Toluenesulfonate

PTSA – *para*-Toluenesulphonic Acid

RCM – Ring Closing Metathesis

RRCM – Relay Ring Closing Metathesis

RT – Room Temperature

SEGPHOS – SEaGull-PHOS - (4,4'-bi-1,3-benezodioxole)-5,5'-diyl-bis-(dipheneyl-phosphine)

SOMO – Singly Occupied Molecular Orbital

TBAF – *tert*-Butylammonium Fluoride

TBAI – *tert*-Butylammonium Iodide

TBDPS – *tert*-Butyldiphenylsilyl

TBHP – *tert*-Butyl Hydroperoxide

TBS – t*ert*-Butyldimethylsilyl

TEA – Triethylamine

TEMPO – (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

TES – Triethylsilyl

TFA – Trifluoroacetic Acid

THF – Tetrahydrofuran

TIPS – Triisopropylsilyl

TLC – Thin Layer Chromatography

TMG – Tetramethylguanidine

TMS – Trimethylsilyl

TPAP – Tetrapropylammonium Perruthenate

Xc – Chiral Auxiliary

General introduction

Organic Synthesis

Organic synthesis can be nominally divided into two complementary parts: synthetic methodology and total synthesis. The development of new methodologies has always been a large part of organic synthesis but always hand in hand with the practical application of the methods to the synthesis of molecules of interest. The relationship between the two is somewhat symbiotic, the development of new methodologies opens up new routes to target molecules, and in the same way difficulties in synthesis highlights gaps in the synthetic library available. In this manner the field of synthetic organic chemistry advances in a pseudo-iterative cycle: synthetic difficulties leading to new reactions being developed leading to the synthesis of new molecules which highlight new challenges leading to new reactions being developed and so on the wheel turns (Figure 1).

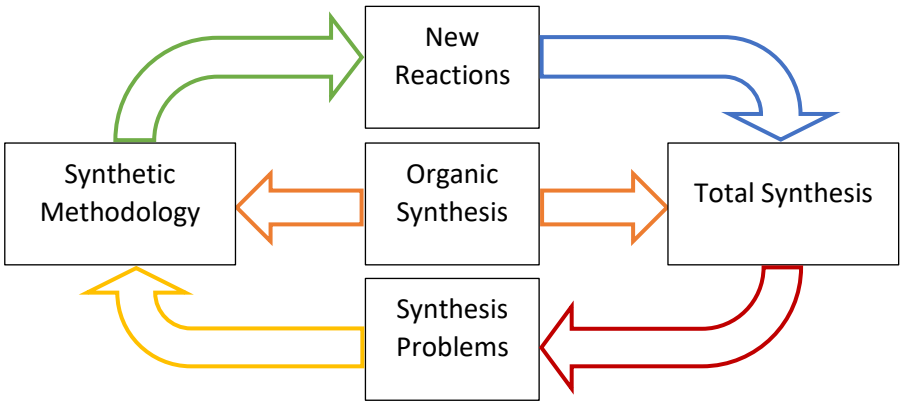


Figure 1: Relationship between methodology and total synthesis in organic synthesis

Progress is not limited to solely the development of novel routes or transformations but also the improvement of current methods; in the current climate selectivity, efficiency, cost and ease of the process are ever more important. Selectivity can be expressed as either chemoselectivity (the preference of one functional group over another), regioselectivity (selectivity in the site of reaction) or stereoselectivity (the favouring of one stereoisomer over another), with stereoselectivity generally being the hardest to control. One of the most important concepts in reaction efficiency is **Atom Economy** introduced by Trost.[1] The more efficient a reaction is the more atoms from the starting materials incorporated into the product. Therefore, the use of additives, reagents which are not incorporated fully into the product, and by-products all lower the atom efficiency ans place catalysis in a prominent position amongst synthetic challenges. This also works in hand with reaction yields and selectivity as an atom economic reaction which is low yielding and/or non-selective is useless. Hence, for a reaction to have applicable synthetic value it must be both selective and high yielding, low selectivity implies the separation of isomers and low yields the loss of product. While not always a problem for first syntheses, it can hinder the development of biologically active molecules and the synthetic chemist must have these parameters in mind when developing and applying new methodologies.

Within the branch of methodology there are three main stages: inception and discovery; optimization; scope and limitations. The first stage involves more theoretical work: the awareness of a necessary transformation in synthesis or the realisation of a potential reaction pathway, followed by an experimental probe. The optimisation then consists of a thorough investigation into all of the reaction conditions: quantitates and nature of all of the reagents, temperature, time, solvent, additives etc.; (this process is usually the most time consuming). Finally, the reaction is screened with different substrates, changing one or more of the starting materials to find how versatile the reaction is and if it tolerates the presence of differing functional groups with the aim to find the methodology's limitations.[2] The wider the scope the more likely the uptake of the reaction to total synthesis. Once

the reaction is fully developed it is commonplace for it to be applied to the synthesis of a small molecule to highlight its utility in a synthetic environment.

For total synthesis the process is considerably different. It starts with a retrosynthetic analysis to identify the key bonds to be formed in the synthetic route to the molecule and which starting materials are most appropriate. Once the route has been established, the required transformations are then searched for in the literature with the focus on the most highly selective and yielding. It is common for syntheses (and their corresponding retrosynthesis) to be designed around one or more specific transformations. The reactions are then conducted, with necessary changes or optimisations usually required for the specific case; if one or more reaction does not work or is not selective enough or gives low yields then another is usually looked for to replace it. The process is fairly fluid and experimental results tend to feed back into the search for more reactions or even changes in the retrosynthetic analysis until a sufficiently efficient and selective process is achieved.

Both processes are pillars in organic synthesis and their effective cooperation is key for the advancement of the field as a whole. While there is a need for the synthesis of target molecules there will always be the need for the tools to achieve it and for those who develop them. One way or another the synthetic chemist is and always will be an indispensable tool within the chemical infrastructure.

Chirality

Since the discovery of molecular chirality by the rotation of light in enantiomers of tartaric acid by Biot in 1832 (Figure 2),[3] and the further work by Pasteur in 1848 the synthesis of enantiopure compounds has constantly risen in number.[4] It was first defined by Lord Kelvin in 1893 when he stated: "*I call any geometrical figure, or group of points, 'chiral', and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself.*"[5] This was further refined by Mislow, who said "*An object is chiral [sic] if and only if it cannot be superposed on its mirror image [sic] otherwise it is achiral*" which removed the limitation to rigid geometrical bodies which Lord Kelvin's definition contained.[6] This can be seen clearly in Figure 2 with the different isomers of tartaric acid: the top two molecules are mirror images of the other and cannot be superposed on the other (no matter how they are rotated) and therefore a pair of chiral enantiomers; the bottom compound can have its mirror images superposed (by simple rotation) and therefore is not chiral. In this case because there are two chiral centres with the overall structure being achiral, the compound is called the **meso** isomer.

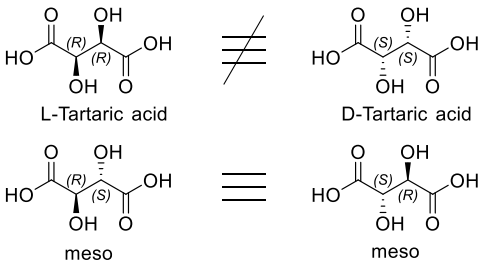


Figure 2: Isomers of tartaric acid have been crucial in the development of ideas on chirality. Top: Chiral enantiomers; Bottom: The achiral meso isomer.

The importance of enantiopure compounds is great and there are various motives for this, the most important of these is the effect that differing stereoisomers can have on the body. We ourselves are made fundamentally of chiral components. Even the basic building blocks of our bodies, amino acids and sugars, are chiral and found in complete enantiomeric purity within the larger molecules they make up. Chiral sugar molecules make up the backbone of our DNA while sequences of amino acids form up proteins and larger enzymes, all with a deep-rooted chirality.

It is not surprising therefore, that different enantiomers of molecules interact differently within our bodies. Take drug molecules for example: in the best (and most uncommon) of cases both enantiomers have a similar activity;[7,8] however, the reality is usually either the other enantiomer is inactive or has a different interaction in the body.[9–11] If the other enantiomer is inactive then there are two options available: enrichment of the active enantiomer or use of the racemic mixture where half is useless. In the case the enantiomer has a different effect on the body (either malignant or benign) the use of an enantiopure isomer is required. In the food industry different isomers may have different tastes and in the perfume industry differing smells. In many cases the pure enantiomer is preferred or required.

Enantiomerically Pure Compounds

Due to the importance of chirality and its effect on our biological systems the obtention of enantiomerically pure compounds is of upmost importance in the field of chemistry. When the enantiopure version of a molecule is needed, there are various methods available to chemists to achieve this. The first requires no significant complication in the synthetic process but more in the purification and is known as **chiral resolution**.[12] The other is **stereoselective synthesis**, or the design of the synthetic route to only (or preferably) obtain one enantiomer of the product and requires a different synthetic pathway to the achiral synthesis.

Chiral resolution

Chiral resolution is the separation of enantiomers from a mixture in a usually racemic ratio but also from enantioenriched mixtures. It can be broken down into two styles: physical resolution and chemical resolution. Physical resolution involves the separation of the enantiomers by a mechanical method, either chromatography using a chiral phase or crystallisation where the enantiomers crystallise spontaneously.[13,14] Chemical resolution involves the manipulation of one or both of the enantiomers through derivatisation or reaction, to be able to separate them. The three main methods of chiral resolution used are therefore: crystallisation, derivation, and chiral HPLC (Figure 3).[12,15,16]

The original method used by Pasteur was crystallisation, in which various solids containing mixtures of enantiomers can be separated by this method. Whilst the enantiomers can be enriched from the direct crystallisation of the racemic mixture, this process can be enhanced and hastened by the use of a seed crystal of the desired enantiomer (enantiopure or enriched).[17,18] This process usually requires a few cycles of crystallisation-separation-dissolution-crystallisation to achieve a high level of optical purity; the process also requires not only a crystalline solid but one in which the enantiomers crystallise separately (Top Route, Figure 3).[19]

The derivatization method is less time-consuming and can be achieved via different methods, but the idea is turning the pair of enantiomers with the same physical properties into a pair of molecules, generally diastereomeric pairs, which have differing chemical and physical properties and therefore much easier to separate.[20] The method may require the reaction with a chiral agent forming a covalent bond which has to be broken once the separation is complete,[16] although the formation of salts is also used.[21] Once the pairing is complete the molecules can be separated by methods such as column chromatography, distillation or crystallisation, depending on the differences in the properties. This method requires an accessible functional group which can be reacted with a chiral agent so is not applicable to all enantiomeric pairs (Centre Route, Figure 3).

Another related method is kinetic resolution which involves the favoured reaction of just one of the enantiomers creating a new compound and leaving the other enantiomer untouched and therefore easily separable. This works by one enantiomer reacting faster than the other and therefore creating an enrichment of the enantiomers. However, as the reaction of exclusively one enantiomer is

extremely difficult the result is usually enantioenriched mixtures to varying purities; one solution to this is repeated cycles (as seen in with crystallisation in Figure 3). In either way the maximum yield is 50%. A solution to both impure mixtures and to remove the limit in the yield is using a dynamic kinetic resolution method. This works when the enantiomers can easily be racemised, this way with one being favoured in the reaction and the other being able to convert to the favoured enantiomer; it creates a kinetic well pushing the reaction profile towards the reactive enantiomer, affording a more complete de-symmetrisation.

If these methods are not available, or the separation is not successful then the last option is separation via chiral HPLC.[22,23] This requires the use of a chiral stationary phase in the HPLC column, generally based on the chiral sugars amylose or cellulose.[24,25] The difference in interaction of the two enantiomers with the chiral stationary phase allows for their separation and collection in enantiopure batches. The drawback of this method is the high cost and the limit of scale. It is also time consuming due to the need to find conditions (chiral media, eluent, flow rate, etc.) in which to separate the enantiomer analytically first. However, due to the large library of both mobile and stationary phases available it is highly probable that any pair of enantiomers is able to be separated and is therefore a reliable fallback (Bottom Route, Figure 3).

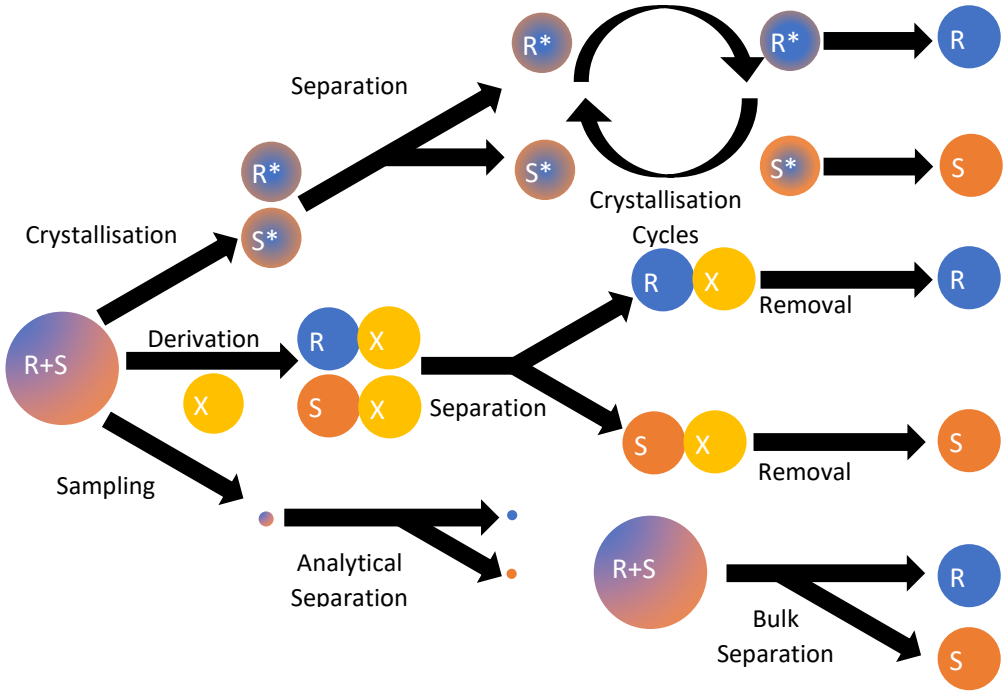


Figure 3: Representation of the methods of chiral resolution. Top: Crystallisation; Middle: Derivation; Bottom: Chiral HPLC.

Whilst the separation of enantiomers is in principle always possible, the need for chiral resolution is best avoided. To do this the initial synthesis of enantiopure molecules is required. This avoids one of the major drawbacks of chiral resolution which is that innately half of the product (the other enantiomer) is generally waste and therefore limits the maximum yield to 50% (except in the case of dynamic kinetic resolution). This is where stereoselective synthesis becomes important and why it remains the largest focus of organic chemistry. The use of stereoselective reactions in the synthetic pathway leads to enantiomerically pure target molecules.

Stereoselective Synthesis

Stereoselective synthesis may be defined as the formation of one isomer of the product in chemical reactions/synthesis over others in a controlled manner. It is a method of selectively forming one stereoisomer of a given product by the design of reactions and synthetic routes that use stereo-differentiation and chiral elements. Stereoselective synthesis can be broken down into smaller disciplines: chiral pool synthesis, chiral auxiliaries and asymmetric or enantioselective catalysis. Each discipline is a large and diverse field in itself and there are numerous synthetic tools available in each; there are benefits and downsides to each approach and they each have differing limitations which make them suitable for different applications.[26] Some are more versatile and have wider use than others, but each holds an important place in organic synthesis.

Chiral pool synthesis

Chiral pool synthesis involves the use of chiral starting materials with specific configuration incorporated, molecules from the so called "chiral pool".[27] This chiral pool contains small molecules that are usually simple in nature and most importantly readily available. A large amount derive from sugars and amino acids or other abundant natural sources, such as isoprene based terpenes and their derivatives (Figure 4).[28–31] Simple transformations of these and other naturally occurring enantiopure molecules significantly deepen the chiral pool with relative ease, meaning there is a large library of small chiral molecules to draw upon.[32–35]

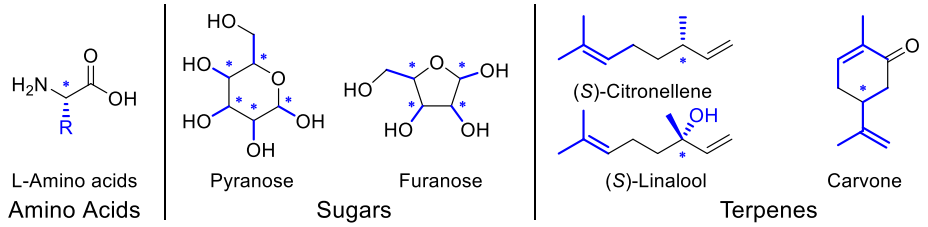
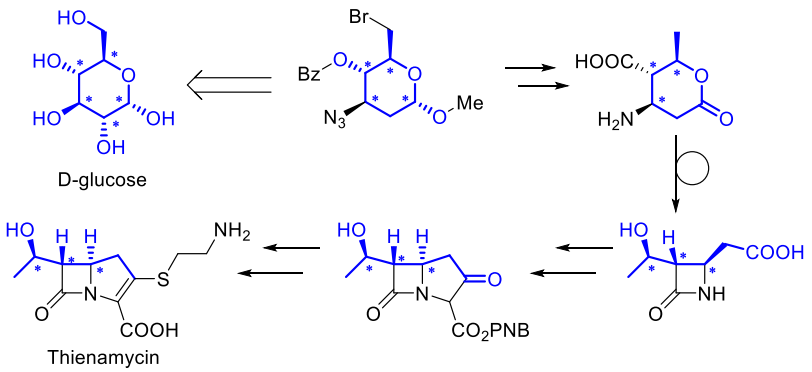


Figure 4: Common sources of molecules in the chiral pool. Left: Natural amino acids; Centre: Sugars, mainly based on pyranose and furanose structures; Right: Terpenes and terpenoid structures based on isoprene subunits. Chiral centres and isoprene units highlighted in blue.

The stereocontrol in this process hinges on the configuration of the staring materials. This ingrained stereochemistry is either maintained as it is, inverted via an S_N2 process or transformed in one way or another but the important point is the stereochemical information is rooted from the starting material and not an external source. Indeed, manipulation and/or removal of stereocentres embedded in starting materials whilst modifying their structure can provide the desired target molecule. This can be seen more commonly starting from carbohydrates or terpenes which already contain various chiral centres in varying combinations.[29–31,35]

One such example is the 1991 synthesis of Thienmycin by Ikota et al. starting from the simple sugar glucose (Scheme 1).[36] Initially the glucose is selectively protected and then one of the hydroxy groups is removed via an epoxide formation followed by displacement to give an azide product. Further transformations and an oxidation to remove another chiral centre leaves an amino acid which is promptly rearranged into the β-lactam. Further transformations lead to the bicyclic core, before attack at the cyclic ketone and deprotection lead to the target molecule. All three of the chiral centres in the final molecule derive from the five present in the initial D-glucose molecule. Meanwhile in the synthesis the superfluous centres are removed, with one being used to facilitate a ring opening via its oxidation.



Scheme 1: Total synthesis of Thienmycin from D-glucose. [36]

This initial stereochemistry can be used to selectively introduce other chiral centres in a process known as **internal asymmetric induction**.[37] This allows for the construction of enantiomerically pure complex molecules starting from select simple chiral synthons.

Whilst chiral pool based synthesis can be rewarding it is fundamentally limited in scope. The imagination and synthetic capability of the chemist will always be handicapped by the size of the chiral pool. Both the stereochemistry and the structural foundations are bound to the starting molecules and the transformations available to them. Another drawback is the complexity of controlling and predicting the outcome of the internal asymmetric inductions, especially as the complexity of the molecule increases, and incompatible isomers or lower selectivity may be produced. Its success for small molecules is notable but when complex targets are desired it is common to use other methods or combinations with chiral pool synthesis.

Chiral Auxiliary Based Synthesis

Chiral auxiliaries are small chiral molecules which are chemically bonded to the substrate molecule and used to control the stereochemical outcome of a reaction. When the transformation is complete the auxiliary is then removed leaving the substrate with the new stereocentre(s) formed. Whilst this method requires two additional steps (insertion and removal) the high stereocontrol exerted by an internal chiral auxiliary is often worth it.

Most chiral auxiliaries derive from small molecules found in the chiral pool.[38–43] They were first introduced in 1975 by Corey who used a citronellol terpinoid derivative for the preparation of a prostaglandin intermediate via a selective Diels-Alder reaction.[44] After this discovery various chiral auxiliaries were developed to achieve stereocontrol in differing reactions. Three types of chiral auxiliary proved more successful than others and have been widely used, these are (Figure 5): Evans's oxazolidinone based,[43,45] Myers's pseudoephedrines,[41,46] and Oppolzer's camphorsultam auxiliaries.[42,47]

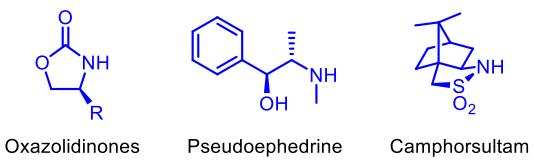


Figure 5: Widely Used Chiral Auxiliaries: Evans' Oxazolidinones, Myers's Pseudoephedrine and Oppolzer's Camphorsultam.

All three chiral auxilaries have in common a secondary amine, through which it can be attached to the substrate, usually through an acylation, to provide the stereocontrol. Due to their success many variants of the initial auxiliaries have been developed, both by the original authors and numerous others. For the oxazolidinones, the addition of geminal dimethyl groups by Davies led to the "*super-*

quat" auxiliaries.[48] Changing the heteroatoms led Crimmins and Fujita/Nagao to develop the oxazolidinethiones and thiazolidinethiones respectively.[49,50] There now exists a large number auxiliaries based on these four heterocyclic auxiliaries (Figure 6).[43,51] Even more reactions are now available after a great number of papers published on the use of auxiliaries in asymmetric synthesis.[52–55]

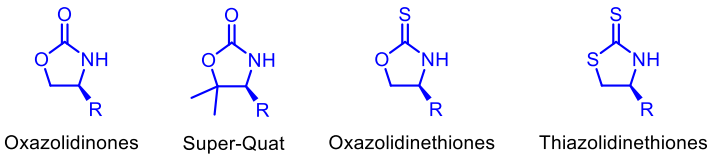
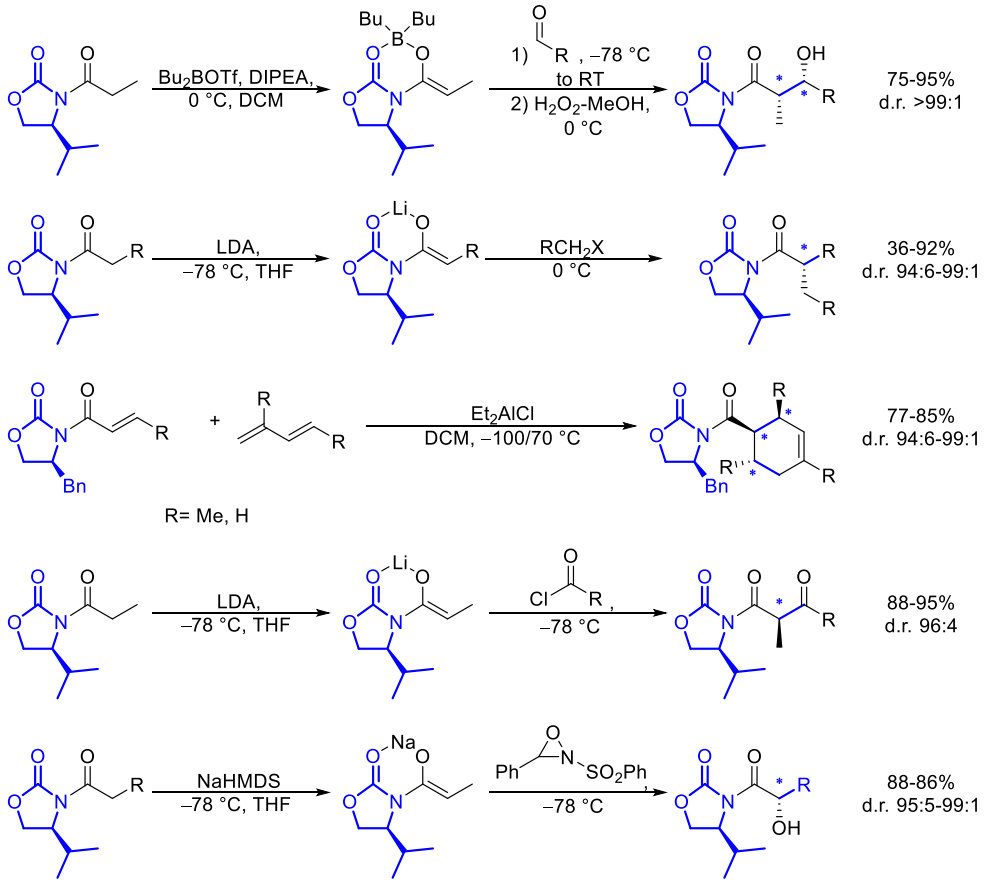


Figure 6: Variations of Evans Oxazolidinones

Evans's original papers showed the potential of the use of chiral oxazolidinones in aldol reactions;[45,56] however, he also demonstrated the versatility of such heterocycles in α-alkylations,[57] acylations,[58] Diels-Alder reactions,[59] and α-oxidations (Scheme 2).[60] These advances proved that a wide range of selective transformations are available from a single starting material which is an important feature for their general use.



Scheme 2: Examples of Reactions with Evans Auxiliary. A: Aldol Reaction;[45] B: α-Alkylation;[57] C: Diels Alder Reaction;[59] D: Acylation;[58] E: Oxidation.[60]

Each chiral auxiliary was also demonstrated to be removable leaving various functional groups with the auxiliary being able to be recovered and reused, which is key to the use of auxiliaries as a platform for stereoselective transformations. The reusability of the auxiliaries helps offset one of their inherent drawbacks, which is the need for a stoichiometric amount compared to the substrate. Another is the need for additional steps to add and remove the auxiliary, but this is somewhat compensated by the

ability to choose different functional groups when removing, allowing various synthons to be made from the same product.

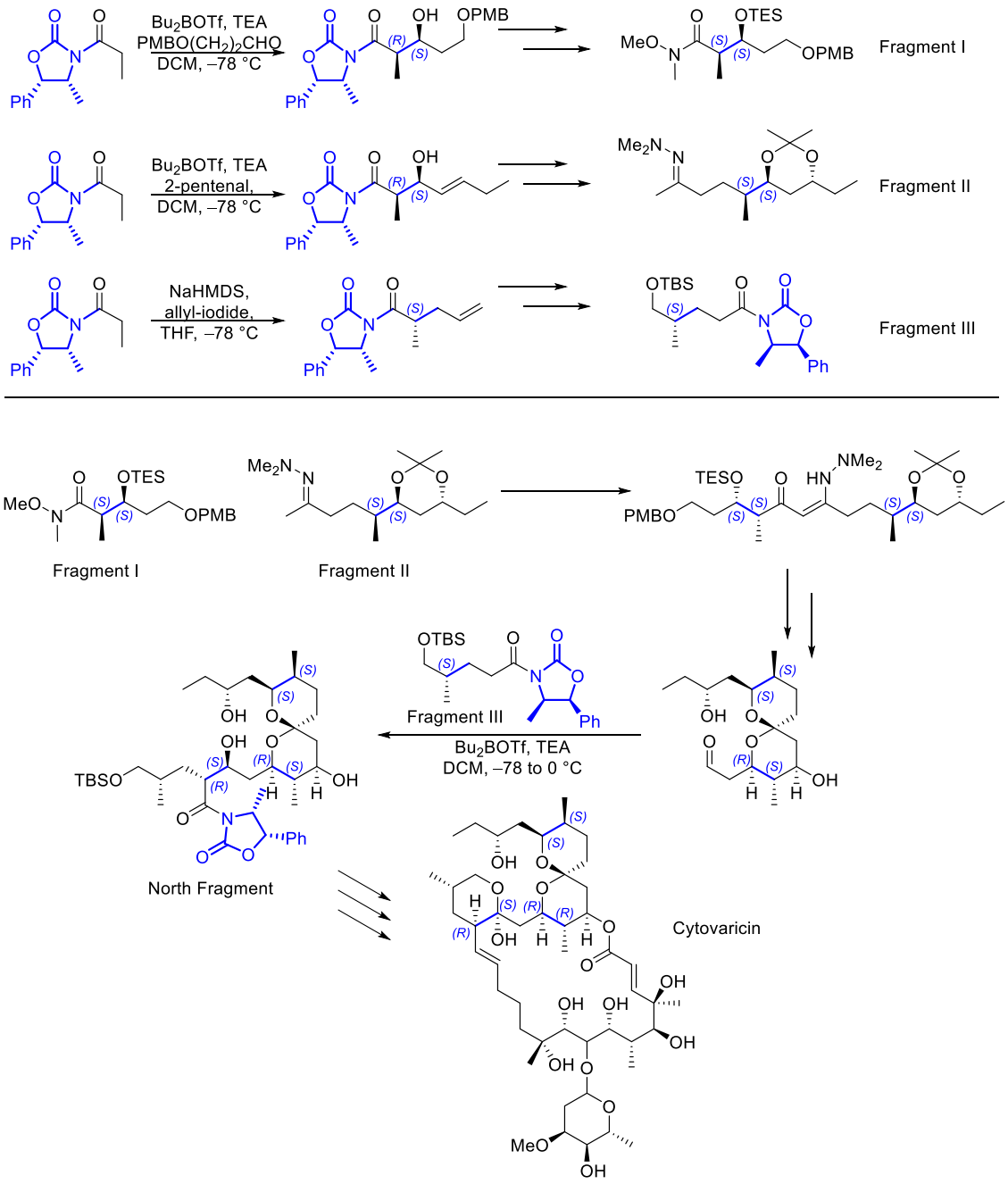
The popularity of the chiral auxiliary has been demonstrated in its use in total synthesis. Numerous total syntheses rely on chiral auxiliaries in the key steps and although in recent years their popularity have decreased in methodological studies they remain a reliable staple within total synthesis and drug discovery.[53,61,62]

One such example is the synthesis of biologically active antibiotic macrolide Cytovaricin by Evans which uses various reactions which take advantage of chiral oxazolidinone auxiliaries.[63] The synthesis hinges on various alkylation and aldol reactions based on *N*-acyl oxazolidinone starting materials. There are five steps which use these chiral auxiliaries, four of which are shown below in Scheme 3 in the synthesis of the north fragment. Initially three separate fragments are constructed (Top, Scheme 3) which are then sequentially combined, one with the aid of the chiral auxiliary once again.

The first fragment is obtained through an initial aldol reaction of the boron enolate of the acylated chiral auxiliary with a protected β-hydroxy aldehyde in which the stereocontrol comes from the chirality of the auxiliary. The initial aldol adduct is then protected and the auxiliary removed to make the Weinreb amide required for the first fragment. The second fragment is similarly prepared using an initial aldol reaction, again controlled by the auxiliary, which is then further transformed to give the fragment. This time a hydration of the double bond and protection as an acetonide for the right side was conducted and on the left the removal of the auxiliary and the transformation to an aldehyde, amide, ketone and finally hydrazone was aided by a Wittig reaction. For the third fragment, the initial reaction was an alkylation reaction between the sodium enolate of the acylated chiral auxiliary with allyl iodide. The auxiliary was then removed, and the terminal double bond transformed into a carboxylic acid, to which the chiral auxiliary was then attached to give the third fragment.

With the three fragments in hand Evans then moved to join them sequentially to make the north fragment (Bottom, Scheme 3). The first two fragments were combined by the formation of the metallo-enamine of the hydrazone which then proceeded to displace the Wienreb amide to form the combined fragment. After a series of reactions, the resulting spiroketal compound was prepared to be joined to the third fragment to create the north fragment. This was achieved by the aldol reaction of the boron enolate of fragment three with the aldehyde of the spiroketal, with the stereocontrol arising from the chiral auxiliary. The synthesis is then completed with the joining of the south fragment which also starts from the aldol reaction of the boron enolate of the acylated chiral auxiliary.

The synthesis of Cytovaricin, containing five key steps in which the oxazolidinone auxiliary is central in both the high yields and complete control over the stereochemistry, highlights the power of chiral auxiliaries as a platform for stereoselective transformations. It is widely regarded as a milestone in stereoselective total synthesis.



Scheme 3: Top: Synthesis of Fragments. Bottom: Joining of Fragments and Completion of Cytovaricin.

Enantioselective Catalysis Based Synthesis

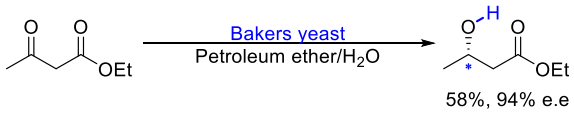
The demand for more selective methods under the premises dictated by Atom Economy has triggered the development of catalytic procedures able to produce enantiomerically pure compounds. Nowadays, enantioselective and catalytic transformations are at the forefront of the research for new stereoselective methods. Depending on the type of catalytic species, enantioselective catalysis may be classified as biocatalysis, organocatalysis, and organometallic catalysis.

Biocatalysis

Biocatalysis covers the use of biological systems such as enzymes to perform chemical transformations.[64,65] As with the chiral pool, nature provides a great source of chirality where the large enzymatic structures can be taken advantage of to elicit stereoselective reactions. A wide range of

transformations are then available, depending on the enzyme's function in its natural environment, as living systems require a large variety of transformations.[65,66]

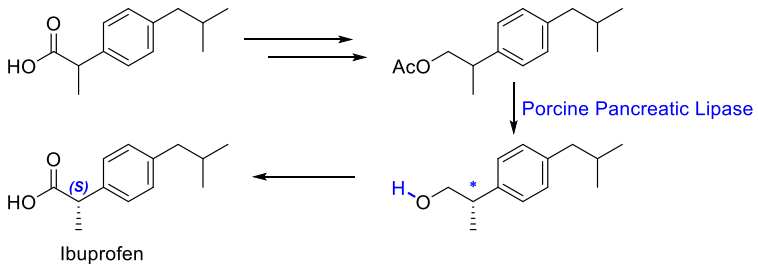
As enzymes naturally work within living cells and organisms their optimal use is in water; this somewhat fetters their use as most small organic molecules have low solubility in aqueous media. After some pioneering work by Klibanov,[67] one major advance for biocatalysis in organic synthesis came in 1993 when Jayasinghe et al. described a stereoselective biocatalysis in an organic solvent.[68] They showed the effective and highly selective reduction using yeast in wet petroleum ether (Scheme 4) and since there have been numerous advances in biocatalysis in organic medium.[69–71]



Scheme 4: The reduction of ethyl acetoacetate in organic media with baker's yeast.[68]

Another limitation of biocatalysis is enzyme specificity, due to their functions in their natural environment enzymes tend to have very limited scope in either the substrates, transformations available or both.[72,73] This limitation is also what accounts for their high selectivity in their given transformations, they have evolved to be highly efficient in their roles; natural enzymes are commonly a trade-off between substrate tolerance for high stereo-, chemo- and regioselectivity. Enzymes also are affected by the reaction conditions, with small deviations potentially blocking catalytic activity. Notwithstanding these drawbacks biocatalysis remains popular due to high effectivity in the right circumstances.[74,75]

Combinations with simple chemical transformations can lead to short synthesis routes to biologically active molecules such as the biosynthesis of Ibuprofen using the Porcine Pancreatic Lipase enzyme described by Basak et al. (Scheme 5).[76] Other combinations with chemical transformations, especially with organocatalysis or asymmetric catalysis, in chemoenzymatic processes have also proved highly successful.[77–80]



Scheme 5: Biosynthesis of Ibuprofen.[76]

One final advance in biocatalysis is the manipulation of natural enzymes to tune their properties for organic synthesis. This allows for the expansion of substrate tolerance, specific transformations, tuning selectivity, higher tolerance to reaction conditions and more. Many methods exist for this, including the use of additives, modifications, enzyme adsorption/immobilization and enzyme engineering through directed evolution or rational design to improve existing transformations.[81,82]

Organocatalysis

Organocatalysis is the use of organic molecules to catalyse reactions without the use of metals. The use of simple amines as organocatalysts dates back to Emil Knoevenagel in 1898 when he showed that simple amines could catalyse the condensation between β-ketoesters or malonates with ketones and aldehydes.[83] In the years since it has been an ever present curiosity in the literature, until around

twenty years ago when the field really took off.[84–88] Organocatalysts interact with the substrates (activation mode) to form enamines, iminium or radical intermediates, through hydrogen bonding or counterion interactions with the former three being the most prominent.[89–95]

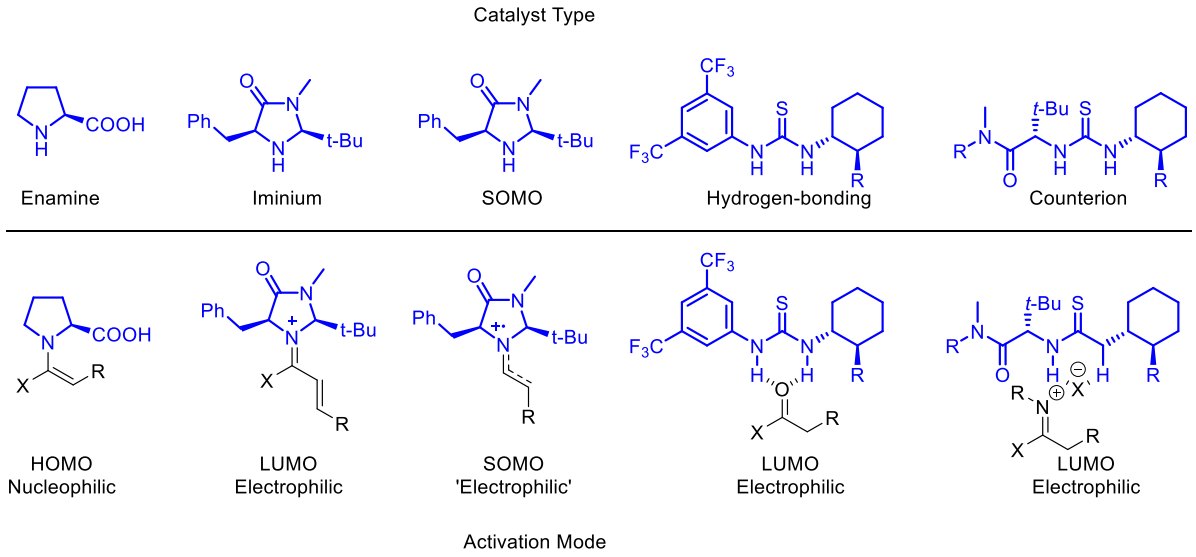
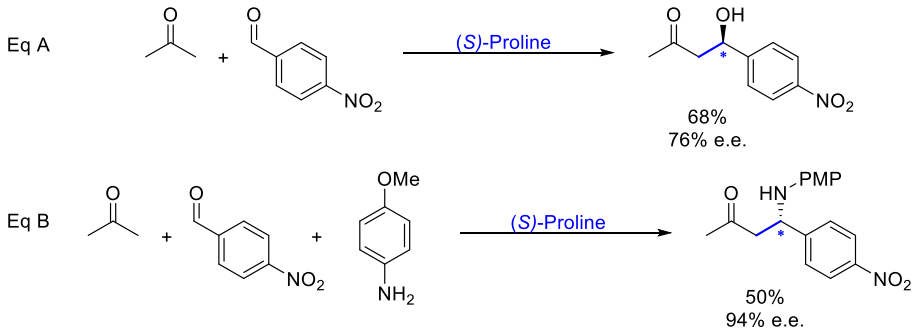


Figure 7: Types of Organocatalyst and their Activation Modes.

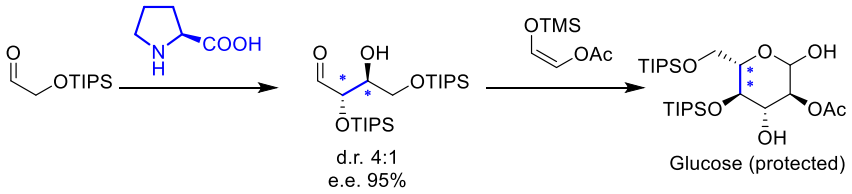
The differing types shown in Figure 7 have differing limitations and uses but the main variations can be seen within the activated compound. Enamine organocatalysis hinges on a HOMO based activation of the carbonyl to create the enamine species, being the only nucleophilic activated species. The resultant chiral enamine can then be used in a wide variety of additions such as: aldol, Michael, Mannich, alkylation and related reactions.[84,93] One of the pioneers in the use of proline in asymmetric enamine catalysis, List, showed the possibility of an intermolecular aldol reaction of acetone with various aromatic aldehydes (Scheme 6, Eq A).[96] He also described the first asymmetric organocatalytic Mannich reaction using proline as the organocatalytic species (Scheme 6, Eq B).[97]



Scheme 6: A: List's Proline Catalysed Asymmetric Aldol Addition.[96] B: List's Proline Catalysed Asymmetric Mannich Reaction.[97]

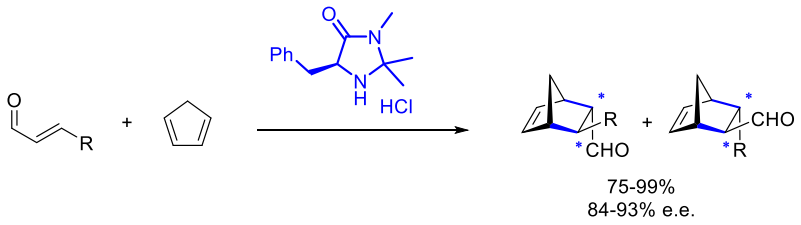
A nice example of this can be found in MacMillan's two-step synthesis of various protected carbohydrates, including glucose (Scheme 7).[98] The first step involves a proline catalysed self-condensation aldol reaction, with the aldehyde acting as both the electrophile and nucleophile. This is achieved by HOMO activation and the formation of an enamine species with the aldehyde and proline, which then reacts with an un-activated aldehyde molecule introducing two new stereocentres. These stereocentres then form the basis for a substrate controlled Mukaiyama aldol reaction in the second step. The stereocentres introduced in the first step therefore map the

configuration of the new stereocentres. The product then finally spontaneously cyclises to form the hemiacetal product, or more specifically the carbohydrate structure.



Scheme 7: MacMillan's Synthesis of Glucose Using Proline Organocatalysis.[98]

Other organocatalysts can be grouped together as electrophilic activated species with differing activations. The most widely used is the formation of an iminium species via LUMO activation which allows for various types of conjugate addition or Diels-Alder reactions.[94] Iminium catalysis, popularised by MacMillan, started with the first asymmetric organocatalysed Diels-Alder reaction with numerous subsequent contributions.[99] The initial reaction utilised a chiral amine derived organocatalyst (now known as Macmillan generation I) to perform Diels-Alder reactions between cyclopentadiene and various α,β-unsaturated aldehydes to give highly enantioselective mixtures of the *endo*- and *exo*-products (Scheme 8).



Scheme 8: MacMillan's Diels-Alder Addition of Cyclopentadiene to αβ-unsaturated Aldehydes.[99]

SOMO organocatalysis is similar to iminium catalysis, using the same family of catalyst and a similar activation state. However, the active species arise from the oxidation of the enamine intermediate and the reactivity is therefore derived from a radical cation.[90,95] This allows for alternate reaction pathways.

It is worth mentioning that forming a covalent bond between the catalyst and substrate is not essential. Hydrogen bond forming thiourea organocatalysts activate the substrate via mainly electrostatic interactions.[91,92] Thioureas can similarly be used in counterion organocatalysis when used with protected chloroamines or chloroalcohols, forming activated oxocarbenium and iminium salts which make great electrophiles.[89,100]

Various other counterion pair catalyst systems exist and it is a diverse field including notably phase transfer catalysts and phosphonium salts.[101,102]

In summary, organocatalysis has provided a large range of efficient transformations. However, the scope is currently limited. Most organocatalysis requires the use of either an aldehyde or cyclic/activated ketone as the starting material and the substrate scope is sometimes small. Another factor which can sometime hinder the application is sometimes low enantioselectivities obtained.

Organometallic Catalysis

Asymmetric organometallic catalysis relies on the use of metals as catalytic centres in which ligands attached to the metal create a chiral species.[103] Chiral catalysts can be divided in two categories:

heterogenous catalysts which act in another phase to the substrates and homogenous catalysts which react in the same phase.

The first use of chiral organometallic compounds as catalysts in organic synthesis was described by Izumi in the 50's when he used a palladium-protein heterogenous complex (initially arising from tethering the palladium complex to a silk fibroin) to perform hydrogenations.[104,105] Horner was one of the first chemists to raise the possibility of a chiral homogenous catalyst, suggesting the use of chiral phosphines in rhodium complexes for hydrogenation reactions.[106] These developments were fully taken advantage of by now Nobel prize winners Noyori and Knowles who independently developed the two first homogenous chiral catalysts for organic synthesis; they, with Sharpless, who developed an enantioselective epoxidation of allylic alcohols,[107] were awarded with the 2001 Nobel prize (Figure 8).[108–110]

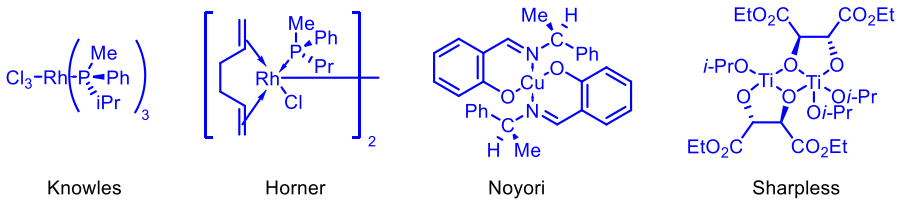
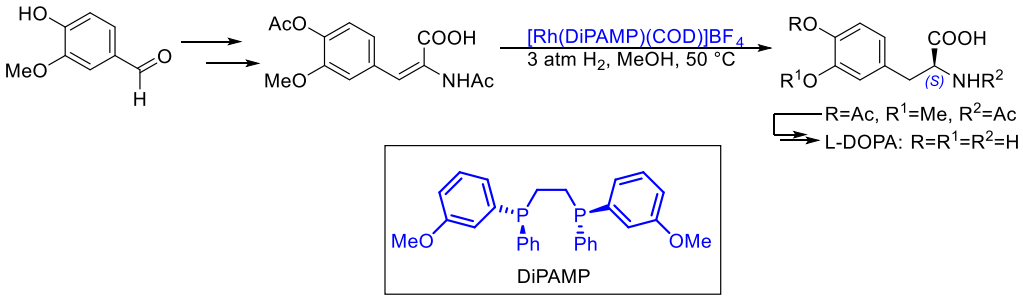


Figure 8: The First Asymmetric Catalysts Developed by Knowles, Horner, Noyori and Sharpless

Knowles also developed the ligand DiPAMP to great success (Scheme 9).[111–113] The use of chiral catalysis in industrial processes was likewise pioneered by Knowles in the synthesis of L-DOPA using chiral phosphine catalysts in a hydrogenation procedure (Scheme 9).[114] These developments and the wide use of the DIPAMP ligand led to Knowles being awarded the Nobel prize in chemistry in 2001.[115]



Scheme 9: Knowles's Commercial Synthesis of L-DOPA and DiPAMP Ligand.

Seminal studies by Knowles and Noyori were crucial for the introduction of chiral phosphines as DIPAMP and BINAP that have inspired a number of asymmetric and catalytic processes.[116–122] Particularly, BINAP diphosphines containing a chiral axis have been largely used as ligands for ruthenium complexes in highly enantioselective hydrogenation of alkenes.

Noyori in 1980 developed the ligand BINAP which was used in asymmetric atom transfer hydrogenations to great effect (Figure 9).[123–125] The scope included functionalised ketones with nitrogen, oxygen or halide substituents, and functionalised olefins. With the success of his BINAP ligand, he continued his search for chiral ligands which led to the discovery of TsDPEN (Figure 9), which provided high enantioselectivity in the reduction of aromatic ketones.[126] Noyori went on to develop one of the most well-known and widely used hydrogenation catalysts to date when he realised the use of TsDPEN and BINAP in one Ruthenium catalyst increased the selectivity and allowed the hydrogenation of simple ketones, even in the presence of olefins.[127]

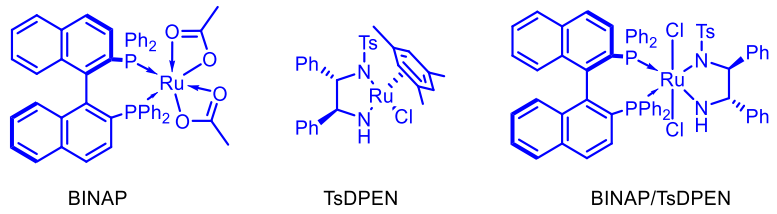
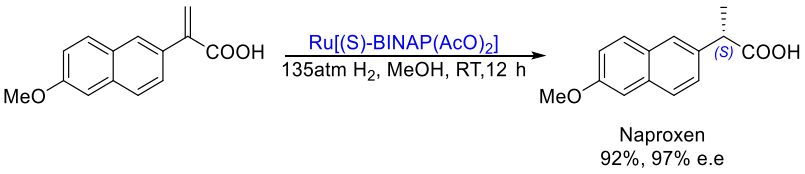


Figure 9: Noyori's BINAP, TsDPEN and Combined Ruthenium Catalysts

His chemistry has been applied to numerous synthetic pathways. For instance, one of his own earlier examples showed the facile synthesis of naproxen through enantioselective reduction of an olefin.[128] For his pioneering work on developing chiral ligands and in asymmetric hydrogenation catalysis he was awarded the Nobel prize along with Knowles.[129]



Scheme 10: Noyori's Synthesis of Naproxen Using his Asymmetric Hydrogenation Catalysis Reaction.[128]

The other winner of the 2001 Nobel prize, Sharpless, was also recognised for his role in the development of asymmetric catalysis.[110] His main contributions revolve around the enantioselective oxidation of alkenes: the epoxidation of allylic alcohols (AE) catalysed by tartrate-derived titanium complexes, and the dihydroxylation (AD) and aminohydroxylation (AA) of olefins using osmium based catalysts containing quinine (and quinuclidine) ligands (Figure 10).[130]

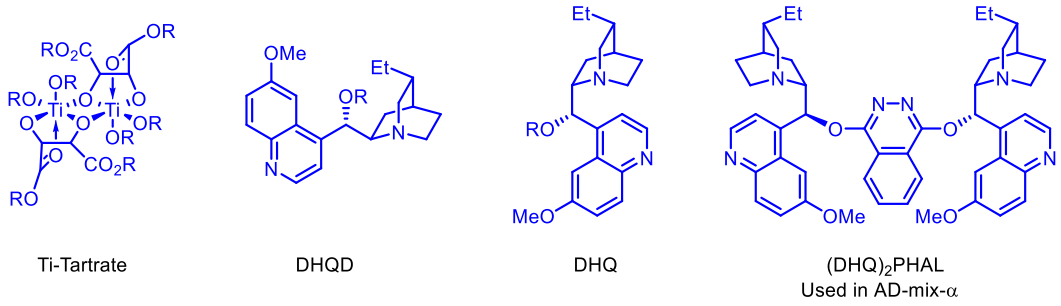
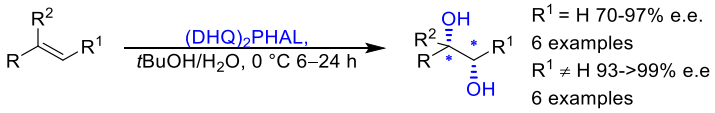


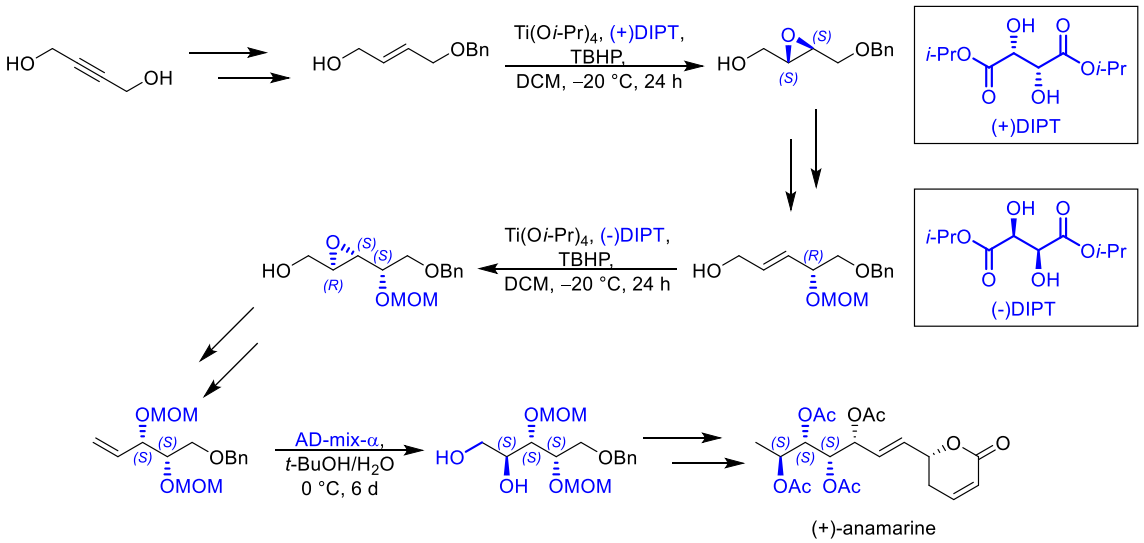
Figure 10: Sharpless's Titanium Tartrate Catalyst, Dihydroquinidine (DHQD), Dihydroquinine (DHQ) and Phthalazine-linked DHQ Ligand: $(DHQ)_2$PHAL Used in AD-mix-α. $(DHQD)_2$PHAL Used for AD-mix-β not Shown but is Equivalent to the DHQ Dimer.

The preliminary ligands showed the potential of such a process but the enantioselectivity was lower than needed for the process to be widely used;[131] this led Sharpless to conduct an improvement on the ligands used in the reaction in order to increase the selectivity. Initial studies showed the variance of the alcohol protecting group had a direct effect on the selectivity of the reaction.[132] This was investigated with a large variety of groups attached to the oxygen with an overall large improvement. This effort culminated in the linkage of two DHQ/DHQD ligands via a linker in a mixture known as AD-mix-α (DHQ) and AD-mix-β (DHQD) which gave wide substrate scope and high enantioselectivity.[133] Shown below in Scheme 11 is an example of the dihydroxylation reaction developed by Sharpless using AD-mix-α using either singly or doubly substituted terminal olefins or doubly or triply substituted *trans*-olefins.[133]



Scheme 11: Sharpless Dihydroxylation Reaction Using AD-mix-α.

A good example of using both the Sharpless epoxidation (AE) and Sharpless dihydroxylation (AD) can be found in the synthesis of the natural product (+)-anamarine by Sabitha (Scheme 12).[134] In this synthesis two Sharpless epoxidations followed by a Sharpless dihydroxylation are used to introduce the stereochemistry of the first three stereocentres. The epoxidations are conducted with different enantiomers of the isopropyl derivative of the titanium tartrate catalyst and the dihydroxylation with AD-mix-α as the source of the chirality. This core is then used to control the adjacent stereocentre through chelated induction and the fragment is then bound to another to complete the backbone of the natural product.



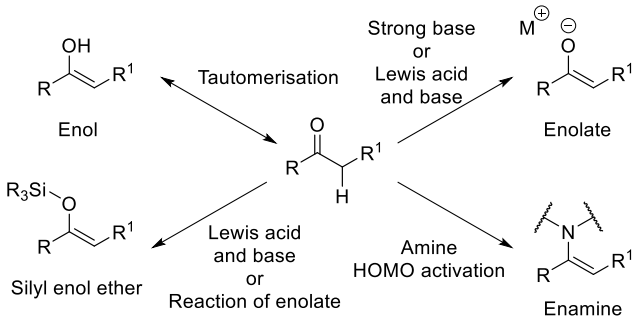
Scheme 12: Sabitha's Synthesis of (+)-Anamarine using AE and AD.

Carbon-Carbon Bond Forming Reactions

One of the most important challenges in organic synthesis is the stereoselective formation of carbon-carbon bonds.[135,136] These reactions allow the construction of the carbon backbone of target molecules, ideally furnishing the molecule with the required functional groups in a stereoselective manner. Many initial syntheses of natural products or designed/derivatised drugs start with a non-stereoselective approach to form the carbon backbone and the isomers are later separated; this is especially true when it is unclear which stereoisomer of the final product is the biologically active one. However, once the molecule is proved to be biologically active and the correct isomer identified a stereoselective synthesis is required. This is where stereoselective carbon-carbon bond forming reactions have a real importance in the field of organic chemistry.

Carbonylic Compounds

One of the best candidates for the stereoselective construction of carbon–carbon bonds are carbonylic compounds containing a Cα-hydrogen. Indeed, removal of this hydrogen leads to different nucleophilic species from the same starting material (Scheme 13). Through this, various options for nucleophilic species are available depending on the situation. Silyl enol ethers for example, can be stored stably, whereas enols, enolates and enamines are generated *in-situ*. Once formed these species can react with electrophilic species such as: alkyl halides or sulphonates, carbenium intermediates, carbonyls, epoxides, imines and activated olefins in a variety of reactions such as: alkylations, aldol, Mannich and Michael additions.



Scheme 13: Utility of Carbonyls with α-Hydrogens as Nucleophilic Precursors.

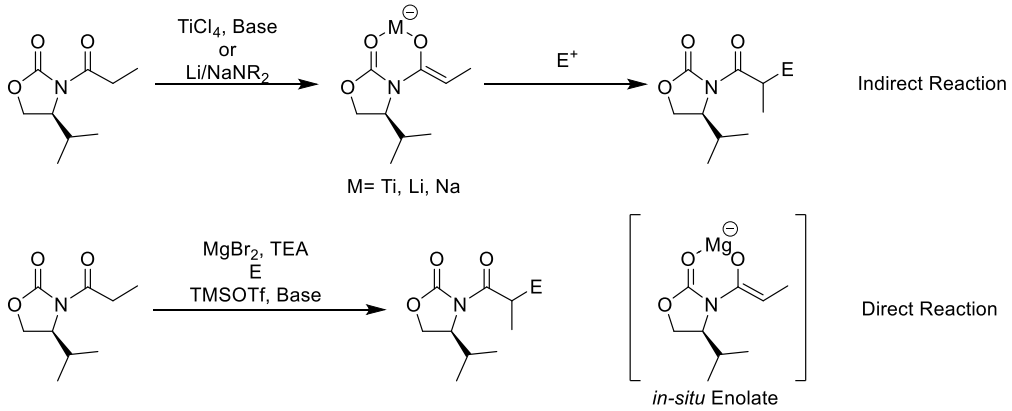
Adding a chiral element to these nucleophiles to create an asymmetric reaction is an appealing way to attain highly stereocontrolled transformations and a large number of methods have been developed with this aim. For this reason, it is one of the most widely used approaches for the stereoselective construction of carbon-carbon bonds.

Direct Reactions

Despite of being excellent platforms from which to carry out a wide number of stereoselective carbon-carbon bond forming reactions, enols, silyl enol ethers, enamines, and metal enolates suffer from a serious drawback that hinder the development of catalytic approaches adapted to the tenants dictated by atom economy. Indeed, their use usually requires two stages: 1) treatment of the carbonylic precursor with strong bases, amines, or Lewis acid/R_3N and, if required, trapping of the resultant nucleophilic species and 2) once prepared, addition to the appropriate electrophile to undergo the desired reaction. Such a scheme requires that the roles of nucleophile and electrophile are well defined from the very beginning in order to avoid undesired mixtures of products. This is

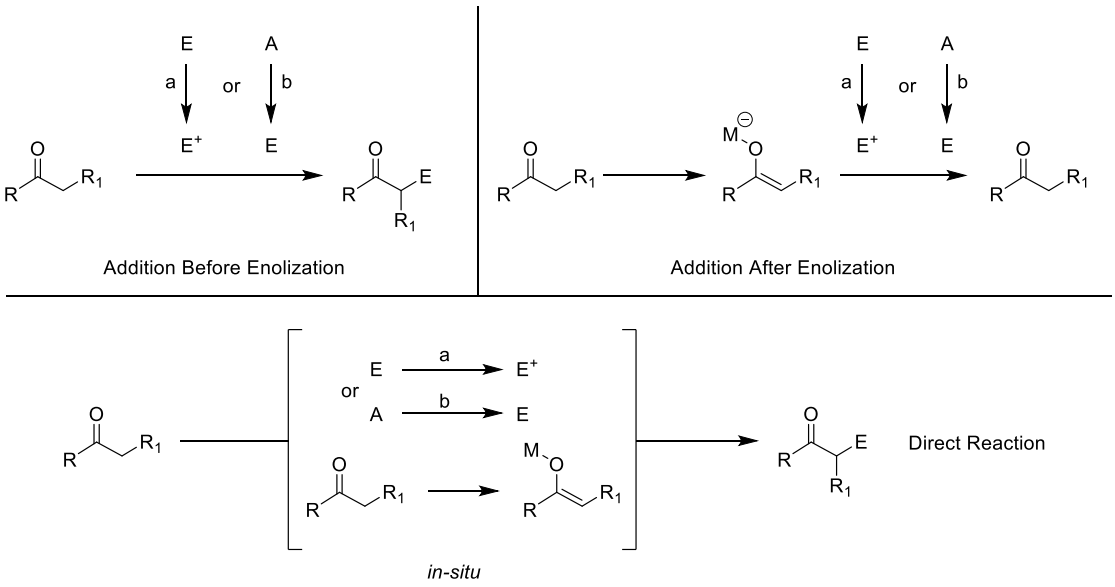
particular important if the reaction involves two potential sources of nucleophiles and electrophiles, as occurs in aldol reactions and Michael addition.

Such an approach, called **indirect reactions**, has been commonly followed during the last decades and is at the centre of the most successful approaches in stereoselective synthesis. Unfortunately, this is hardly compatible with catalysis. Mukaiyama aldol reactions are a clear example of this. Silyl enol ethers have been traditionally employed in asymmetric and catalytic aldol reactions promoted by chiral Lewis acids provided that the starting material, the nucleophilic partner, was stoichiometrically prepared and isolated in a previous step. Another example can be seen in the classical Evans oxazolidine titanium or alkaline metal chemistry in Scheme 14. A solution to this to enable a **direct reaction** is the catalytic generation of the enolate *in-situ* allowing all of the reagents to be present throughout the reaction. An example is also shown in Scheme 14 using magnesium catalysis.[137,138]



Scheme 14: Top: Indirect Reaction of Evans Titanium Enolates. Bottom: Direct Reaction Using Magnesnium by Evans.

Another reason that some reactions have to be conducted in two parts is when the electrophile has to be either: prepared in-situ due to instability in atmospheric conditions or rapid degradation; or has to be activated to be able to react. In these cases it is either difficult or incompatible to conduct both the enolate formation and preparation/activation of the electrophile in the same reaction mixture and has to be prepared/activated separately and added either before or after the enolate formation (Top, Scheme 15). Unfortunately, both violate the conditions required for a **direct reaction**, and many methodologies have been developed where the activation and enolization processes occur concurrently in the reaction vessel in direct reactions (Bottom, Scheme 15).

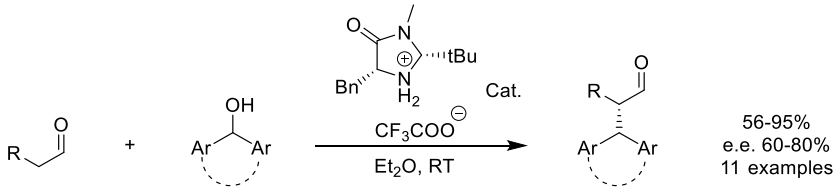


Scheme 15: Indirect Reactions Requiring Either the Pre-activation or Preformation of the Electrophile. Top Left: Addition Before Enolization, Top Right: Addition After Enolization (a: Pre-activation, b: Preformation), Bottom: Direct Reaction.

Therefore, it can be concluded that a more general approach better suited to atom economy conditions would involve the simple mixture of all the reagents without the previous formation of the nucleophilic and electrophilic intermediates. This would be a **direct reaction**. In principle, a **direct reaction** would facilitate any enantioselective and catalytic construction of the carbon architecture because appropriate chiral catalysts could be considered as simple reagents. However, such a plan becomes challenging because the catalytic species must not only provide the necessary chiral environment to make possible the asymmetric carbon-carbon bond forming step but also previously activate in a selective manner just one of the reagents.

As mentioned before, organocatalysis met the challenge and chiral amines derived from α-amino acids have been employed for the activation of aldehydes in such a way that the resultant enamines (HOMO activation) or iminium (LUMO activation) intermediates may react with appropriate electrophiles or nucleophiles respectively.

An insightful application of this design that demonstrates its synthetic potential is the α-alkylation of aldehydes reported by Cozzi. Such a transformation is a S_N1-like reaction of enamines derived from aldehydes with diaryl alcohols using a MacMillan catalyst to achieve an enantioselective alkylation with the configuration controlled via a chiral enamine species as the nucleophile (Scheme 16).[139,140]



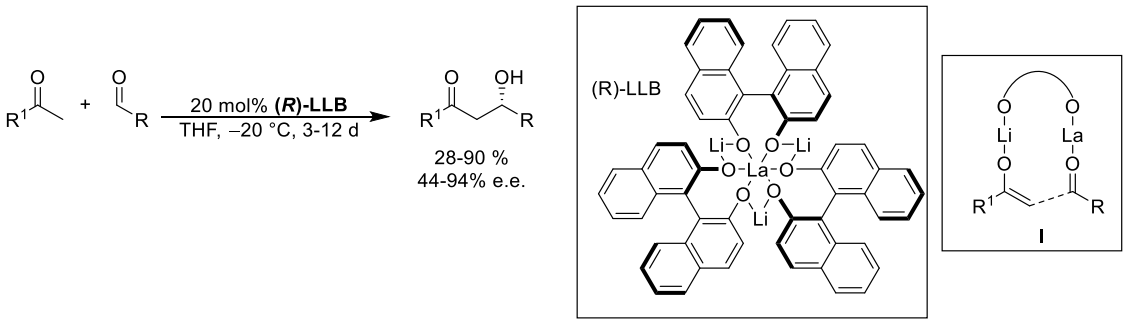
Scheme 16: Example of Chiral Enamine Alkylation by Cozzi.[139]

Unfortunately, and despite their synthetic potential, metal enolates have stayed away from the mainstream interest. Indeed, one of the drawbacks of many direct reactions using enolates is the need to either add the enolate to the other components or the electrophile to the enolate mixture because it is not possible to start with all of the components in the same reaction mixture. This is especially true for stoichiometrically formed enolates: many enolates require strong conditions to form, or low

temperatures for the formation of the enolate to occur. In many cases this excludes the presence of the electrophile or other components due to their degradation, incompatibility with the reaction conditions, or their reaction with the enolizing agents. This is also a problem if the electrophile can be enolized also, in this case the preformation of the enolate is essential and **the indirect reaction** remains imperative.

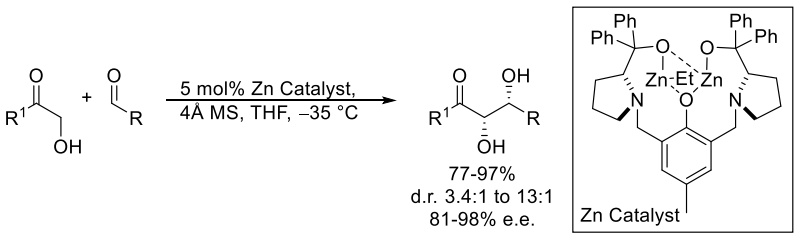
One way to achieve this is moving to softer enolising conditions which usually involve the use of an adequate Lewis acid. For example, traditional enolate chemistry is heavily reliant on titanium, lithium, or sodium enolates, which are unavoidably required to be preformed in the reaction mixture before the addition of other reagents. Otherwise, if the enolization can occur in the presence of the electrophile or concurrently with the activation of the electrophile and vice versa then it becomes a **direct reaction** with benefits in experimental and conceptual simplicity, saving time and hassle in the laboratory.

Shibasaki, towards the end of the 90's, developed chiral lanthanum-based heterobimetallic catalysts containing both Lewis acid and base Brönsted centres that enabled direct, catalytic, and enantioselective acetate aldol reactions of unmodified ketones with aldehyde.[141,142] to produce the corresponding aldol adducts with a moderate to excellent stereocontrol (Scheme 17). The bidentate ligand used was BINOL and the detachment of one of the oxygen linkers leaves an empty coordination site and a free lithium alkoxide. The lithium then acts as a Bronsted base creating the enolate and parallelly the lanthanum metal acts as a Lewis acid coordinating to the aldehyde substrate and activating it, as seen in the intermediate **I**.



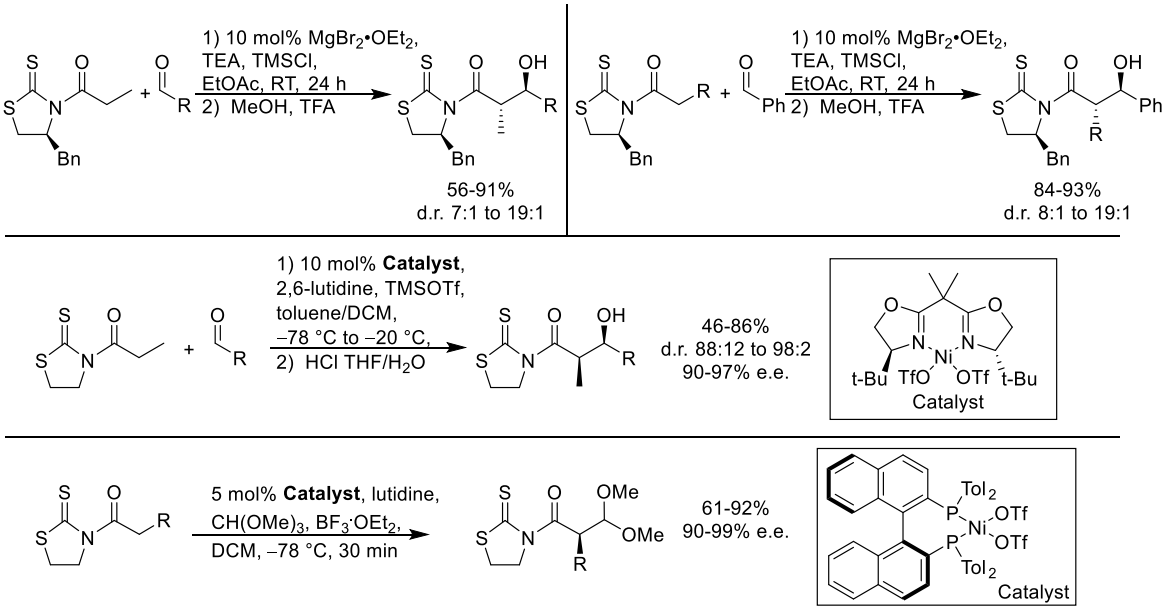
Scheme 17: First Example Described by Shibisaki Using Lanthanum Catalysts to Perform Aldol Reactions.[141]

In turn, Trost reported that zinc also could be used to effect asymmetric aldol reactions.[143–145] Using zinc and a chiral ligand derived from cresol and proline he initially used a mixture of the two to perform selective acetate aldol reactions with varying success.[145] He speculated that the reaction proceeded through a dinuclear based complex with two zinc atoms bridging the three oxygens present in the ligand. Upon preforming the catalyst, Trost was able to perform highly selective aldol reactions catalysed by the zinc dinuclear catalyst (Scheme 174).[144]



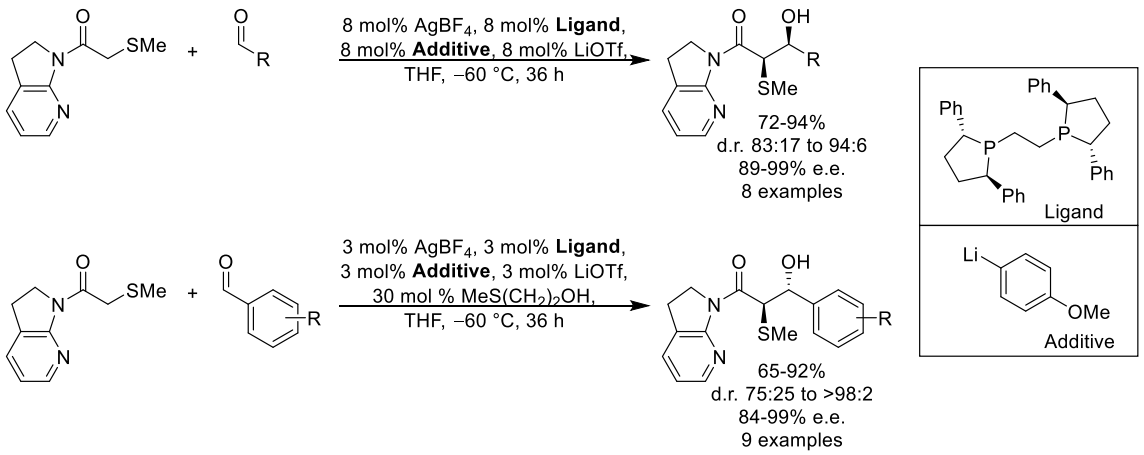
Scheme 18: Trost's Asymmetric Aldol Reaction Using a Dinuclear Zinc Catalyst.

Later on, Evans showed the potential of soft enolization of chiral *N*-acyl oxazolidinones and thiazolidinethiones with magnesium salts (Top, Scheme 19).[137,138] In this case the control on the configuration came from the chiral auxiliary present in the starting material and the magnesium was used sub-stoichiometrically to generate the enolate catalytically. Taking advantage of such findings, Evans unveiled that treatment of achiral *N*-acyl thiazolidinethiones with chiral nickel(II) complexes provided the corresponding metal enolates that enabled aldol reactions (Centre, Scheme 19),[146] or additions to oxocarbenium intermediates derived from trimethyl orthoformate generated in the reaction mixture with $BF_3{\cdot}OEt_2$ (Bottom, Scheme 19),[147] in a highly stereocontrolled manner. All together these reactions took advantage of an achiral starting material, which catalytically forms the enolate species via coordination to the chiral nickel complex. So, in this case the chiral control comes from the metal catalyst. An additional Lewis acid (the boron or silyl triflate) is required to complete reaction with the electrophile.



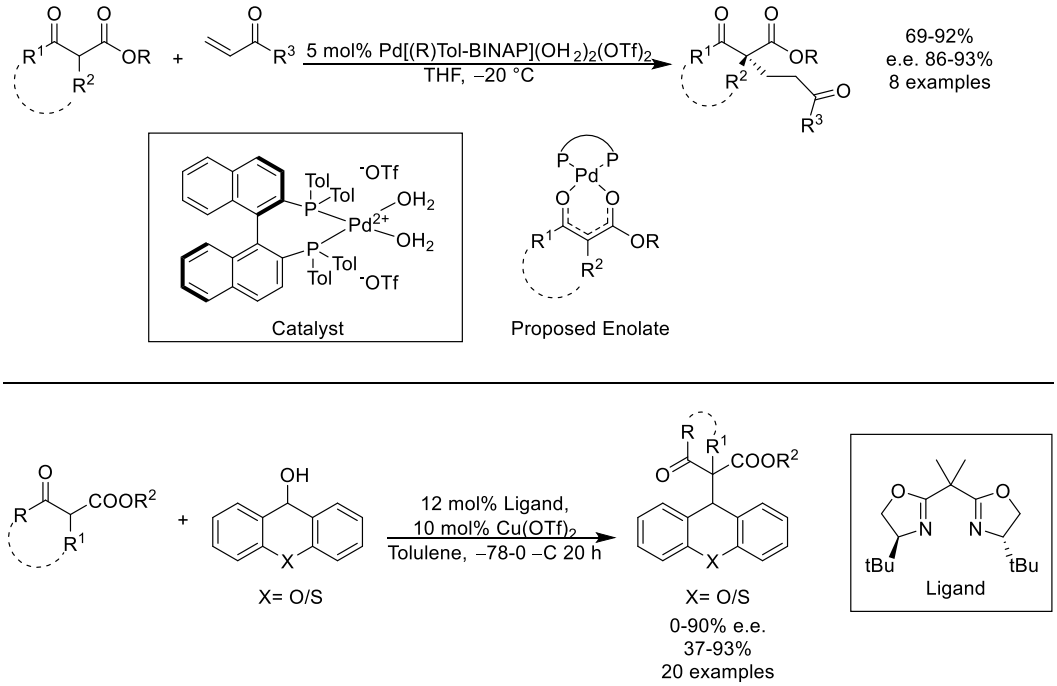
Scheme 19: Evans's Magnesium Catalysed Aldol Reactions from Chiral Thiazolidinethiones and Asymmetric Nickel(II) Catalysed Aldol and Alkylation Reactions.

More recently, Kumagai and Shibasaki have used 7-azaindoline amides to promote highly enantioselective aldol reactions catalysed by copper complexes. Their first attempt involved α-thio azaindoline substrates using a diphosphine ligand and a silver complex to perform highly selective *syn*- and *anti*-aldol reactions depending on the nature of the aldehyde.[148] They also went on to develop similar reactions based on different acyl structures in the starting material and different aldehydes also moving to copper catalysis. [149–151]



Scheme 20: Shibasaki and Kumagai's Asymmetric Aldol Reaction from Achiral Azaindoline Compounds.

Parallel to these aldol-based examples, a few cases of Michael and alkylation reactions have been also reported with different levels of success. Sodeoka found that enolates from cyclic and acyclic β-keto esters could be generated by a chiral palladium complex and can undergo Michael additions to α,β-unsaturated ketones (Top, Scheme 21),[152] to provide the corresponding adducts containing a quaternary stereocentre with excellent stereocontrol. More recently, Nájera has also described that a chiral copper complex catalyses S_N1-alkylations of β-keto esters with alcohols with varying degrees of enantiocontrol (Bottom, Scheme 21).[153] Similar examples were also published by Nishibayashi et al. using phosphonates instead of esters at the beta position.[154,155]



Scheme 21: Top: Catalytic Michael Addition Using a Chiral Palladium Enolate.[152] Bottom: Example of Alkylation of a Enolate Formed with a Chiral Metal Catalyst.[153]

All these procedures demonstrate that metal enolates may be involved in direct and enantioselective transformations provided that the appropriate electrophilic partner is accessible. Unfortunately, the scope of most of these processes is rather narrow, which hampers further development and prevents a comprehensive exploitation of their possibilities. Thus, inspired by the former examples and considering the benefits arising from a general approach, our group launched a few years ago a

research project aiming to develop new **direct**, **catalytic**, and **stereoselective** carbon-carbon bond forming reactions. These processes would take advantage of stable and easy to handle nickel(II) complexes, which could be activated in the reaction mixture and trigger the formation of the corresponding enolates from a single platform. Then, these enolates might participate in a wide array of direct and stereoselective reactions provided that the appropriate electrophiles were simultaneously generated in the reaction mixture and evolve through similar open transition states (Figure 11). Finally, the resultant procedures could then be applied to lucrative synthetic targets.

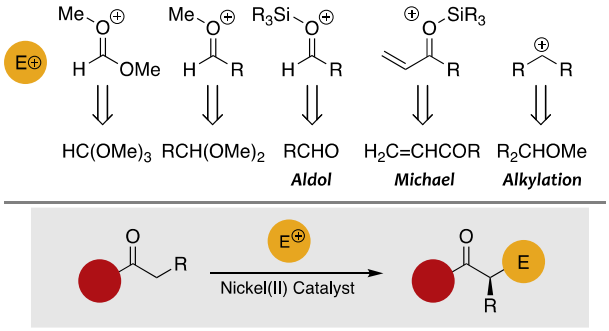
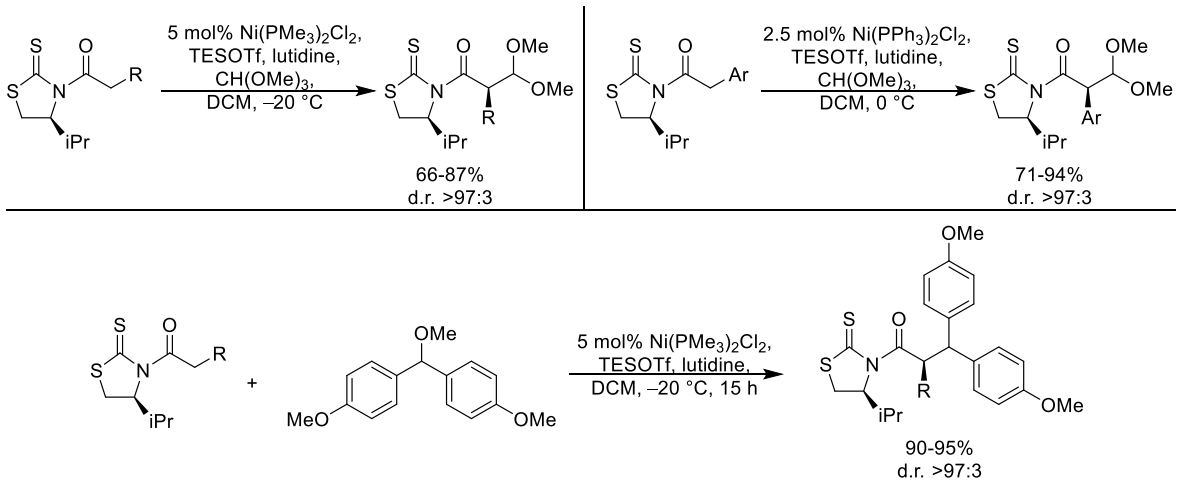


Figure 11: Activated Electrophiles from their Parent Compounds and a Generic Reaction Scheme.

The feasibility of such an approach had been demonstrated at the outset of this Thesis. Indeed, treatment of chiral *N*-acyl thiazolidinethiones with a structurally simple $(Me_3P)_2NiCl_2$ in the presence of TESOTf and lutidine produced the desired nickel(II) enolates that reacted with oxocarbenium and carbenium intermediates generated in the reaction mixture (Scheme 22).[156–158] Remarkably, the role of TESOTf proved to be crucial, since it was necessary to convert $(Me_3P)_2NiCl_2$ into the true catalyst, the more active $(Me_3P)_2Ni(OTf)_2$, and to produce the electrophilic intermediates.



Scheme 22: Previous Work in our Group on Direct Alkylation Reactions Catalysed by Nickel (II) Complexes.

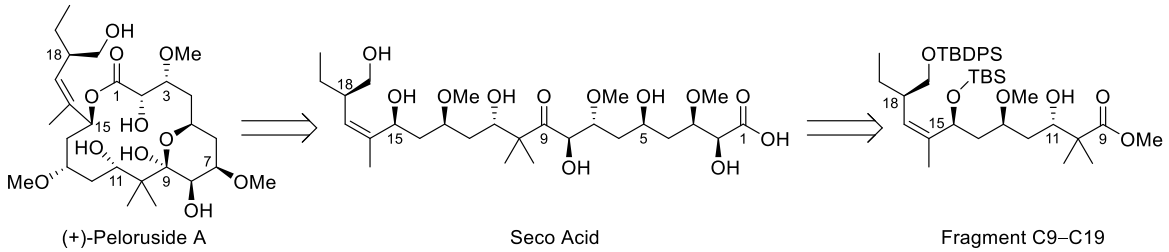
Having thus demonstrated the synthetic potential of nickel(II) enolates arising from a chiral thiazolidinethione platform, we envisaged that the resultant methodology could be applied to the synthesis of a natural product and expand their use to other electrophiles. Likewise, it was time to make a step further and to assess the feasibility of employing chiral nickel(II) complexes for a wide range of truly enantioselective carbon-carbon bond forming reactions.

Objectives for the Current Thesis

In this context, and in keeping with the aforementioned ideas, the aim of this thesis was trifold:

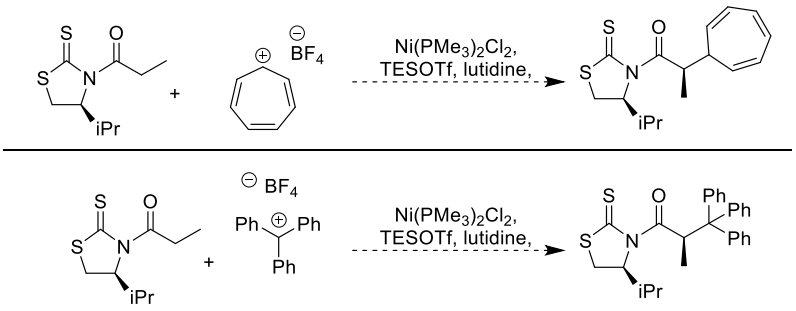
1. Expand the repertoire of reactions based on nickel enolates generated from acylated chiral thiazolidinethiones.
2. Spearhead the project of transferring the chirality from the starting material to the metal and developing new asymmetric metal catalysed reactions.
3. And finally, the application of our methods, both new and old, to the synthesis of biologically active molecules or fragments of them.

In Chapter 1 the methodologies developed in the previous years in the group based on chiral thiazolidinethione auxiliaries with simple nickel (II) complexes or titanium chemistry will be exhibited in a concise synthesis of a fragment of Peloruside A. Peloruside A is a biologically active natural product extracted from sea sponges with great potential in the fight against leukaemia. In this chapter, the synthesis of the fragment C9-C19 (somewhat larger than half the molecule) will be synthesised (Scheme 23). The reactions to be used developed in our group are: a nickel(II) catalysed addition to trimethyl orthoformate; a titanium-mediated acetate aldol reaction; and a titanium-mediated acetate addition to an acetal species. Optimisation of the synthetic route and the application of a new greener approach to synthesis will be applied to both increase the yield, remove chromatographic steps and make the synthesis easier.



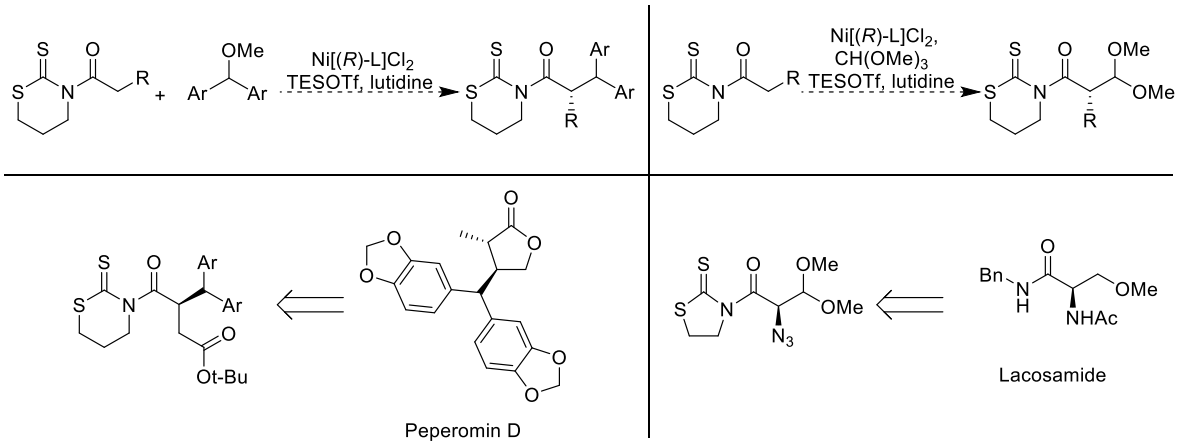
Scheme 23: Retrosynthetic Analysis of Peloruside A to Give Fragment C9–C19.

In Chapter 2 the methodologies based on the nickel(II) catalysed addition of enolates from thiazolidinethiones will be attempted to be applied to a new class of electrophile. Specifically, the functionality of the reaction of these catalytically generated chiral enolates with carbocationc salt compounds will be investigated. The initial study and optimisation will be conducted with the bench-stable tropylium salts (Top, Scheme 24). Once the viability has been established the next objective will be to expand the scope both in terms of starting materials and other commercially available cationic salts (Bottom, Scheme 24). Furthermore, these products will be transformed to various synthons with a wide range of functionality via the removal of the auxiliary in different conditions.



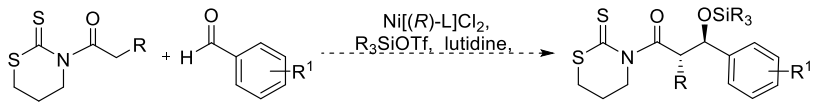
Scheme 24: Proposed Reactions with Stable Carbocationic Salts from Enolates Generated from Chiral Thiazolidinethiones.

Chapter 3 will focus on the development of new asymmetric reactions catalysed by chiral nickel(II) complexes in the aim of removing the chirality from the starting material. The development and optimisation of the reaction will be based on the electrophile class of diarylmethyl ethers (Top Left, Scheme 25). Once the best catalyst, achiral scaffold and reaction conditions are fully optimised an expansion of the scope will then be conducted with a focus on creating and controlling one stereocentre (Top Right, Scheme 25). This will aim to increase the range of both electrophiles and starting materials considerably and will also incorporate an investigation of the removal of the new achiral scaffold to leave various functionality. With this achieved the new reaction(s) will be applied to the synthesis of small biologically active molecules, namely Peperomin D and Lacosamide (Bottom, Scheme 25). The reaction will also be scaled up in the first stages of preparation for its industrial application.



Scheme 25: Top: Proposed Reactions with Chiral Nickel Catalysts. Bottom: Retrosynthesis of Proposed Syntheses.

Chapter 4 will increase on the work of Chapter 3 and take it further in the aim of developing new asymmetric reactions catalysed by chiral nickel(II) complexes where two new chiral centres are created exercising stereocontrol. This Chapter will focus of the development of a new type of aldol reaction where the product formed is the silyl protected aldol adduct (Scheme 26). This is part of the mechanism of the reaction and requires no protection step, rather the silyl triflate activation of the aldehyde leads directly to the protected product when reacted. An initial optimisation of the reaction conditions for the control over two stereocentres is then followed by an extensive investigation of the scope in terms of the aldehydes and starting materials used, including the subsequent removal of the achiral scaffold. Apart from the main content, this Chapter also describes the preliminary studies towards: a new direct and enantioselective Michael addition of the former reagents to α,β-unsaturated aldehydes, aldol additions to protected propargylic aldehydes, and aldol-like addition to dimethyl acetals; all catalysed by chiral nickel(II) complexes.



Scheme 26: Proposed Asymmetric Aldol Reaction with Simultaneous Silyl Protection.

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Chapter 1: Towards the Synthesis of Peloruside A

Synthesis of Fragment C9-C19 Using Chiral Auxiliary Methodologies Developed in the Group

Peloruside A, Discovery, and Properties

Peloruside A is a macrolide isolated in 1999 from the sea sponge *Mycale hentscheli* in the Pelorus Sound (hence the name) region of New Zealand's South Island by Northcote et al. (Figure 12).[1] The sponge had already yielded various bioactive compounds showing either cytotoxic anticancer or antiviral properties and therefore was further studied and yielded Peloruside A.[2–4] It was initially shown to have cytotoxic activity through allosteric microtubule stabilising action similar to the drug Paclitaxel;[1,5] however, it was later shown to have a different binding site on the outer surface of the tubulin macrostructures.[6–11] The binding to the microtubule outer structure promotes the polymerisation of the tubulin units and consequently due to the stabilisation the process of mitosis and cell division is inhibited.[8,12]

Figure 12: Sea Sponge Mycale Hentscheli (image from Northcote),[7] and its Origin in the Pelorus Sound in New Zealand.[13]

Various studies and pre-clinical trials have shown Peloruside A's ability as an antimitotic cytotoxic anticancer agent against various strains of cancer;[1,5,8,14–20] being particularly efficient against leukaemia.[1,5,16,21] Peloruside A has also shown activity against certain neurological diseases,[22,23] and shows some anti-angiogenic properties.[24] It has even shown potential to be used to treat inflammatory and autoimmune disorders.[6,25–27] Due to the vast potential held by Peloruside A and its low natural abundance (3 mg isolated from 170 g sponge specimen,[1] 0.002% mass) it is a very lucrative target for synthesis.

Whilst the initial structure described by Northcote had the correct connectivity and relative stereochemistry, the absolute configuration could not be assigned as the assignation was based on NOE coupling and therefore lacked a known point of reference for the absolute assignation. This problem was later solved by De Brabander with the first total enantioselective synthesis of Peloruside A in 2003; he was able to confirm the absolute configuration by the synthesis of what turned out to be the enantiomer of the natural product and comparing the spectral data and optical rotation to the isolated natural product.[28] The natural configuration was discovered to be 2*S*,3*R*,5*R*,7*R*,8*R*,9*R*,11*S*,13*S*,15*S*,16*Z*,18*R* (Figure 13*)*.

Another related natural product later extracted from the same sponge species had the same structure with a hydroxy group at the C3 position instead of a methoxy; this was denoted Peloruside B and has also been the focus of some syntheses (Figure 13).[29] Two other compounds were also later isolated with changes in the pyran rings position or saturation and were named Peloruside C and D.[30]

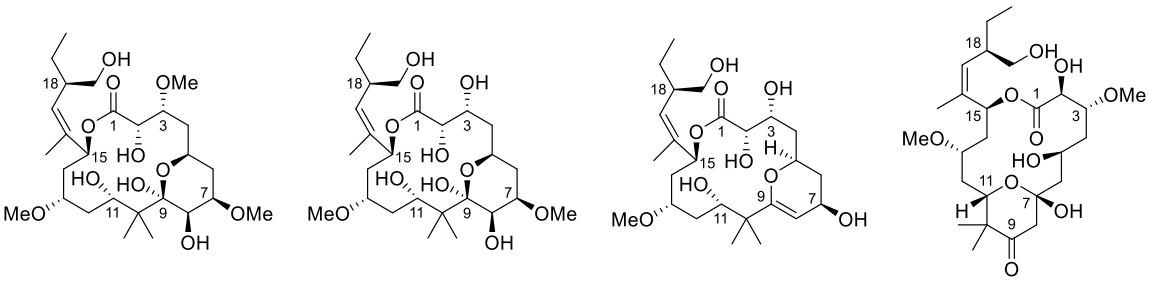
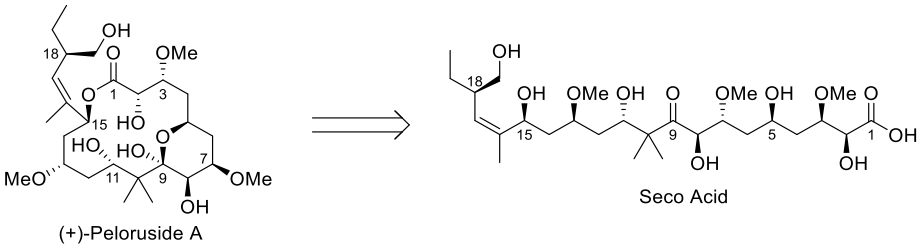


Figure 13: Structure of (+)–Peloruside Natural Products.

Syntheses of Peloruside A

The first synthesis by De Brabander,[28] along with its accompanying insight into the absolute configuration laid the foundations for a variety of both partial and total syntheses of Peloruside A and related compounds spanning more than ten years and involving various well-known synthetic groups.[31]

Most retrosynthetic analyses start with the opening of the lactone bond connecting C1 to C15 and the pyran ring linking C5 to C9, which forms a linear seco acid as a key late stage intermediate (Scheme 27). Some syntheses do form the pyran ring before reaching the seco acid, in fact this was De Brabander's route,[28] but the common strategy is to first form the seco acid, then form the pyran ring and close the macrocycle. As a matter of fact, all five total syntheses published to date of (+)-Peloruside A pass through the seco acid.[32–37]



Scheme 27: Retrosynthetic Analysis of Peloruside A to Give the Seco Acid.

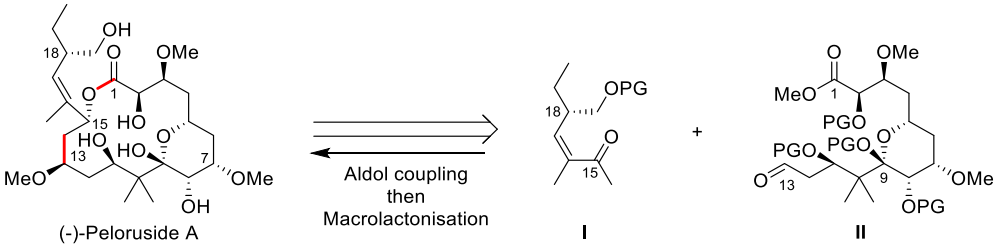
From the seco acid, two strategies emerge, either using two disconnections and three fragments or one disconnection and two fragments. The sole total synthesis that uses the two disconnection strategy involves the breaking of the C6–C7 and C11–C12 bonds to obtain three synthetic fragments.[34,37] The approach that is more common, in the synthesis of fragments as well as total syntheses, is the single disconnection. The two fragment based syntheses described so far disconnect different bonds around the middle with disconnections ranging from C7–C8 all the way to C11–C12 to give the two fragments.[32,33,35,36] For easy comparison the fragments containing the C15 oxygen group of the lactone with be denoted **I** and those containing the carbonyl at C1 will be denoted **II**.

Total Syntheses of (+)-Peloruside A

De Brabander's Initial Synthesis of (–)Peloruside A

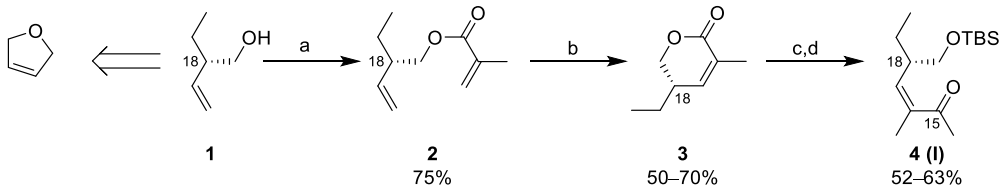
De Brabander started his synthesis of Peloruside A without knowing the exact configuration of the natural product, although through extensive NMR analysis Northcote had narrowed it down to the two probable enantiomers.[1] Nevertheless only through the synthetic construction of Peloruside A would De Brabander be able to confirm the correct diastereoisomer was assigned and figure out which of the two enantiomers corresponded to the natural product.[28]

Working with this disadvantage De Brabander first set out his retrosynthetic pathway; this consisted of making two fragments by first opening the lactone and then disconnecting the C13–C14 bond giving Fragment **I** and the larger Fragment **II** (Scheme 28). He then continued to synthesise each fragment separately.[28]



Scheme 28: De Brabander's Retrosynthetic Analysis to Give Fragments I and II.

For the smaller Fragment **I** the starting point was a chiral synthon (**1**) derived from dihydrofuran described by Hoveyda in his synthesis of Fluvirucin B_1 (Scheme 29).[38] This was then reacted with methacryloyl chloride in the presence of DMAP to acylate the alcohol position to give compound **2** in a high yield. This was then subjected to metathesis conditions using Grubbs second generation catalyst to furnish the lactone **3** with yields ranging from moderate to high and varying amounts of sub-product arising from the dimerisation of **2**. This lactone was then opened using methyl lithium as an alkylating agent to free the alcohol and introduce methyl ketone at the C15 position. The resulting alcohol was subsequently protected to give compound **4** (or Fragment **I**) in moderate to good yields over two steps. Therefore, in just a four-step sequence with yields between 20% and 33% overall De Brabander was able to successfully acquire the first fragment of Peloruside A.



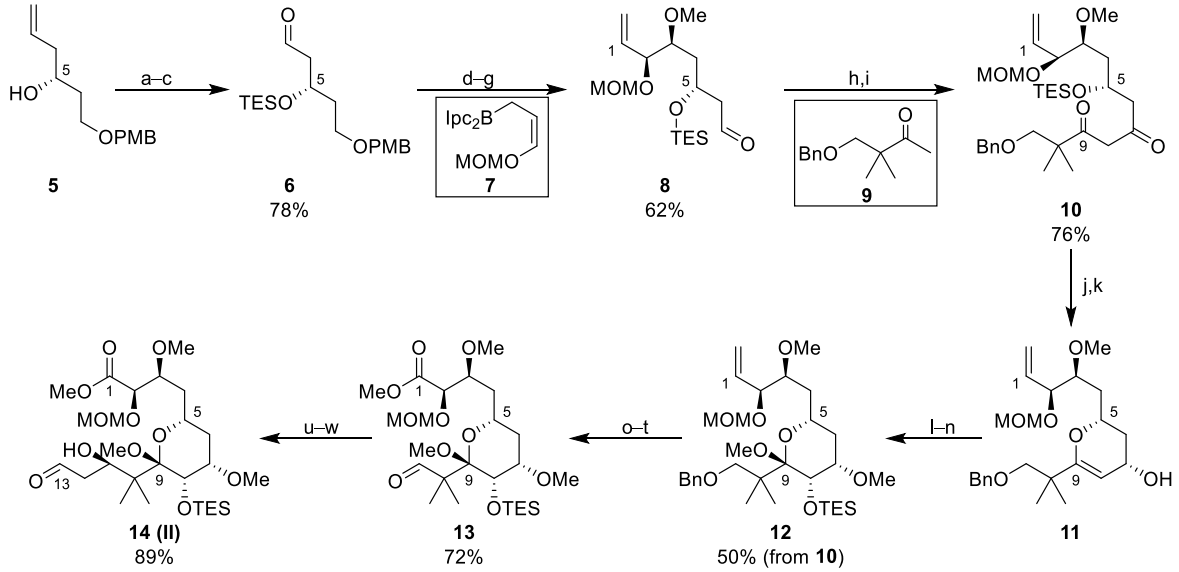
a: H_2C=CMeCOCl, DIPEA, DMAP, DCM; b: 10 mol% Grubbs 2nd Gen, DCM, reflux;
c: MeLi, THF, –78 °C; d: TBSCl, imidazole, DMAP, DMF.

*Scheme 29: De Brabander's Synthesis of Fragment **I** of (–)-Peloruside A.*

He then moved to the synthesis of the remaining Fragment **II** (Scheme 30). The starting point for this fragment was a synthon (**5**) previously described by De Brabander and Amos Smith III.[39,40] This was then transformed to aldehyde **6** via protection of the alcohol followed by osmium catalysed oxidative double bond cleavage, with a good yield over the three steps. Addition of (*Z*)-alkoxyallylborane **7** to aldehyde **6** with methylation of the resulting alcohol followed by deprotection and oxidation of the alcohol at C7 gave the aldehyde **8** in a good yield. The lithium enolate of **9** was then added to this aldehyde, which following oxidation of the aldol product with Dess-Martin periodinane gave the 1,3-diketone **10** in a high yield. Acidic promoted cyclisation followed by a Luche reduction of the resulting enone, furnished the pyran **11**. This was then reacted, without further purification, with mCPBA to form the epoxide, which was opened *in-situ* by methanol. After methylation of the alcohol at C7 and protection of the new alcohol at C8 led to the pyran **12** in a moderate overall yield.

To pass from **12** to **13** a complex sequence was then employed. First, the double bond at C1 was transformed to the methyl ester through the formation of the carboxylic acid, using an oxidative double bond cleavage, followed by methylation with diazomethane. Second, the alcohol at C11 was deprotected and then oxidised to give aldehyde **13** in a high yield over six steps. Finally, the addition

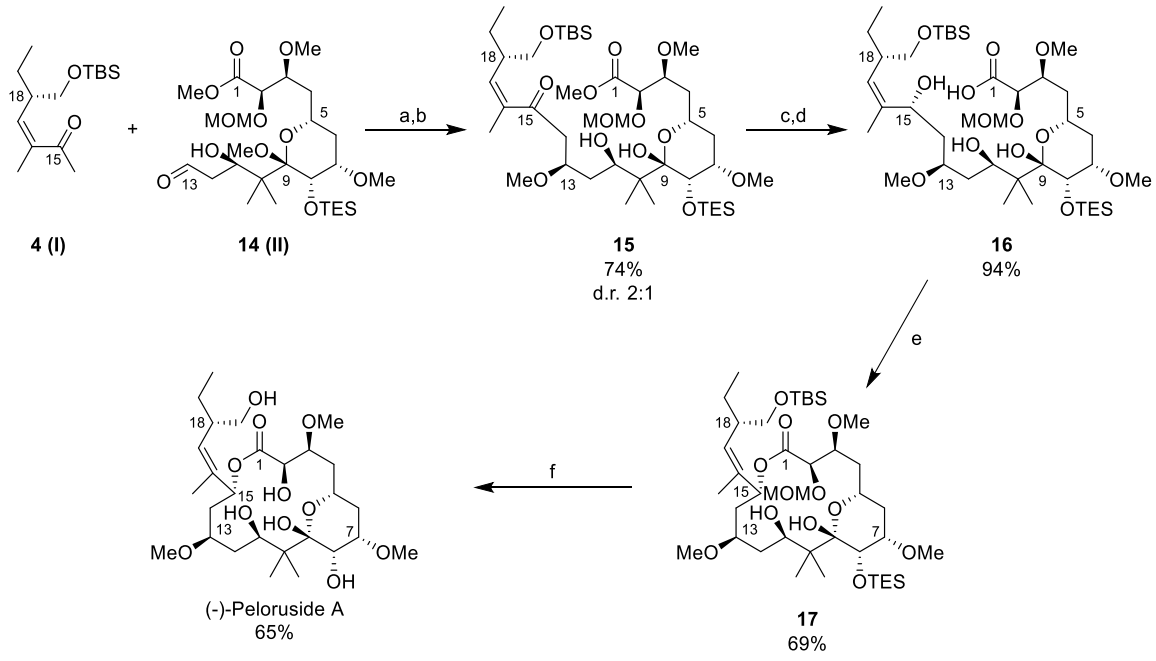
of allyldiethylborane to aldehyde **13** and the use again of osmium in an oxidative cleavage of the resulting allyl motif gave aldehyde **14** in a high yield. This represents Fragment **II** in the retrosynthesis in an overall yield of 12%.



a: TESOTf, 2,6-lutidine, DCM; b: cat. OsO_4, NMO, acetone/H_2O; c: $Pb(OAc)_4$, pyridine, DCM; d: **7**, *sec*-BuLi, THF, –78 °C, 15 min, then (+)-Ipc_2BOMe, 1 h then 1.5 h 0 °C, then **6**, –95 °C to RT, 3 h, quench 30% H_2O_2, NaOH; e: NaH, MeI, DMF; f: DDQ, DCM/H_2O; g: py·SO_3, TEA, DMSO, DCM; h: **9**, LDA, THF, –78 °C, then **8**; i: DMP, DCM, –10 °C; j: PTSA, PhMe; k: $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –30 °C; l: *m*CPBA, $NaHCO_3$, DCM/MeOH, 0 °C; m: *t*BuOK, MeI, THF, 0 °C; n: TESOTf, 2,6-lutidine, DCM; o: cat. OsO_4, NMO, acetone/H_2O; p: $Pb(OAc)_4$, pyridine, DCM; q: $NaClO_2$, NaH_2PO_4, 2-Me-but-2-ene, *t*BuOH/H_2O; r: CH_2N_2, Et_2O; s: H_2, 10 mol% Pd/C, MeOH; t: py·SO_3, TEA, DMSO, DCM; u: allylBEt_2, Et_2O, –10 °C; v: cat. OsO_4, NMO, acetone/H_2O; w: $Pb(OAc)_4$, pyridine, DCM.

*Scheme 30: De Brabander's Synthesis of Fragment **II** of (–)-Peloruside A*

With both fragments prepared the joining of the two and the completion of the synthesis was conducted (Scheme 31). Aldol reaction of the boron enolate prepared from **4** with **14** gave a low 2:1 diastereomeric ratio. Fortunately the isomers were easily separable and the major isomer was then methylated at C13 with concomitant hydrolysis of the hemiketal at C9 to give **15** in a high yield. Selective reduction of the C15 ketone furnished the stereocentre required and set up one half of the groups needed for the macrolactonisation; the other half was prepared by hydrolysis of the C1 methyl ester to give **16** in an excellent yield. Macrolactonisation was conducted under Mitsunobu conditions to give compound **17** in a 69% yield. Finally, total deprotection in acidic conditions gave (–)-Peloruside A in a total yield of 0.7–1.2% over all the steps.



a: **4**, DIPEA, Et_2BOTf, DCM, –78 °C, 15 min, then –30 °C 45 min, then **14**, –78 °C, 2 h; b: Me_3OBF_4, DTBMP, DCM; c: (*S*)-*B*-Me-CBS, $BH_3{\cdot}SMe_2$, DCM, –30 °C, 1 h, then 4 h at RT, MeOH quench; d: 0.3 M $LiOH_{aq}$, THF; e: PPh_3, DIAD, THF, RT, 15 min, then **16** over 2 h, then 1 h at 0 °C; f: 4 M HCl_{aq}. THF.

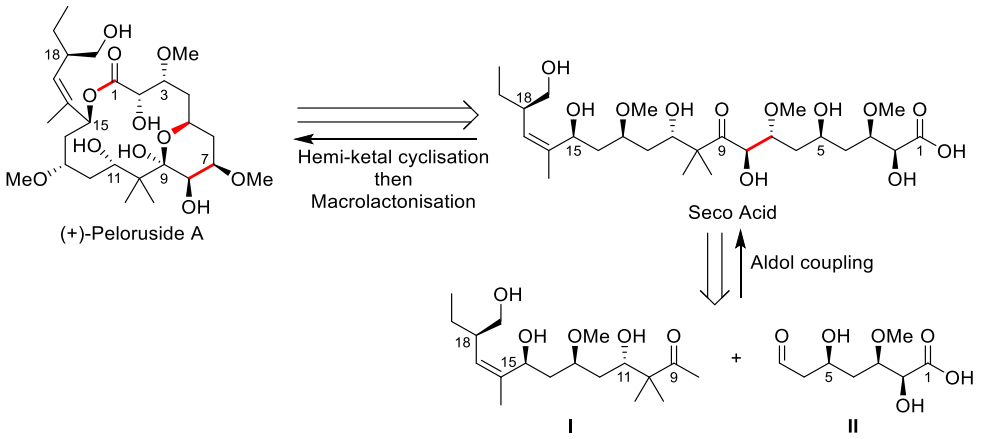
Scheme 31: Completion of the Synthesis of (–)-Peloruside A by De Brabander.

Unfortunately, whilst being the first total synthesis and being able to confirm the absolute configuration of the natural adduct, the synthesised molecule was the enantiomer and was shown to have no activity in the same cell lines as (+)-Peloruside A. With the synthetic confirmation of the structure many other groups turned their attention to the synthesis of the natural product and over the following years five total syntheses of (+)-Peloruside A were published.

Taylor's Synthesis

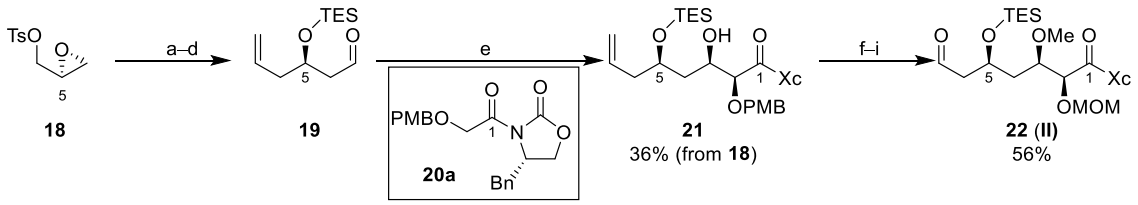
Taylor was one of the first to publish work on the synthesis of Peloruside A, which first involved a synthesis of the C8–19 fragment.[41] Later he reported the completion of the synthesis which was the first total synthesis of the correct enantiomer of the natural product.[32]

His retrosynthetic analysis started with the seco acid from Peloruside A which would be formed through a hemi-ketal cyclisation and then the macrolactonisation (Scheme 32). Unlike De Brabander, the formation of the pyran ring would be performed after the fragments were coupled; he also decided to use a Yamaguchi coupling method for the macrocyclisation instead of the Mitsonobu. Also differing from the original strategy was the elaboration of the pyran ring, which Taylor left until after the lactone formation. This route was chosen in order to minimise the use of additional protecting groups. The seco acid was then disconnected at the C7–C8 bond, which would be formed through an aldol coupling, to give Fragments **I** and **II**.



Scheme 32: Taylor's Retrosynthetic Analysis of Peloruside A to Give Two Fragments.

Taylor first published the synthesis of Fragment **I** separately. This will be discussed in more detail starting on page 55 in the section: Synthesis of Fragment C9–C19 and Related Fragments. As for the smaller Fragment **II** the synthesis was consequently shorter, starting from the chiral epoxide **18** which transformed into aldehyde **22**, in just nine steps (Scheme 33). The epoxide was first opened with the lithium anion of 1,3-dithiane, the tosylate group then displaced by vinyl magnesium bromide in the presence of copper(I) salts, and the alcohol at C5 then protected with a triethylsilyl group. Removal of the dithiane gave the deprotected aldehyde **19**, which was reacted with the boron enolate of **20a** in an aldol reaction to give **21** in a moderate yield from the starting material **18** over five steps. This compound was then methylated at the C3-oxygen, the PMB protecting group exchanged for a MOM group and finally the terminal double bond cleaved through ozonolysis to give Fragment **II** in an overall yield of 20%



a: *n*-BuLi, 1,3-dithiane, –10 °C, 2 h, then **18**, -78 °C, 4 h, then 2 h at RT; b: CuI, vinylMgBr, –50 °C to –10 °C, 1 h 40 min; c: TESCl, imidazole, DMAP, DMF, 12 h; d: MeI, $CaCO_3$, ACN/H_2O, 45 °C, 2.5 h; e: **20**, TEA, Bu_2BOTf, –50 °C 1.5 h, then **19**, –30 °C, 2.5 h; f: Me_3OBF_4, proton sponge, DCM, 15 h; g: DDQ, DCM/H_2O, 2 h 20 min; h: MOMCl, DIPEA, DCM, 15 h; i: O_3, pyridine, DCM, –78 °C, then PPh_3, RT, 4 h.

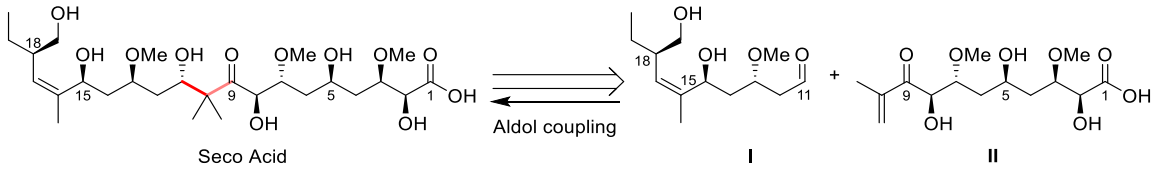
*Scheme 33: Taylor's Synthesis of Fragment **II** of his Total Synthesis of Peloruside A.*

With both Fragments In hand, Taylor finished the synthesis in an additional twelve steps with an overall yield of 0.1%. This represented the first synthesis of the natural (+)-Peloruside A with its correct configuration.

Ghosh's Synthesis

Similarly to Taylor, Ghosh first published the synthesis of fragments of Peloruside A,[42,43] before later publishing the completed total synthesis;[33] the fragments both initially and finally synthesised used a different disconnection in the carbon backbone. Unlike Taylor, the described total synthesis deviated from the published synthesis of the initial fragment with a change in the disconnection from the C9–C10 to the final C10–C11 (see Scheme 34). While this had no effect on using an aldol coupling to connect the fragments, it reversed the order of which was the nucleophile and electrophile. Again, the synthesis passed through the seco acid, but in this case the macrolactonisation was performed

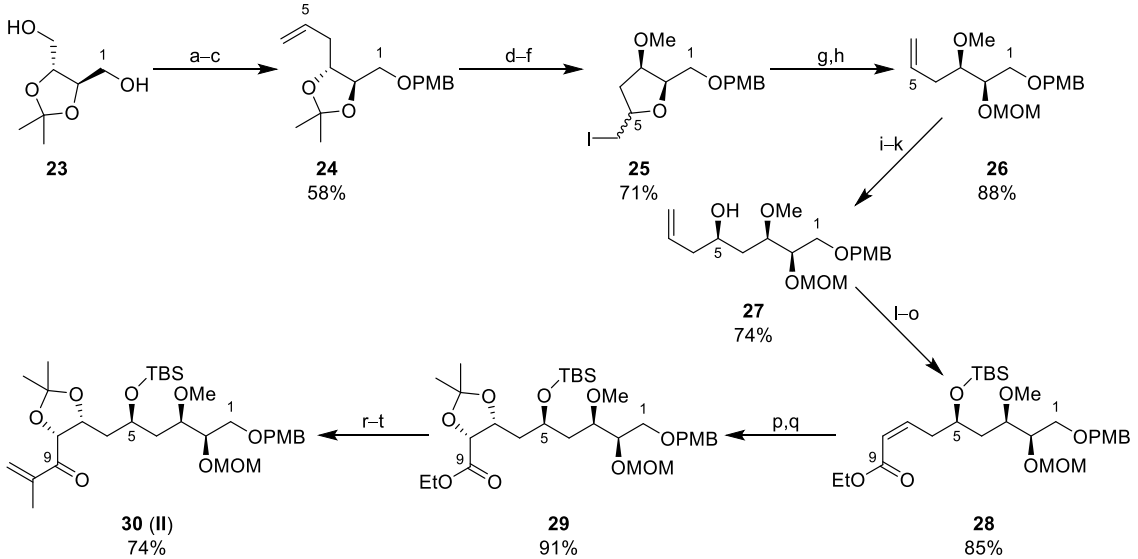
before the pyran ring was formed. The cyclisation was achieved using the Yamaguchi conditions,[44] with the pyran being formed by acid promoted hemi-ketal cyclisation.



Scheme 34: Ghosh's Retrosynthetic Analyses. Original Disconnection Shown in Pink, Final Shown in Red.

Again, the synthesis of Fragment **I** will be more closely discussed in the section Synthesis of Fragment C9–C19 and Related Fragments on page 56.

As for Fragment **II**, the synthesis starts from commercially available (–)-2,3-*O*-isopropylidene-D-threitol **23** (Scheme 35). This was transformed into the terminal alkene **24** by mono-alcohol protection, alcohol/iodine exchange and then displacement of the introduced iodine with vinylmagnesium bromide catalysed by copper (I) in a good yield. Deprotection of the 1,2-diol followed by cyclic iodoetherification produced a furan ring, and methylation of the remaining alcohol gave a high yield for compound **25**. Zinc promoted reductive cleavage of the iodoether with protection of the liberated alcohol with MOMCl gave **26** in an excellent yield. The terminal alkene was transformed to an aldehyde using a Lemieux–Johnson oxidation, followed by a Brown allylation to give compound **27** in a good yield. TBS protection of the resulting alcohol followed by another oxidative cleavage gave an aldehyde which was submitted to Ando *Z*-olefination resulting in compound **28** in an excellent yield. Sharpless asymmetric dihydroxylation with AD-mix-α, with protection of the resulting diol gave **29** in an exceptional yield. Finally, reduction of the ester and addition of the isopropenyl Grignard to the resulting aldehyde, followed by a with Dess-Martin oxidation gave the Fragment **II** equivalent **30** in an overall yield of 15%.



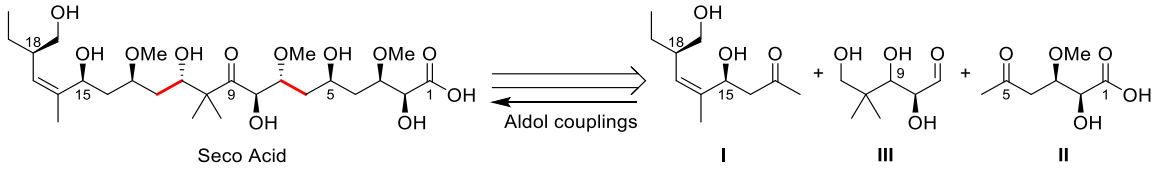
a: NaH, **22**, THF, 1 h, then PMBCl, RT, 1 h; b: PPh_3, I_2, imidazole, THF, O/N; c: HMPA, CuI, THF, –30 °C, then vinylMgBr, 2 h; d: 10% HCl_{aq}, MeOH, 12 h; e: I_2, $NaHCO_3$, ACN, 0 °C to RT, 3 h; f: Me_3OBF_4, proton sponge, O/N; g: Zn_{dust}, EtOH, 80 °C, 6 h; h: MOMCl, DIPEA, DCM, O/N; i: OsO_4, NMO, acetone/H_2O, 3 h; j: $NaIO_4$, THF/H_2O, 2 h; k: Ipc_2BOMe, allylMgBr, Et_2O, 0 °C to RT, 1 h, then crude from j, –78 °C 2 h; l: TBSCl, imidazole, DMAP, DMF, O/N; m: OsO_4, NMO, acetone/H_2O, 5 h; n: $NaIO_4$, THF/H_2O, 3 h; o: $(O\text{-cresol})_2P(=O)CH_2CO_2Et$, NaI, NaH, THF, 0 °C, then crude from n, –78 °C, 2 h; p: AD-mix-α, $MeSO_2NH_2$, ^{t}BuOH/H_2O, 0 °C 4 d; q: PPTS, 2-MeO-propene, DCM, 30 min; r: DIBAL-H, DCM, –78 °C, 1 h; s: isopropenylMgBr, THF, 0 °C, 15 min; t: DMP, $NaHCO_3$, DCM, 30 min.

*Scheme 35: Ghosh's Synthesis of Fragment **II** of Peloruside A.*

With the fragments synthesised, Ghosh needed a further nine steps to complete the synthesis of (+)-Peloruside A. Among these were the aldol reaction used to join the two fragments and the lactonisation. The overall yield for the synthesis was 0.6%.

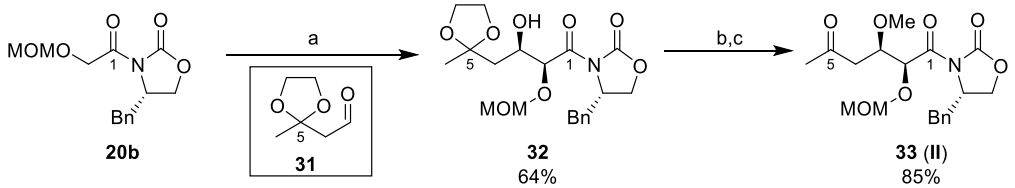
Evans's Aldol Based Synthesis

Evans followed a more convergent synthesis based on his hallmark aldol reactions.[34] Indeed, the work was highlighted by Floreancig due to the innovation of the longest linear sequence being only 22 steps, compared to 29 for De Brabander and Taylor and 30 for Ghosh.[37] The disconnections from the seco acid were chosen to be the C6–C7 and C11–C12 to give the left hand Fragment **I**, right hand Fragment **II** and finally the central Fragment **III** (Scheme 36).



Scheme 36: Evans's Retrosynthetic Analysis of Peloruside A.

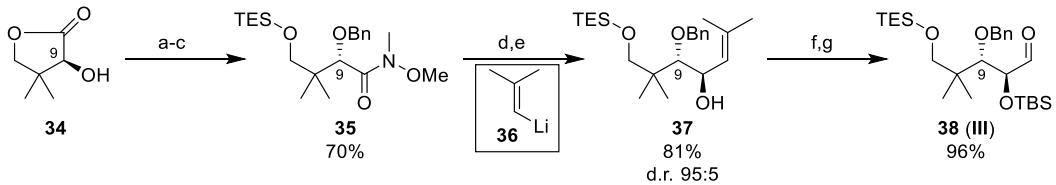
The synthesis of Fragment **I** is described in the section Synthesis of Fragment C9–C19 and Related Fragments on page 58 with an overall yield of 26%. The synthesis of the carboxylate terminus (Fragment **II**) started with a boron mediated aldol reaction of protected glycolic analogue **20b** with **31** which gave aldol adduct **32** in a good yield and complete stereocontrol (Scheme 37). Careful methylation of this sensitive adduct, followed by acidic deprotection of the masked ketone at C5 gave Fragment **II** in an overall yield of 54%.



a: **20b**, Bu_2BOTf, TEA, DCM, Ar, –30 °C to –78 °C then 0 °C, 3 h + 30 min, then **31**, –70 °C, O/N; b: Me_3OBF_4, proton sponge, DCM, Ar, dark, 1 d; c: PPTS, acetone/H_2O, 8.5 h.

*Scheme 37: Evans's Synthesis of Fragment **II**.*

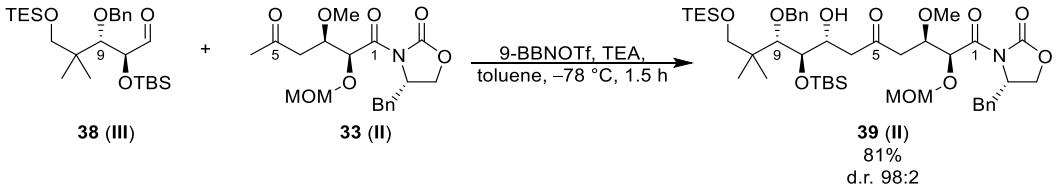
The synthesis of the central Fragment **III** started from the pantolactone **34** derived from vitamin B_5 (Scheme 38). Benzyl protection of the alcohol, opening the lactone to give the Weinreb amide, and protection of the resulting alcohol gave **35** in a high yield. Addition of vinyl lithium **36** to amide **35** and stereoselective zinc borohydride reduction gave alcohol **37** in an excellent yield and selectivity. Finally, protection of the alcohol and ozonolysis gave Fragment **III** in an overall yield of 54%.



a: $BnOC(NH)CCl_3$, TfOH, DCM/hexanes, 3 h; b: MeO(Me)NH·HCl, $AlMe_3$, DCM, Ar, 1 h, then product from a, 0 °C, 1.75 h; c: TESCl, TEA, DMAP, DCM, 12h; d: **36**, Et_2O, 0 °C, 15 min; e: $Zn(BH_4)_2$, Et_2O, Ar, –20 °C to RT, 14 h + 5 h; f: TBSCl, TEA, DMAP, DMF, 1 d; g: O_3, PPh_3, –78 °C to RT.

*Scheme 38: Evans's Synthesis of the Central Fragment **III** of Peloruside A.*

The C6–C7 bond was then formed through a boron mediated aldol reaction between Fragments **II** and **III** (Scheme 39). Using the large BBN triflate as the Lewis acid **39** was obtained in an excellent yield and exceptional diastereoselectivity. This result is more impressive considering the difficult nature of acetate aldol reactions.[45]



*Scheme 39: Joining of Fragments **II** and **III** in Evans' Synthesis.*

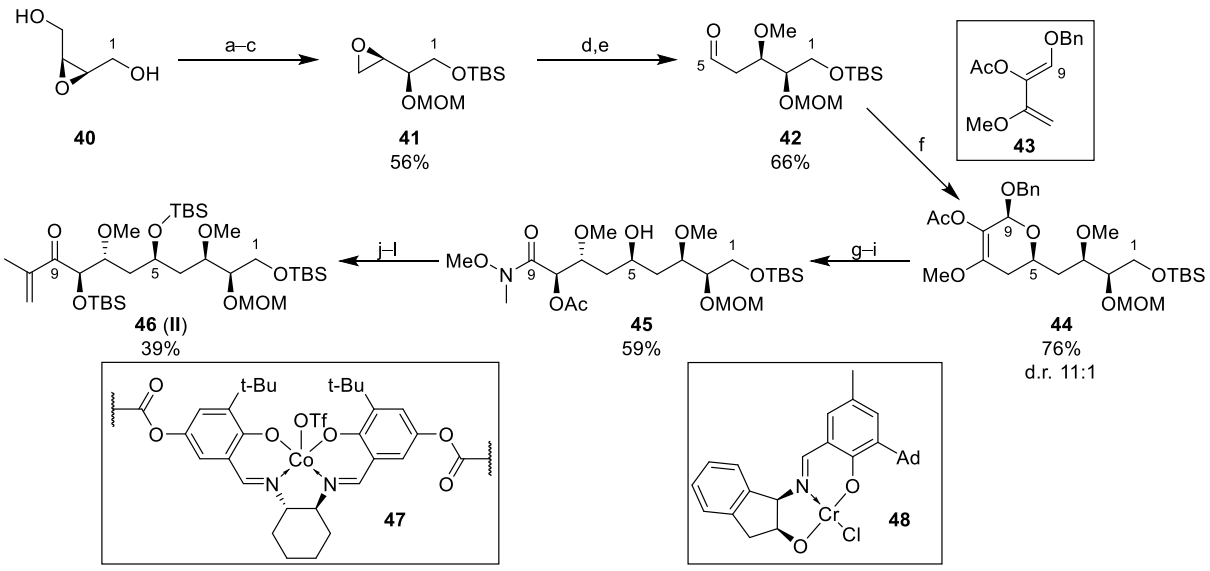
Five further steps: reduction, protection, methylation, deprotection and finally an oxidation then prepare the **II**–**III** joined fragment to be coupled to the **I** fragment to form the C11–C12 bond, again through a boron mediated aldol reaction. Finally, the synthesis of (+)-Peloruside A was completed with eight additional steps including the Yamaguchi macrocyclisation and formation of the pyran ring in an overall yield of 0.8%.

Jacobsen's Synthesis

The synthesis of Peloruside A reported by Jacobsen adapted the same retrosynthetic analysis as Ghosh's final route with a disconnection at the C10–C11 bond (see Scheme 34 on Page 51), but the syntheses of the fragments differ somewhat.[35] Once the two fragments are achieved the formation of the seco acid and completion of the synthesis are somewhat analogous to that of Ghosh.[33]

Again the synthesis of Fragment **I** by Jacobsen will be discussed in the section: Synthesis of Fragment C9–C19 and Related Fragments on page 57.

The synthesis of Fragment **II** started from the achiral epoxide **40** (Scheme 40). This was then subjected to an enantioselective Payne rearrangement with polymeric cobalt-salen catalyst **47**,[46,47] and the two free alcohols orthogonally protected to give **41** in a moderate yield. The terminal epoxide was then opened using a vinyl cuprate reagent, directly methylating the resulting alcohol and cleaving the double bond through ozonolysis to give aldehyde **42** in a good yield. This aldehyde was then reacted with diene **43** in a hetero-Diels-Alder reaction catalysed by Jacobsen catalyst **48**,[48,49] to give **44** in a high yield and diastereoselectivity. Face selective reduction of the double bond with concomitant removal of the benzyl protecting group, followed by oxidation of the lactol and opening of the resulting lactone gave the Weinreb amide **45** in a moderate yield. TBS protection of the C5 alcohol was then followed by the nucleophilic substitution of the Weinreb amide by the isopropenyl Grignard reagent to give an α,β-unsaturated ketone, which due to deprotection of the C8 alcohol required protection to give compound **46** as Fragment **II** in an overall yield of 6%.



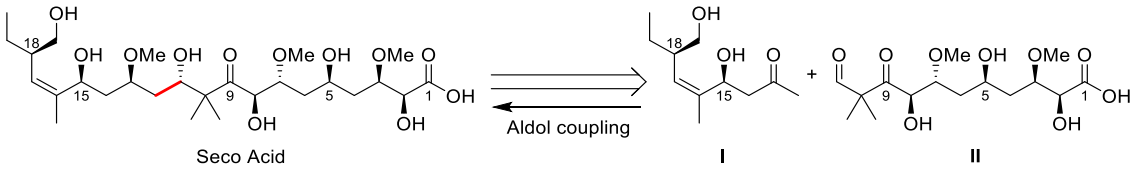
a: (*S,S*)Co-salen catalyst **47**, ACN, RT, 14 h, b: TBSCl, TEA, DMAP, DCM, –20 °C, 3 h; c: MOMCl, DIPEA, toluene, 16 h; d: vinylMgBr, CuBr, THF, dark, –40 °C, 2 h, then HMPA, Me_2SO_4, RT, 2 d; e: O_3, PPh_3, DCM, –78 °C to RT, 3 h; f: **43**, catalyst **48**, molecular sieves, MTBE, RT, 48 h; g: H_2/Pd/C (200psi), ^{i}PrOH, pH 7 buffer, 18 h; h: NaOCl, KBr, TEMPO, NaCl, pH 7 buffer, DCM, 1.5 h; i: MeO(Me)NH·HCl, $AlMe_3$, toluene, –10 °C, 1.5 h; j: TBSOTf, 2,6-lutidine, DCM, –78 °C, 2 h; k: IsopropenylMgBr, THF, 4 h; l: TBSOTf, 2,6-lutidine, DCM, –10 °C, 4 h.

*Scheme 40: Jacobsen's Synthesis of Fragment **II** of Peloruside A.*

Fragments I and **II** were then coupled through a reductive aldol reaction as in the synthesis of Ghosh. Seven further steps were required to finish the synthesis including the Yamaguchi macrocyclisation, hemi ketal cyclisation and protection/deprotection steps to give (+)-Peloruside A with an overall yield of 0.06% in thirty steps.

Hoye's Synthesis

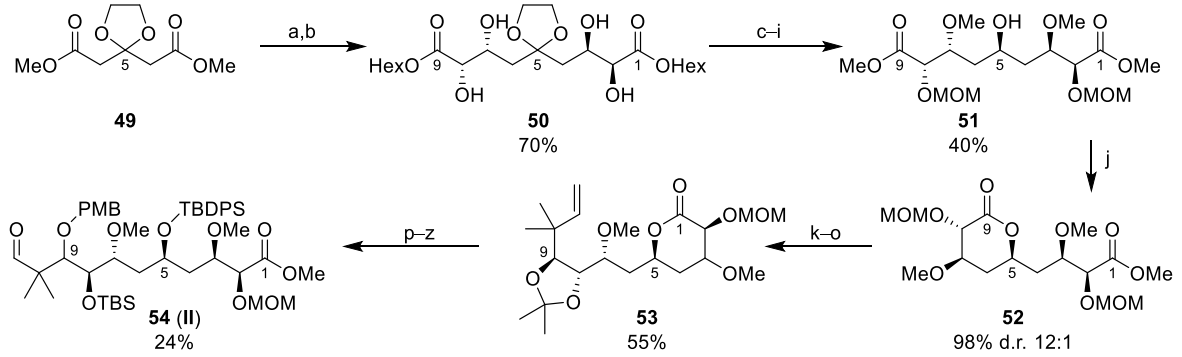
Hoye's retrosynthesis opted to disconnect the C11–C12 of the seco acid, similarly to Evans; however, his strategy hinged on a two-fragment disconnection not three as Evans used (Scheme 41).[36] Again, an aldol reaction was chosen to unite the fragments and a Yamaguchi macrocyclisation to form the lactone. The strategy by Hoye for the synthesis of the two Fragments Is highly differing from the previous routes; while Fragment **I** is discussed later on page 59, a summary of the synthesis of Fragment **II** is shown below in Scheme 42. Interestingly it is the first total synthesis of Peloruside A where one of the fragments arises from the de-symmetrisation of an achiral starting material.



Scheme 41: Hoye's Retrosynthetic Analysis of Peloruside A.

Starting from the achiral diester **49**, DIBAL reduction and subsequent double Horner-Wadsworth-Emmons reaction of the resulting dialdehyde, followed by a double Sharpless dihydroxylation, to introduce the C2–C3/C7–C8 diols, afforded **50** in a high yield. This was followed by a ketal metathesis promoted by iodic acid and methylation of the resulting spirocyclic ketal alcohols. The resulting ketal was then transformed by transketalization to a thioketal analogue of **50**, final protection of the C2 and C8 alcohols, deprotection and reduction of the C5 ketone and an Otera ester exchange gave **51** in a low yield. De-symmetrisation was achieved by tetramethylguanidine catalysed lactonization to give **52** in an exceptional yield and excellent selectivity (d.r. 12:1). Reduction of the lactone and opening of

the lactol with an allyl-indium reagent introduced the C11 geminal dimethyl group and re-lactonised to the C1 carbonyl; deprotection and protections steps then led to **53** in a moderate yield. Finally, a complex sequence of lactone opening, protecting group manipulation, redox reactions and ozonolysis gave **54** in an overall yield of 4%.



a: DIBAL-H, Et_2O, –78 °C; then $(EtO)_2P(O)CH(Na)CO_2Hex$, –78 °C to RT, 2 h; b: OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $^tBuOH/H_2O$, 3 d; c: HI, THF, 3 h; d: Me_3OBF_4, proton sponge, 18 h; e: 1,2-Ethanedithiol, $BF_3{\cdot}OEt_2$, 3.5 h; f: MOMCl, DIPEA, DCM; g: I_2, $NaHCO_3$, acetone/H_2O, 3 h; h: $(ClBu_2SnOSnBu_2OH)_2$, MeOH, toluene, 90 °C, 3 d; i: H_2 (50psi), Raney nickel, EtOH; j: TMG, benzene, 1 d, then TFA, 5 min; k: L-Selectride, THF, –78 °C, 1h; l: 1-Br-3-Me-but-2-ene, In_{powder}, DMF, 55 °C, 18 h; m: $AlCl_3$, NaI, ACN/DCM, 8 min; n: (*p*-MeO)-$C_6H_4CH(OMe)_2$, CSA, molecular sieve, DCM, 9 min; o: MOMCl, DIPEA, DCM; p: $LiAlH_4$, THF, 1 h; q: TBDPSCl, imidazole, DMAP, DMF, 1 d; r: DIBAL-H, DCM, –78 °C, 2 d; s: DMP, $NaHCO_3$, DCM, 18 h; t: $Zn(BH_4)_2$, DCM, 50 min; u: TBSOTf, 2,6-lutidine, DCM, 2 h; v: HF·pyridine, THF, pyridine, 6 h; w: DMP, $NaHCO_3$, DCM; x: $Me_2C{=}CHMe$, $NaClO_2$, NaH_2PO_4, $^tBuOH/H_2O$, 1 h; y: CH_2N_2, DCM; z: O_3, pyridine, DMSO, DCM/MeOH, –78 °C.

*Scheme 42: Hoye's Synthesis of Fragment **II** of (+)-Peloruside A.*

The completion of the synthesis was achieved through an aldol coupling of the two fragments followed by nine additional steps, including the macrolactonisation, with an overall yield of 0.02%.

Synthesis of Fragment C9–C19 and Related Fragments

Our synthetic target was the C9–C19 fragment arising from the disconnection of the C8–C9 bond of the seco acid of Peloruside A, in a two fragment strategy (Figure 14). Apart from the total syntheses,[28,32–37] various partial syntheses,[50–52] or synthesis of fragments of Peloruside A have been reported over the years.[41–43,51,53–56] The synthesis of fragments related to the synthesis of Fragment **I** which contains the C15 oxygen from the lactone of Peloruside A, especially those with disconnections around the C8–C9 bond were of particular interest to us.[33,35,36,41,43,54–56]

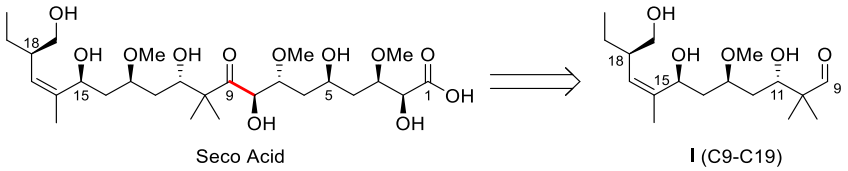
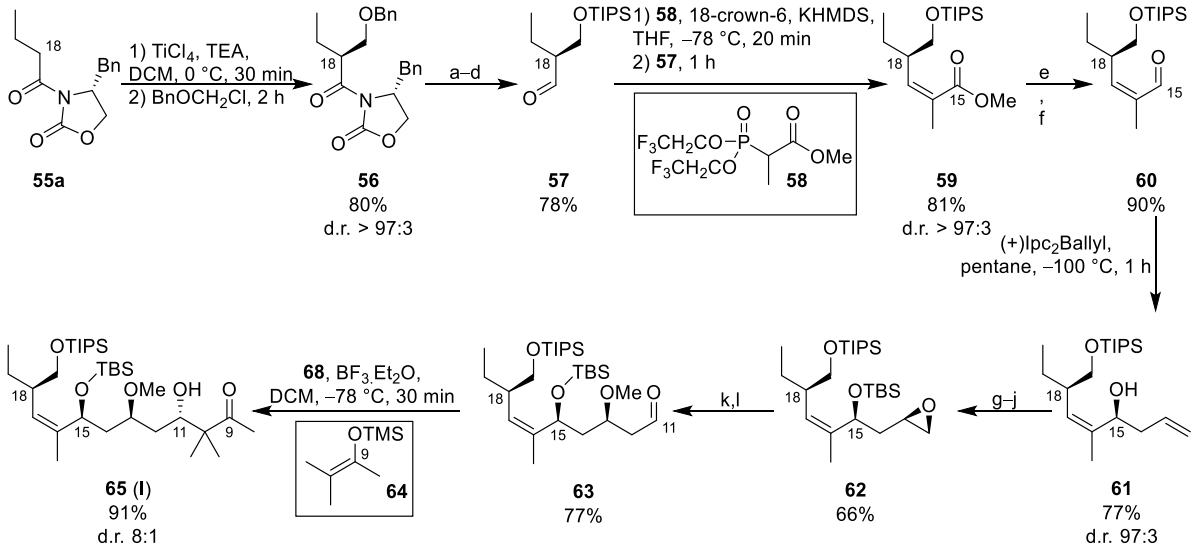


*Figure 14: Retrosynthetic Analysis to Give Fragment **I** as C9–C19.*

Taylor's Synthesis of Fragment C8–C19

As mentioned already, Taylor was the first to synthesise the natural enantiomer of (+)-Peloruside A. His disconnection strategy at the C7–C8 of the seco acid is similar to ours with the adjacent disconnection leaving a fragment one carbon longer than our chosen target molecule.[32,41] Therefore his construction of Fragment **I** was an important consideration in planning our strategy. This route is summarised in Scheme 43 with the key steps highlighted.



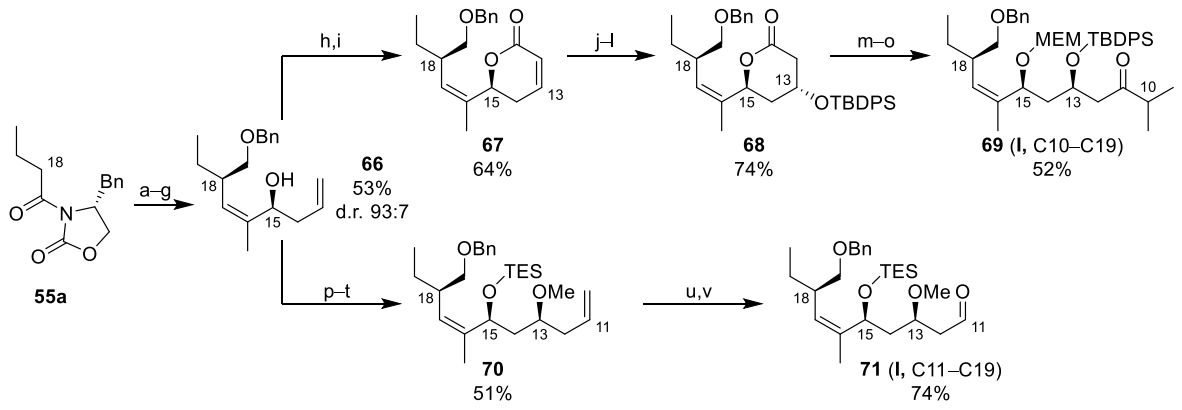
a: H_2 (atm), Pd/C, EtOH, 3 d; b: TIPSCl, TEA, DMAP, DCM, 5 h; c: $LiBH_4$, Et_2O/THF/H_2O, 5 h; d: DMP, pyridine, DCM, 1 h; e: DIBAL-H, DCM, –78 °C; f: DMP, pyridine, DCM, 1h; g: *n*-BuLi, Boc-ON, Et_2O/THF, –78 °C to 0 °C, 30 min + 4 h; h: NIS, ACN, –40 °C to 0 °C, 12 h; i: K_2CO_3, MeOH; j: TBSCl, imidazole, DMAP, DMF, 12 h; k: 1,3-dithiane, *n*-BuLi, THF, –40 °C to –10 °C, 2 h, then **66**, –40 °C to 0 °C, 1.5 h, then HMPA, Me_2SO_4, –40 °C to 0 °C, 1 h; l: MeI, Na_2CO_3, ACN/H_2O, reflux, 1.5 h.

Scheme 43: Taylor's Synthesis of Fragment C8–C19.

The first step is the alkylation of the titanium enolate of chiral acylated oxazolidinone **55a** (Scheme 43). This furnished the protected alcohol **56** in an excellent yield with the configuration at the C18 completely controlled by the chiral auxiliary. This was then deprotected by hydrogenation and re-protected. This approach was previously described by Fukumoto,[57] and later Evans adopted it in his synthesis of Peloruside A.[34] The auxiliary was then removed in reductive conditions and oxidised by Dess-Martin periodinane to give the aldehyde **57**. This was then prepared for the next key step: a Still-Gennari olefinic coupling reaction using phosphonate **58**,[58] which gave an excellent yield of exclusively *Z*-alkene **59** from the crude of the oxidation step. The terminal ester group introduced was then reduced to the alcohol and oxidised to the aldehyde once again with the Dess-Martin procedure to furnish **60**. This was then reacted in an asymmetric Brown allylation to introduce the C15 stereocentre in a high yield of product **61**. A series of six transformations were then required to furnish the starting material for the last key transformation. After protection an iodine induced cyclization developed by Bartlett and Amos Smith was used to induce the C13 configuration.[59,60] The opening and protection of the cyclic carbonate led to the epoxide **62** in a good yield. This epoxide was then opened by the anion of 1,3-dithiane with *in-situ* methylation of the C13 alcohol, and then the masked aldehyde reformed by hydrolysis of the dithiane gave **63** in a high yield. Finally, a BF_3 mediated Mukaiyama aldol reaction gave compound **65** as an analogue of Fragment **I** in an excellent yield and a diasteroeselectivity of 8:1.[61] The overall yield for Taylor's synthesis of Fragment **I** was 16% over sixteen steps.

Ghosh's syntheses of Fragments C10–C19 and C11–C19

Ghosh prepared two differing molecules for Fragment **I**; initially he synthesised the C10–C19 fragment,[43] but in his final synthetic route he used the C11–C19 fragment.[33] The two fragments are slightly smaller than our proposed fragment (1 and 2 carbons shorter) and both proceed through the same intermediate (**66**). In fact this intermediate is synthesised in much the same way as Taylor describes in Scheme 43 and Evans in Scheme 46 on page 58 from **55a**: with the alkylation of the *N*-acyl oxazolidinone, removal and redox formation of the aldehyde, olefination and then the redox formation of an aldehyde which is used in a Brown allylation (reactions a–g, Scheme 44). The main differences are the maintenance of the benzyl alcohol and the use of the Ando modification of the Horner-Wadsworth-Emmons over the Still-Gennari.[62]



a: $TiCl_4$ TEA, DCM, 0 °C, then $BnOCH_2Cl$, 1.5 h; b: $LiBH_4$, MeOH/THF, 1 h; c: $(COCl)_2$, DMSO, TEA, DCM, –60 °C, 45 min; d: $(O\text{-cresol})_2P{=}O(Me)CHCO_2Et$, NaH, THF, –78 °C to –20 °C, 2 h; e: DIBAL-H, DCM, –78 °C to –40 °C, 1 h; f: DMP, $NaHCO_3$, DCM, 1.5 h; g: (+)-$Ipc_2Ballyl$, Et_2O, –80 °C, 3 h; h: $CH_2{=}CHCOCl$, TEA, DCM, 2 h; i: Grubbs 1st gen, DCM, 40 °C, 12 h; j: H_2O_2, 6 M $NaOH_{aq}$, MeOH, 1.5 h; k: $NaBH_4$, $(PhSe)_2$, AcOH, $^{i}PrOH$, 30 min; l: TBDPSCl, imidazole, DMAP, DMF, 13 h; m: $AlMe_3$, MeO(Me)NH·HCl, DCM, 2.5 h; n: MEMCl, DIPEA, 9 h; o: $^{i}PrMgCl$, THF, 5 h; p: TESOTf, lutidine, DCM, 5 min; q: OsO_4, NMO, $^{t}BuOH$/acetone/H_2O, 0 °C, 2 h; r: $Pb(OAc)_4$, pyridine, DCM, RT, 30 min; s: (+)-Ipc_2allyl, Et_2O, –78 °C, 2 h; t: Me_3OBF_4, proton sponge, RT, 3 h; u: OsO_4, NMO, $^{t}BuOH$/acetone/H_2O, 0 °C, 2 h; v: $Pb(OAc)_4$, pyridine, DCM, RT, 30 min.

Scheme 44: Ghosh's Synthesis of Fragments C10–C19 and C11–C19.

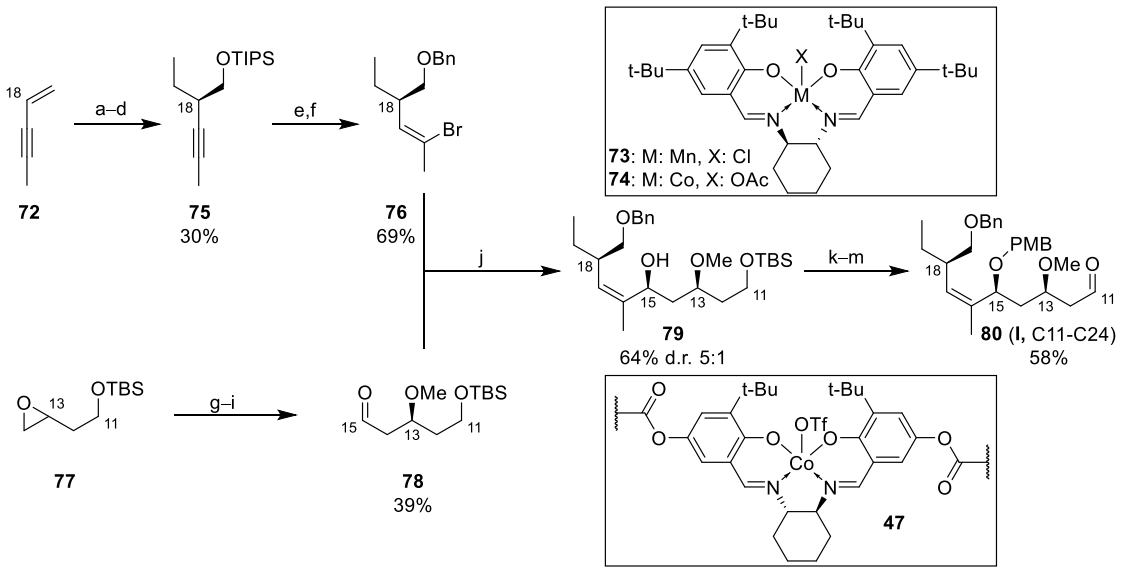
From the intermediate **66** the two syntheses diverge (Scheme 44). For the C10–C19 fragment the synthesis continues with the acylation of the C15 alcohol to give a molecule with two terminal double bonds, which are then joined in a ring closing metathesis reaction with Grubbs first generation catalyst to give **67** in a good yield. Face selective epoxidation followed by its reductive opening and protection of the resulting alcohol gave **68** in a high yield and set the C13 stereochemistry; the lactone was then opened to form the Weinreb amide, the alcohol protected and the amide displaced with the isopropyl Grignard to give **69** in an overall yield of 13% over fifteen steps.

Fragment C11–C19 was prepared from intermediate **66** by protection of the C15 alcohol, oxidative cleavage of the double bond with OsO_4/$Pb((OAc)_4$ and an asymmetric Brown allylation to give **70** in a moderate yield. Finally another oxidative cleavage with OsO4/$Pb(OAc)_4$ gave **71** in an overall yield of 20% over fourteen steps.

Jacobsen's Synthesis of Fragment C11–C19

Jacobsen made the same strategy as Ghosh in his final route disconnecting the C10–C11 bond and making the C11–C19 fragment.[35] His strategy was completely different to the previous syntheses of Fragment **I**; interestingly he took a more convergent route to other syntheses, combining two smaller elaborated fragments (Scheme 45).

The synthesis of **76** started from enyne **72**. This was first epoxidized using a manganese salen catalyst **73**,[63,64] and then a hydrolytic kinetic resolution to increase the enantiomeric excess using the cobalt salen catalyst **74**.[65] The enriched epoxide was then opened using ethylmagnesium bromide and the resulting alcohol protected giving **75** in a low overall yield. The triple bond was then submitted to a one-pot hydroboration/bromination/elimination/deprotection sequence, which after an alcohol protection gave **76** in a good yield. In turn, racemic epoxide **77** was transformed into aldehyde **78** through another hydrolytic kinetic resolution, this time using the polymeric cobalt salen complex **47** to fix the C13 configuration. The epoxide was then opened using vinyl cuprate, methylation of the C13 alcohol and finally ozonolysis gave **78** in a low yield.



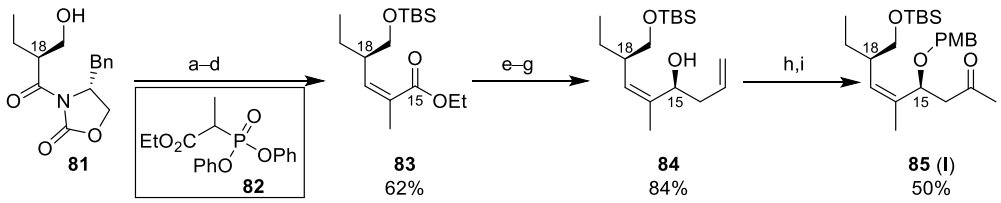
a: **73**, NaOCl, DCM, 0 °C, 6.5 h, b: **74**, H_2O, Et_2O, 0 °C to RT, 24 h; c: EtMgCl, THF, –78 °C to RT, 4 h; d: TIPSCl, imidazole, DMF, 16 h; e: Catecholborane, 40 °C to 50 °C, 48 h, then Br_2, DCM, –78 °C, 10 min, then TBAF, THF, 40 °C, 2.5 h; f: BnO-1-methylpyridinium-OTf, MgO, CF_3Ph, 83 °C, 24 h; g: **47**, ACN/H_2O, RT, 30 h; h: CuBr, vinylMgBr, –40 °C, 2 h; then HMPA, Me_2SO_4, 2 d; i: O_3, DCM, –78 °C, then PPh_3, RT, 3 h; j: **76** *sec*-BuLi, THF/Et_2O, –78 °C, then **78**, –78 °C to RT, 16 h; k: PMBBr, NaH, DMF, 2 h; l: AcOH, H_2O, THF, 16 h; m: DMP, DCM, 4 h.

Scheme 45: Jacobsen's Synthesis of Fragment C11–C19.

With the advanced intermediates **76** and **78** prepared, the two were combined using the vinyl lithium adduct of **76** to attack the aldehyde **78** giving alcohol **79** in a good yield and diastereoselectivity. Protection of the C15 alcohol and deprotection of the terminal alcohol followed by Dess-Martin oxidation led to **80** in an overall yield of 3% over 13 steps.[35]

Evans's Synthesis of Fragment C12–C19

Evans's three fragment strategy meant the Fragment **I** was smaller than many using the two-fragment synthesis strategy.[34] His disconnection at the C11–C12 gave the fragment C12–C19. The synthesis of this fragment started from the compound **81** previously described by Fukumoto (Scheme 46).[57] First the alcohol was protected as a silyl ether, then the auxiliary was removed in reductive conditions to leave an alcohol which was then oxidised to the aldehyde and used in an Ando olefination reaction with phosphonate **82** to give **83** in a good yield. The ester was then transformed to an aldehyde using a reduction/allylic oxidation with DIBAL-H/manganese oxide, followed by allylic allylboration to give alcohol **84** in an excellent yield. Finally, protection of the alcohol and a modified Tsuji-Wacker oxidation gave **85** as Fragment **I** with an overall yield of 26%.



a: TBSCl, imidazole, DMF; b: $LiBH_4$, H_2O, Et_2O, 2 h; c: $(COCl)_2$, DMSO, TEA, DCM, –78 °C, 1 h; d: **82**, NaH, THF, 0 °C, 1.5 h, then product from c, –78 °C to 0 °C, 3 h; e: DIBAL-H, DCM, –78 °C, 10 min; f: MnO_2, DCM, 30 min; g: (+)Ipc_2Ballyl, Et_2O, –78 °C, 3 h; h: NaH, THF, 0 °C, 1.5 h, then PMBBr, DMF, RT, O/N; i: O_2, $PdCl_2$, $[Cu(OAc)_2(H_2O)]$, DMF/H_2O, RT, O/N.

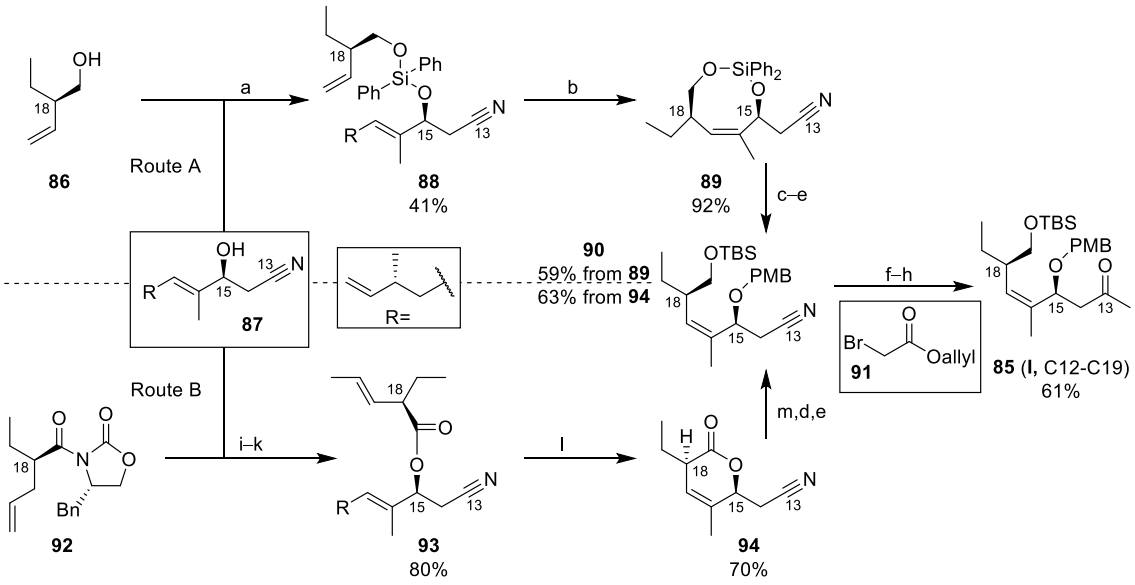
Scheme 46: Evans's Synthesis of Fragment C12–C19.

This route only required nine steps and gave a high overall yield to a fragment a few carbons smaller than our proposed fragment.

Hoye's Synthesis of Fragment C12–C19

Hoye used a disconnection at the C11–C12 position meaning his Fragment **I** was slightly smaller than the other synthetic routes (and even studied the smaller C13–C19 fragment as a possibility),[36] but it is the same as one of the three fragments used by Evans in his convergent approach.[34] Two parallel routes to the synthesis of fragment were investigated starting from alcohol **86** or acylated oxazolidine **92**, with both routes converging through intermediate **90** (Scheme 47).

Route A starts from alcohol **86**, containing the C18 stereocentre, which is reacted with (*R*)-citronellene derived alcohol **87**, containing the C15 stereocentre, and diphenylsilylchloride to form the silicon bridged diol **88** in a low yield. This was then submitted to Relay Ring Closing Metathesis (RRCM),[66] using Grubbs second generation catalyst, to form the 8-membered cyclic silicone diol **89** in an exceptional yield. The diol was then deprotected and selectively protected to reach the intermediate **90** in a moderate yield. A modified one-pot Blaise reaction with **91** and subsequent hydrolysis at pH 3 gave a β-keto ester which upon decarboxylation with a palladium catalyst gave **85** (same fragment as Evans),[34] in an overall yield of 14% over eight steps.



a: Ph_2SiCl_2, pyridine, DCM, O/N, then **87**, pyridine, O/N; b: Grubbs 2nd gen, toluene, 65 °C, 2 d; c: TBAF, THF; d: TBSCl, TEA, DMAP, DCM, O/N, then PMBO(HN=)$CCCl_3$, CSA, DCM, 1 d; f: Zn_{dust}, $TiCl_2Cp_2$, **91**, 60 °C, 5 h; g: pH 3 buffer, $^{i}PrOH/THF/H_2O$, 22 h; h: $Pd(PPh_3)_4$, DIPEA, HCOOH, THF, RT, 12 h; i: $RhCl_3{\cdot}3H_2O$, $EtOH/H_2O$, 80 °C, 7.5 h; j: LiOH, H_2O_2, THF/H_2O, 14 h; k: **87**, DCC, DMAP, DCM, 17h; l: Grubbs 2nd gen, DCM, 45 °C, 25 h +12 h; m: $NaBH_4$, AcOH, EtOH, 1 h.

Scheme 47: Hoye's Syntheses of Fragment C12–C19.

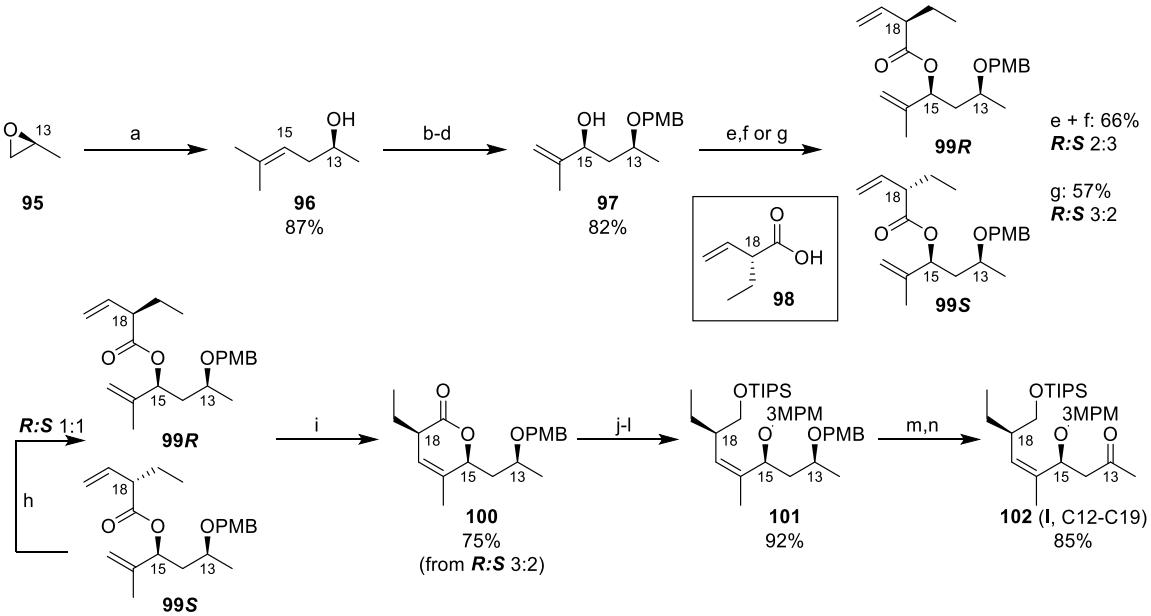
Route B starts from compound **92** previously described by Evans.[67] This was submitted to alkene isomerisation using rhodium chloride to give the more stable internal alkene. The chiral auxiliary was then removed to leave the carboxylic acid which was coupled to alcohol **87** using a DCC promoted esterification to give ester **93** in an excellent yield. RRCM was then again used with Grubbs second generation catalyst to form the six-membered lactone **94** in a high yield.[66] The lactone was opened in reductive conditions to give the same diol arising from the desilyation of **89**, it was then protected in the same way to give **90** in a good yield. The completion of route B is thus analogous with route A and gave an overall yield of 22% over ten steps, so although route B is slightly longer it gave a higher overall yield than route A.

Ermolenko's Synthesis of Fragment C12-C19

The ring closing metathesis of esters was also used in the synthesis of the same fragment previously reported by Ermolenko.[54] However his route to the ester, the ester itself and the completion of the

fragment varied somewhat. He also used standard ring closing metathesis as opposed to the relay adaption used by Hoye. Unfortunately, problems with the selectivity in forming the ester used to form the lactone could not be overcome by kinetic resolution or offset by the substrate discrimination in the ring closing metathesis.

The synthesis started from the chiral epoxide **95** which was opened using isopropenyl magnesium bromide and copper iodide to give the alcohol **96** in an excellent yield (Scheme 48). The double bond was then selectively epoxidised using a vanadium complex with the alcohol as a directing group, the alcohol was then protected, and the epoxide was submitted to base-promoted isomerisation to give the allylic alcohol **97** in an excellent yield. The synthesis then continued in one of two methods: either the reaction of the alcohol with crotonyl chloride and then alkylation of the α-position (e,f) or the ester coupling with **98** using a coupling agent (g). The acid **98** was synthesised in a five-step process in a 30% yield (see paper for synthetic route). The two methods both lead to mixtures of **99*R***/**99*S***. Using the two-step method gave a higher yield but a lower selectivity to the desired *R* product, whereas coupling with **98** gave a lower yield but with a better ratio (the loss in stereo-purity is due to racemisation). It was also found the ratio could be equilibrated to 1:1 using a base (h). The mixture was then subjected to ring closing metathesis to form the lactone **100**. The product arises from the reaction of **99*R*** with the corresponding reaction of **99*S*** being almost inexistent, in fact its isomerisation to **99*R*** was faster, allowing for a slow dynamic kinetic resolution. Therefore, using higher ratios of **99*R*** the yield was able to increase further (75% from 66% **99*R***), furthermore the remaining **99*S*** recovered was enantiopure and can be racemised (h) and used again in the metathesis to increase the yield further. The lactone was then opened and the alcohols selectivity and orthogonally protected to give **101** in an exceptional yield. finally, The C13 was deprotected and oxidised (to fit with an aldol coupling strategy to the other potential fragment), giving **102** as Fragment **I** in an excellent yield.



a: Me_2C=CHMgBr, CuI, THF, −35 °C, 2 h; b: 2 mol% $VO(acac)_2$, t-BuOOH, DCM, −25 °C, 3 d; c: PMBCl, NaH, TBAI, THF, 1 d; d: iPrNMgBr, reflux, 2 h; e: MeCH=CHCOCl, TEA, 1 h; f: LDA, EtI, HMPA, THF, −78 °C, 20 min; g: **98**, DCC, DMAP, DCM, 5 h; h: LDA, THF, −78 °C, 10 min; i: Grubbs 2nd gen, DCM, reflux, 3 d; j: $LiAlH_4$, THF, −78 °C to RT, 1 h; k: TIPSCl, pyridine, 55 °C, 3 d; l: 3-MPMCl, NaH, imidazole, TBAI, THF, reflux, 1.5 h; m: DDQ, DCM/H_2O, 1 h; n: TPAP, NMO, 4Å MS, DCM, 2.5 h.

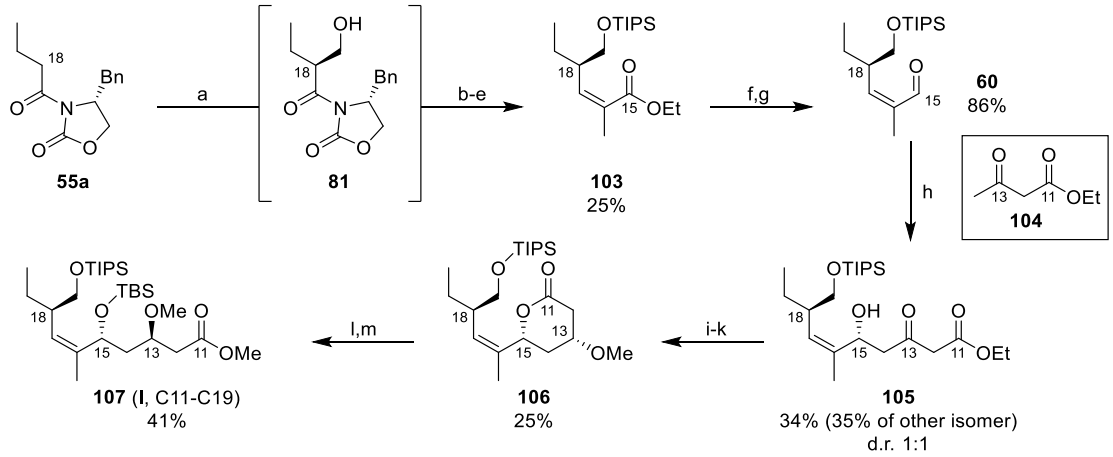
Scheme 48: Ermolenko's Synthesis of Fragment C12-C19.

Ermolenko's synthesis consisted of a minimum total of eleven steps and a maximum yield of 24% (sixteen steps and 13% yield taking into account the synthesis of **98**), although the yield can be increased through racemisation of the recovered **99** and its reuse in the metathesis.

Zhou's Synthesis of Fragment C11-C19

Zhou also published a synthesis of Fragment **I**, namely the C11-C19 fragment, however one of the stereocentres (the C15) appears to have the wrong stereochemistry required for the natural product.[55] Notwithstanding, the synthesis is useful as it highlights a slightly different strategy.

The synthesis starts from the acylated oxazolidine **55a** (Scheme 49), used by Ghosh and Taylor as the starting point for their Fragments **I**. This was then transformed to **103**, passing through the intermediate **81** used by Evans as his starting point through a titanium mediated alkylation. This was then protected, the auxiliary removed to leave an alcohol, which was oxidised to an aldehyde and reacted in an Ando olefination to give **103** in a moderate yield after five steps. The ester group was transformed to an aldehyde through a redox process giving the aldehyde **60** in an excellent yield (used by Taylor as an intermediate). An aldol reaction of the acetate enolate of **104** then gave the acetate aldol product **105** in a high overall yield but with no diastereoselectivity. Although the selectivity was low for the aldol it did introduce a large amount of the carbon backbone of the fragment and the stereochemistry is used in the next step to control the reduction. The desired isomer was then reduced with the alcohol acting as a directing group, and acid promoted lactonisation followed by methylation gave the lactone **106** in a low yield over three steps. Finally, the acidic opening of the lactone followed by alcohol protection gave **107** as Fragment **I** (with the wrong C15 configuration) in a moderate yield.



a: trioxane, $TiCl_4$, TEA; b: TIPSCl, TEA; c: $LiBH_4$, THF/H_2O; d: $(COCl)_2$, DMSO, TEA, –78 °C; e: $(O\text{-cresol})_2P{=}O(Me)CHCO_2Et$, THF, –78 °C; f: DIBAL-H, DCM, –78 °C; DMP, DCM; h: 1) **104**, NaH, 2) BuLi, –78 °C, 3) **60**; i: $NaBH(OAc)_3$, THF; j: PPTS, DCM; k: MeI, Ag_2O, $MgSO_4$, DCM; l: PPTS, MeOH; m: TBSCl, imidazole, DMAP, DMF.

Scheme 49: Zhou's Synthesis of epi*-15 Fragment C11-C19.*

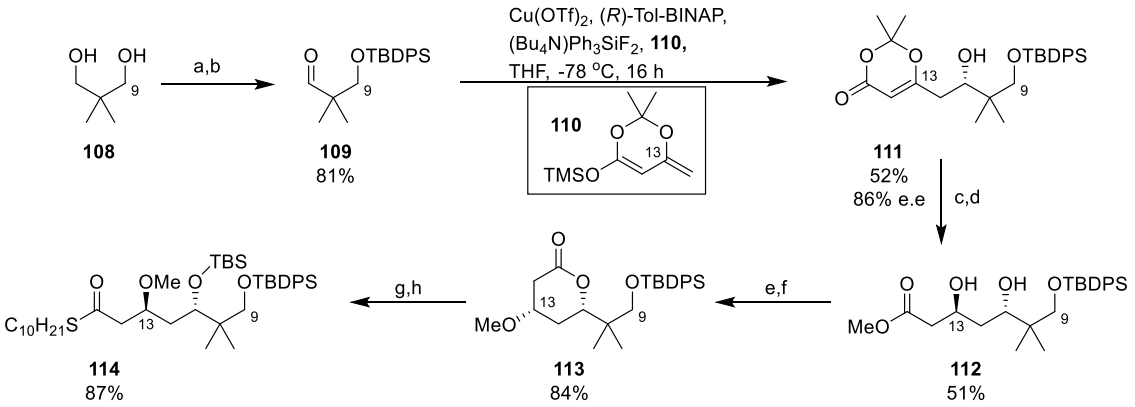
Zhou's route to *epi*-15 Fragment **I** had a total of twelve steps and a total yield of 0.7%. One of the limiting factors for the yield was the maximum yield of 50% arising from the non-selective acetate aldol reaction, highlighting again the difficulty of stereocontrolled acetate aldol reactions. However, other low yields for other key steps also contributed to the low yield so fixing the one step and correcting the stereochemistry would require further improvement still to compete with other methods.

Raghavan's Synthesis of Fragment C9–C19

One previous synthesis tackled the same fragment as our proposed C9–C19 fragment of Peloruside A was published by Raghavan, and was one of the most recent synthetic approaches published.[56] The synthetic route to the fragment was convergent with the synthesis and combination of two fragments (**114** and **119**) starting from two simple racemic materials (Scheme 50).

The larger fragment **114** started from dimethylpropanediol **108** which was monoprotected and the remaining alcohol oxidised with iodoxybenzoic acid (IBX) to give **109** in an excellent yield (Scheme 50).

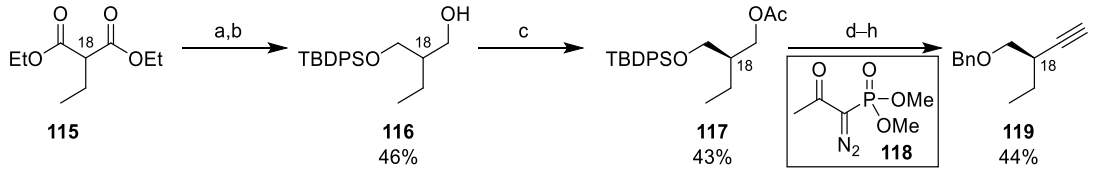
Then an enantioselective vinylogous Mukaiyama aldol reaction, adapted from Carreira's procedure,[68,69] with silyl ketene acetal **110** furnished aldol adduct **111** in a moderate yield with good enantioselectivity (86% e.e.). Heating with methanol led to the β-keto methyl ester, with a small amount of the β-keto lactone side product, which was then transformed into **112** using an *anti*-selective directed reduction protocol described by Evans and Carreira with a moderate yield but complete selectivity.[70] The lactone side product from the previous reaction can be transformed to **112** through methylation and reduction to recover additional yield in a process used by Evans in the synthesis of Phorboxazole B.[71] Compound **112** was then submitted to zinc promoted lactonization described by Jones,[72] which was subsequently methylated to give lactone **113** in an excellent yield. Opening of the lactone with the odourless dodecanethiol, followed by protection of the resulting alcohol gave compound **114** with a total yield of 16%.



a: NaH, THF, 16 h, then TBDPSCl, 3 h; b: IBX, EtOAc, reflux, 6 h; c: MeOH, toluene, reflux, 1 h; d: $Me_4NBH(OAc)_3$, ACN/AcOH, –35 °C, 18 h; e: $ZnCl_2$, molecular sieve, THF, reflux, 3 h; f: MeI, AgO, molecular sieve, Et_2O, reflux, 1 h; g: $H_{21}C_{10}SH$, $AlMe_3$, DCM, 1.5 h; h: TBSOTf, 2,6-lutidine, DCM, 15 min;

*Scheme 50: Raghavan's Synthesis of Compound **101** for Fragment C9–C19*

The other component to form fragment C9–C19 started from diester **115** formed from the simple alkylation of diethyl malonate (Scheme 51). The ester was first reduced to the diol, which was then monoprotected as the silyl ether to give the alcohol **116** in a low yield. The racemic alcohol was then submitted to enzymatic resolution through selective acylation of the alcohol to give enantiopure compound **117** in a low yield (excellent if the maximum yield of 50% is taken into account). The acetate group was then removed, and the alcohol oxidised in Swern conditions; the aldehyde was then reacted using the Ohira-Bestmann protocol for the formation of alkynes from aldehydes. An exchange of protecting groups gave alkyne **119** in an overall yield of 9%.

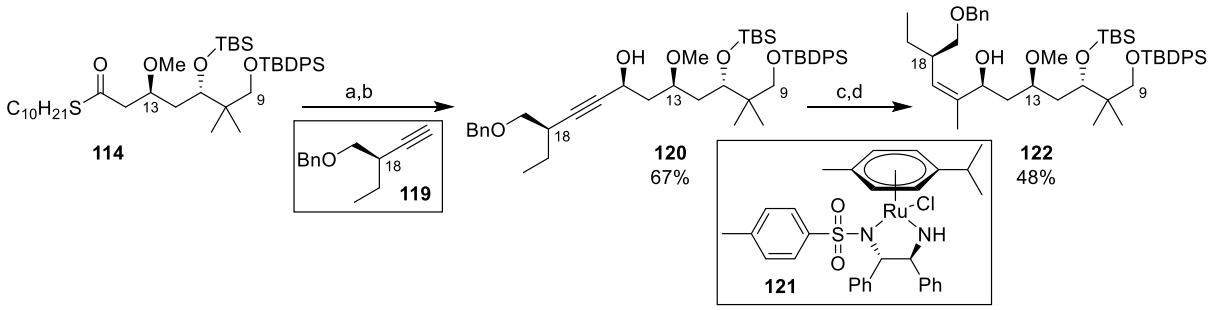


a: LAH, THF, –10 °C to RT, 16 h; b: NaH, THF, 16 h, then TBDPSCl, 3 h; c: Amano lipase PS, *i*-Pr_2O, CH_2=CHOAc, 12 h; d: K_2CO_3, MeOH, 2 h; e: $(COCl)_2$, DMSO, DCM, –78 °C, 1.5 h; f: **105**, K_2CO_3, MeOH, 8 h; g: TBAF, THF, 1 h; h: $BnOC(NH)CCl_3$, TfOH, DCM/hexane, 16 h.

*Scheme 51: Raghavan's Synthesis of Compound **106** of Fragment C9–C19.*

With compounds **114** and **119** synthesised they were then coupled using a palladium catalysed reaction described by Fukuyama for the coupling of thioesters with alkynes (Scheme 52).[73,74] The resulting ketone was submitted to Noyori asymmetric transfer hydrogenation to give **120** in a good

yield and selectivity.[75] Hydrostannation of the triple bond catalysed by palladium with a regioselectivity of 4:1, followed by displacement of the tributyltin by a methyl group using the Lipshutz procedure gave compound **122** in a modest yield.



a: $PdCl_2(dppf)_2$, CuI, PPh_3, TEA, DMF, **119**, 60 °C, 6 $h_{addition}$ + 3 h; b: **121**, HCOONa, 1-Bu-3-Me-imidazolium-BF_4, EtOAc/H_2O, RT, 7 h; c: $Pd(PPh_3)_4$, Bu_3SnH, hexane, 1 h; d: $Me_2Cu(CN)Li_2$, THF, 0 °C, 1 h, then MeI, –78 °C to RT.

Scheme 52: Raghavan's Completion of Fragment C9–C19.

This completed the synthesis of the C9–C19 fragment with an overall yield of 0.4% over a total of 21 steps. The use of a resolution technique for one of the components and the formation of side products or minor isomers in various reactions greatly hindered the overall yield of the synthesis.

Summary of the Different Routes

Shown in Figure 15 is a summary of the main bond disconnections used by the different routes. Where the configuration is controlled in a different step this is highlighted with an arrow pointing to the stereocentre affected. Using this figure an easy comparison of the different key reactions can be made. Most of the syntheses use either the Ando or Still-Gennari olefinations to create the required double bond with the remaining four using alternative procedures.[33,34,41,43,55] Jacobsen creates the double bond through hydroboration/bromination of a triple bond present in the starting material;[35] Raghavan used the Lipshutz procedure to reductively methylate the triple bond present in his starting material;[56] finally Hoye used a Relay Ring Closing Metathesis and Ermolenko Ring Closing Metathesis to form the required double bond.[36,54] The stereocentre at C18 was commonly introduced by alkylation of an enolate species,[33,41,43,55] epoxide opening,[35] or was already present in the starting material;[34,36,54,56] in two of the cases the absolute configuration was established through a resolution step.[35,56] The C15 stereocentre was commonly introduced through a Brown allylation;[33,41,43] also used were: allylboration,[34] aldol,[55] an addition to an aldehyde,[35] a coupling reaction,[56] the formation and opening of epoxides,[54] and for Hoye it was already present in the starting material.[36] In one case the C15 chirality was controlled through the Noyori atom transfer hydrogenation.[56] The fragments containing a chiral C13 used either chiral epoxides/carbonates to introduce the stereochemistry,[41,43] a Brown allylation,[33] kinetic resolution,[35] or a directed reduction reaction.[55,56] For the three fragments that went beyond the C11 position the extra backbone was added through either a Mukaiyama aldol,[41] Mukaiyama-Carreira aldol,[56] or a Grignard substitution of a Weinreb amide.[43]

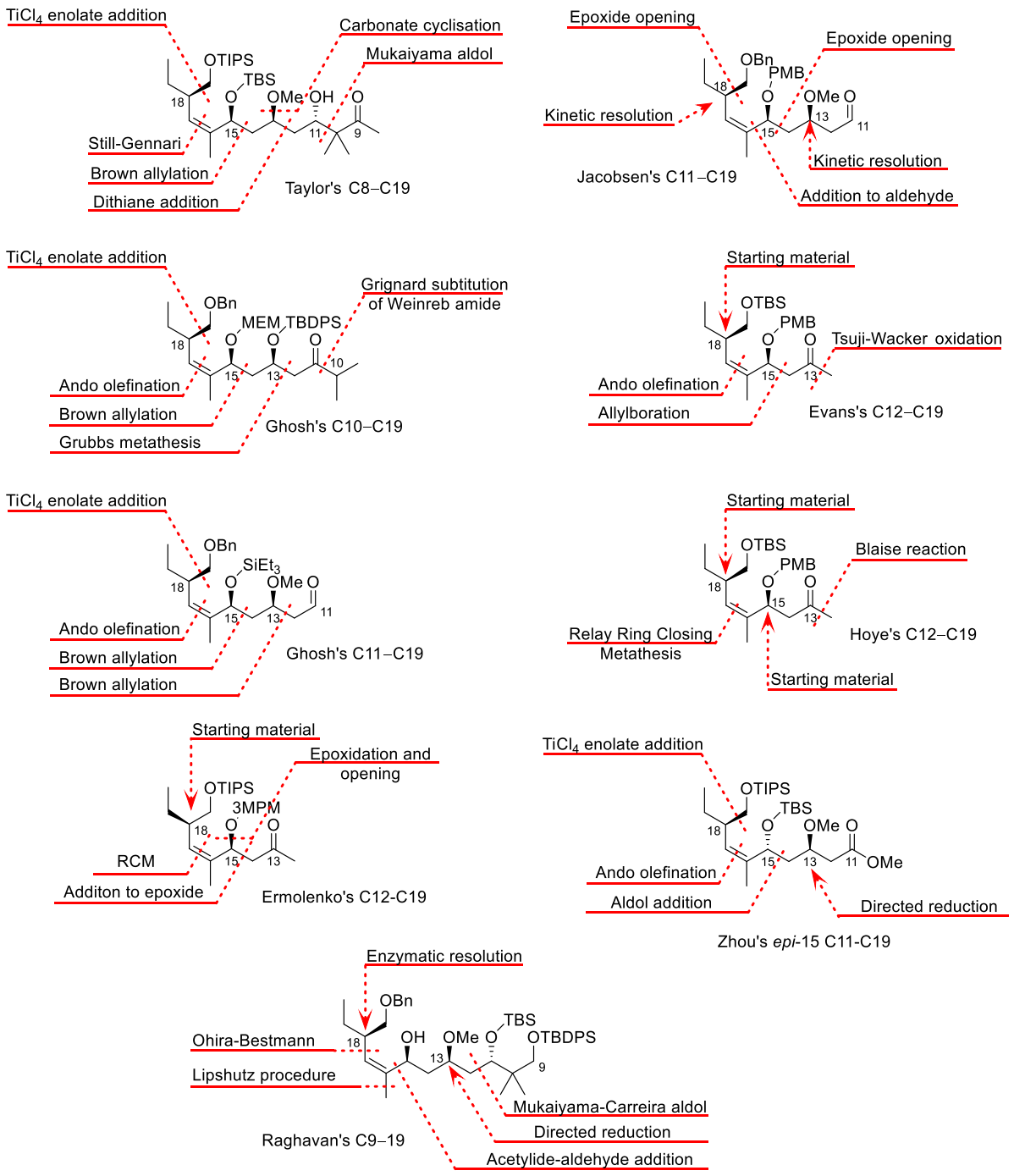


*Figure 15: Summary of Different Synthetic Routes to Fragment **I**. Key Disconnections Shown, Additional Information on Stereochemistry Origin Shown with Arrows.*

This figure can be used to compare our synthetic route (see Figure 17 on Page 65) to the previously published routes.

Basis for Our Approach to the Synthesis of Fragment C9–C19

Our proposed fragment came from the disconnection of the C8–C9 bond. Our strategy both aimed to resolve some of the common issues encountered in the synthesis and also to showcase some of the chemistry developed in our group and prove its feasibility in an applied synthetic environment. With the disconnection decided we chose two protecting groups that would be orthogonal, the TBDPS group at C18 being more stable can be carried through to the final deprotection and the TBS at the

C15 being more labile can be selectively deprotected to perform the macrolactonisation (Figure 16). The terminal ester group also sets up the molecule for various coupling strategies with Fragment **II**.

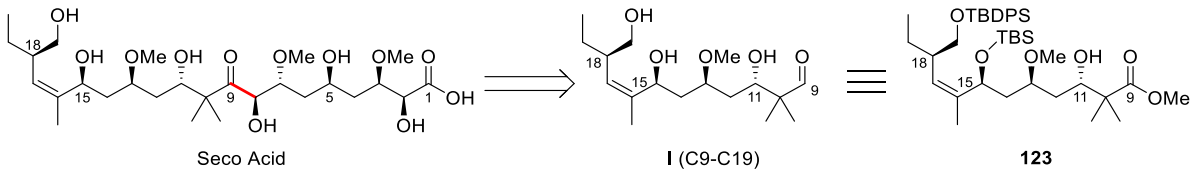


*Figure 16: Our Retrosynthetic Analysis of the Seco Acid of Peloruside A to Give Compound **123**.*

Our aim was also to develop a more efficient and greener process for the synthesis. This, apart from the obvious environmental connotations, should also be reflected in the yield and ease of the process. Therefore, with this aim, after optimisation of each individual step was complete, we then assessed the combination of various steps either in one-pot processes or conducting reactions with crude mixtures to minimise purification steps when possible. Our initial aim was to half the purification steps, therefore for our synthetic route of fourteen steps, have a maximum of seven chromatographic purifications, if the number could be reduced further to one for each of the five key transformations then even better.

Our synthetic route hinged on five key transformations and nine supporting processes such as protection/deprotection and redox steps. The key steps are shown in Figure 17 with their corresponding disconnections. The synthesis started from the left-hand side of the fragment and proceeded with the key steps in order to the right with transformations of the adducts to prepare them for the key steps.

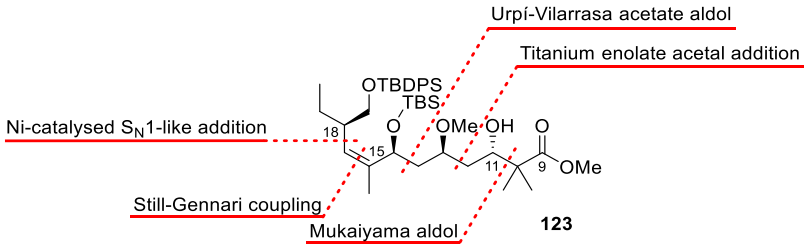
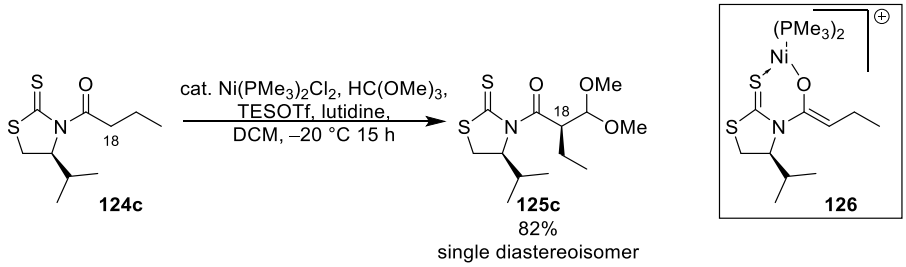


Figure 17: Our Key Steps in the Synthesis of Fragment C9–C19.

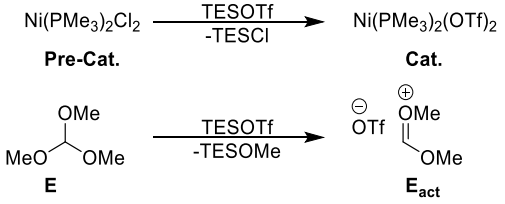
The first reaction and also the first key step in the synthesis was a nickel(II) catalysed direct reaction of a nickel(II) enolate formed from a chiral *N*-acyl thiazolidinethione and an *in-situ* activated oxocarbenium ion. This reaction was developed previously in our group;[76] importantly the orthoformate electrophile used in the reaction would later be used to create an aldehyde and therefore doubly acts as a protecting group. Using the butanoyl chain allowed the introduction of the ethyl chain at the C18 position and control over the C18 configuration (Scheme 53).



Scheme 53: Our First Step in the Synthesis of Fragment C9–C19. A Selective Nickel(II) Catalysed Direct Alkylation Reaction.

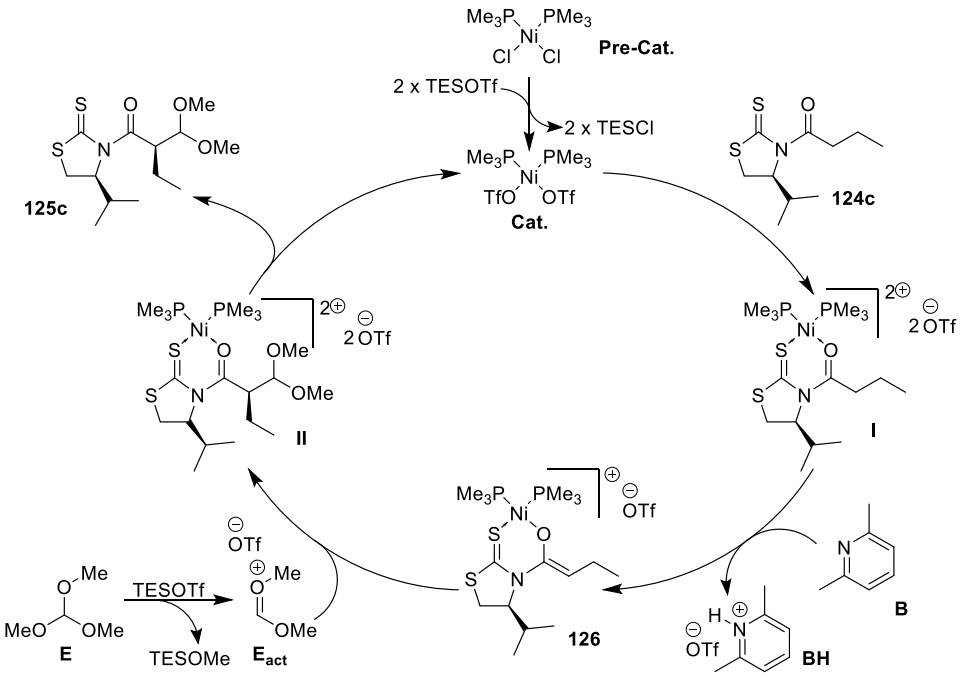
The enolate formed is exclusively the *Z*-enolate **126** which is one of the reasons the stereocontrol is so high, with only one diastereomer being formed. The high control of the Cα configuration is also owed to the highly selective chiral auxiliary used, a variation of the classic Evans auxiliary developed by Nagao.[77]

The achiral nickel complex (**Pre-Cat.**) required activation as the chloride complex was inactive in the carbon-carbon bond forming reaction. This was achieved via a ligand exchange with triflate ligands promoted by TESOTf in an adaptation of a process described by Sodeoka (Top, Scheme 54).[78] Without activation of the pre-catalyst the reaction did not proceed. The silyl triflate doubled as a Lewis acid in the activation of the electrophile (**E**), this converted the initial trimethylorthoformate into the oxocarbenium ion ($\mathbf{E_{act}}$) through the abstraction of one of the methoxy groups to form the charged compound (Bottom, Scheme 54). This species was considerably improved as an electrophile. Indeed, pre-activation of the catalyst followed by the addition of the un-activated trimethyl orthoformate resulted in negligible conversion. The final reaction conditions for this step gave an excellent yield we hoped would improve upon the later combination of reaction steps (see following paper).



Scheme 54: TESOTf Activation. Top: Activation of Pre-Catalyst Through Ligand Exchange; Bottom: Lewis Acid Activation of the Electrophile to form the Oxocarbenium Ion.

The catalytic cycle is shown below in Scheme 55. The importance of the activation steps with triethylsilyl triflate highlighted in Scheme 54 can clearly be seen; the catalyst is introduced into the catalytic cycle by the activation through the ligand exchange. This can then interact with the starting material **124c** to form the coordinated complex **I**, which is deprotonated by the lutidine base to give the *Z*-enolate **126**. This then reacts with the activated electrophile to give the compound **II** which dissociates to give the product **125c** and the catalyst re-enters the cycle.



Scheme 55: Catalytic Cycle of Orthoformate Reaction.

The high selectivity of the reaction is owed to the chiral auxiliary's function in the transition state of the reaction, which arises from the approach of enolate **126** with the activated electrophile $\mathbf{E_{act}}$ in the catalytic cycle (Scheme 55). This carbon-carbon bond forming stage involves an open transition state which is shown in Figure 18. The C4 isopropyl group blocks one face of the *Z*-enolate forcing the approach of the oxocarbenium intermediate to the opposite π-face, in this case the *Si*-face. This restriction is responsible for the absolute stereocontrol observed in the reaction.

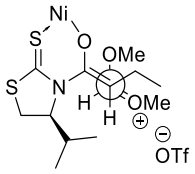
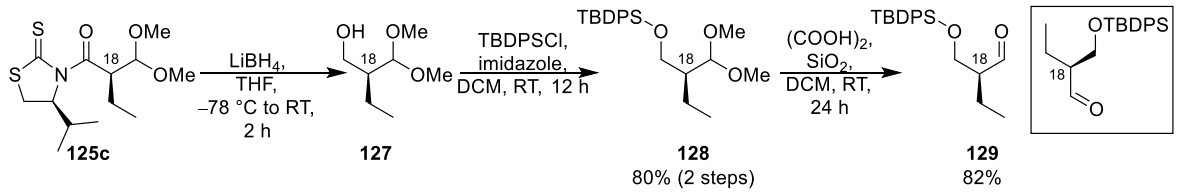


Figure 18: Open Transition State for the Reaction of Orthoformate with the Nickel Enolate.

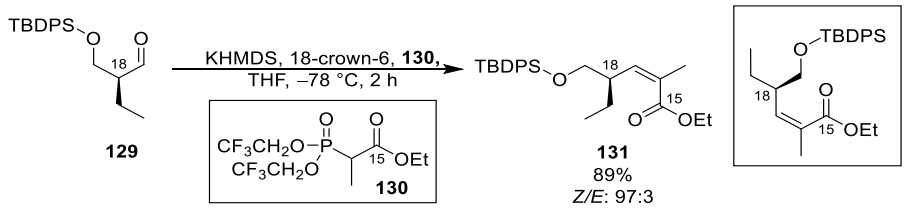
Once the first step was optimised the next sequence of three reactions prepared the molecule for the next key step (Scheme 56). The first transformation was to remove the chiral auxiliary in reductive conditions to leave the alcohol **127**. The resulting adduct **127** was unstable to purification, so the silyl protection had to be performed concurrently to give acetal **128** in an excellent yield over two steps. This acetal was deprotected to the aldehyde **129** through reaction with oxalic acid on silica gel, as described by Ghosh and Denmark,[79] in an excellent yield.



*Scheme 56: Synthetic Sequence from **125c** to **129** in the Synthesis of Fragment C9–C19. Inset: **129** Represented in the Previously Used Orientation of the Fragment C9–C19 for Comparison.*

The use of the trimethyl orthoformate group as an electrophile simplified the formation of the aldehyde; in most cases a redox sequence was generally used to form the alcohol and then oxidise to the aldehyde, whereas our process obtained it with a simple and mild one step process. Ghosh, Taylor and Evans all required first a reduction and then oxidation to form the analogous aldehyde **129**,[33,34,41] with our transformation removing one extra step. Although each step in itself is very high yielding (80% minimum) over the four first steps it implies an overall yield of 54%, which highlights the problem of compounded yield loss in total syntheses and why our aim to reduce the purification processes is so important.

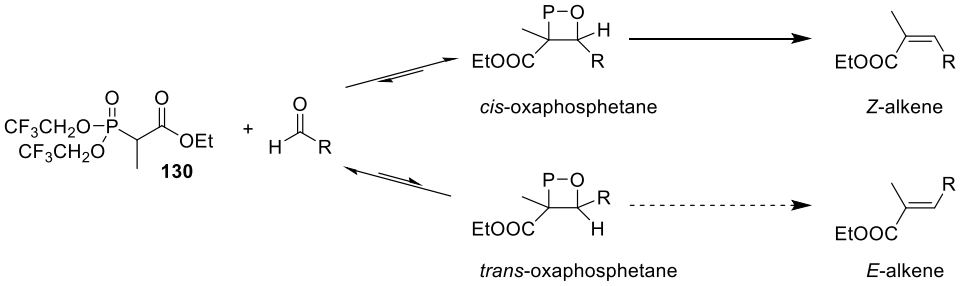
With the aldehyde in hand we then moved to the next key step in the synthesis which consisted of an olefination reaction to form a *Z*-alkene. We decided to go with the Still-Gennari modification due to the facility for the synthesis of the trifluoroethanol substituted phosphonate and our previous experience.[58] As expected, the reaction of **129** with phosphonate **130** gave compound **131** in an excellent yield and exceptional selectivity for the *Z*-isomer (Scheme 57).



*Scheme 57: Still-Gennari Olefination to Give **131**. Insert: **131** in Representative Orientation.*

After success in the stepwise approach to **131**, we moved to investigate combining various steps to remove purification steps. We also proceeded to scale up the reaction to a multigram scale. Both efforts can be seen summarised in the following paper.

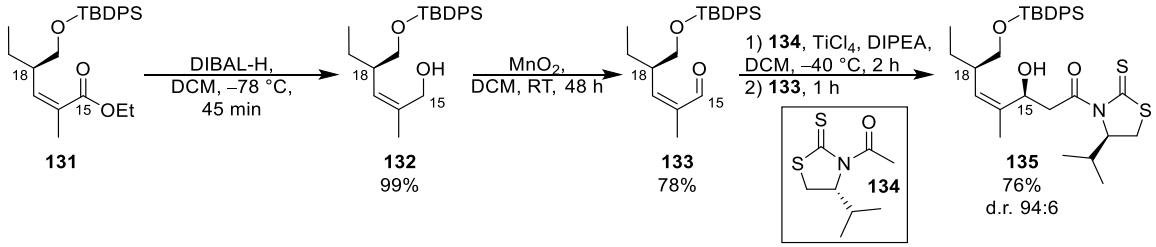
The high selectivity of the olefination comes from the reversible formation of square oxaphosphetane intermediates found in the mechanism (Scheme 58).[80] The reversibility of their formation allows for the resolution of the unfavoured isomer to be converted to the favoured isomer which upon irreversible elimination forms the alkene product. In the Still-Gennari modification the favoured intermediate both kinetically and thermodynamically is the *cis*-oxaphophetane which easily collapses to form the *Z*-alkene. A large initial amount of the *cis*-isomer is created which is mostly transformed to the final product. Over time much of the lesser *trans*-intermediate is converted to the more favoured *cis* through the equilibrium process. This leads to a high selectivity towards the *Z*-alkene as shown in our reaction of the synthesis.



Scheme 58: Mechanistic Representation of a Reaction of a Generalised Aldehyde with 130.

After the Still-Gennari coupling a redox process was required to transform the ester **131** to an aldehyde for use in the next key step (Scheme 59). This was achieved using DIBAL-H to give allylic alcohol **132** in a quantitative yield, which was oxidised with MnO_2 to give aldehyde **133** in a high yield.

This sequence was previously used by Evans in his approach to his analogue of compound **133**.[34] The aldehyde was then ready for the next key step which was an Urpí-Vilarrasa acetate aldol addition developed in our group.[81]



*Scheme 59: Synthesis of **135** with Urpí-Vilarrasa Acetate Aldol Key Step.*

The application of the reaction conditions were particularly challenging due to the complexity of the aldehyde.[45] However, we were able to achieve a high yield and excellent selectivity of **135** (d.r. 94:6). The use of the titanium enolate of the chiral *N*-acetyl auxiliary **134** was crucial for the stereocontrol and also for the following synthetic sequence.

Again, with the stepwise synthesis of **135** successful we looked at both removing purifications by combining steps and scaling up the reaction to over a gram. The results are summarised in the following paper.

The stereocontrol of acetate aldol reactions is particularly challenging. In fact it is easier to introduce two simultaneous α,β-stereocentres than just the β-stereocentre.[45] This is to do with the transition states, looking at Figure 19 the difference between the potential transition states for acetate aldols and the chair-like propionate equivalents on the right can highlight this difference. Whilst the small energy difference between the acetate transition states give no clear favoured transition state this is not the case for the propionate. The presence of the methyl group restricts the transition state to a cyclic chair-like transition state with the alkyl groups positioned in the manner in which the steric interactions are minimised. Depending on the approach of the aldehyde these can be more or less successfully reduced leading to the high selectivity (for example the left-hand chair minimises the R-group interactions much better than the right-hand chair and is therefore more favoured. see: Right, Figure 19). In the case of the acetate aldol reaction the lack of the methyl (or any R-group) substituent permits the transition state to form differing geometries, namely boat-like transition states (Centre, Figure 19). This reduces the selectivity considerably as the reduction of steric interactions are not solely based on the placement of the substituents in equatorial or axial positions but also on the type of geometry also. This means if a chair-like transition state would be unfavoured due to R-group interactions then it could adopt a boat-like geometry to relieve this strain. Therefore, the preference of one isomer over the other is severely diminished.

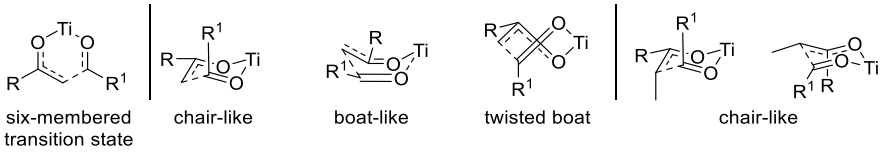
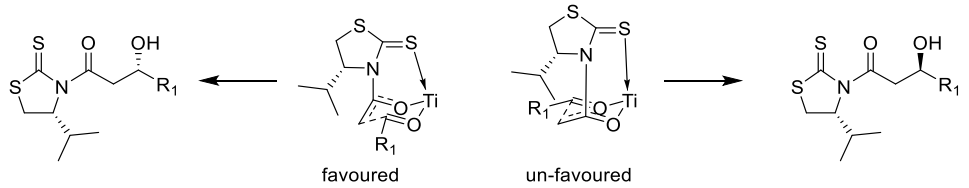


Figure 19: Transition States for Acetate Aldol Reactions. Left: Simplified Representation; Centre: Different Geometry Transition States for Acetate Aldols; Right: Chair-like Transition States for Propionate Aldols.

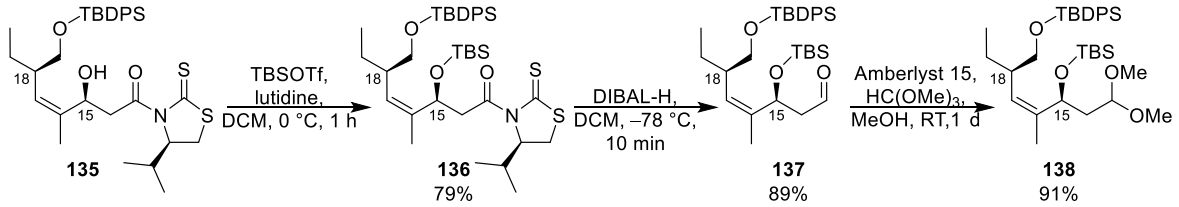
This high stereocontrol was achieved in the Urpí-Vilarrasa acetate aldol reaction by the use of an auxiliary with an exocyclic sulphur which coordinates strongly to the titanium and formed a cage-like transition state, which exerted considerably more control on the stereochemistry (Scheme 60). The

main reason for this was it removed the possibility of other geometries such as boat-like and twisted boat which restricts considerably the geometry and therefore increases the selectivity. This was possible due to the high chelating factor sulphur has with titanium complexes, which allowed the inclusion of the auxiliary in the cage-like structure and provided a remarkable level of stereocontrol. The chiral centre of the auxiliary created an appropriate chiral environment, which significantly restricted the approach of the aldehyde to one face of the enolate. This creates two transition states with one considerably favoured over the other which in our case leads to a selectivity of 96:4.



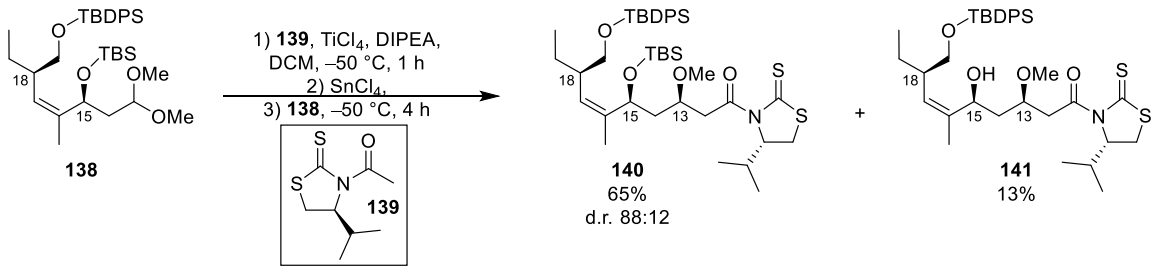
Scheme 60: Cage-like Transition States in the Urpí-Vilarrasa Acetate Aldol Reaction.

Following the aldol reaction, a series of three transformations were required in preparation for the next key step (Scheme 61). First a treatment of the aldol adduct with TBSOTf gave **136** in a high yield, followed by the removal of the chiral auxiliary with DIBAL-H to leave the aldehyde **137** in an excellent yield. Whilst many similar removals of chiral auxiliaries, or other reductions with DIBAL-H (see above), result in the alcohol product, our use of the thiazolidinethione auxiliary allowed the direct formation of the aldehyde and saves an extra oxidation step required upon auxiliary removal in comparable routes.[34,36,41,43] The aldehyde was then submitted to an acidic promoted dimethyl acetal formation catalysed by the acidic polymeric resin Amberlyst®. The reaction of the aldehyde with trimethyl orthoformate in various acidic media initially caused problems with either conversion or deprotection of the TBS group but using the softer Amberlyst® catalyst and methanol and the orthoformate as cosolvents gave an exceptional yield of **138**.



*Scheme 61: Preparation of **138** from **135**.*

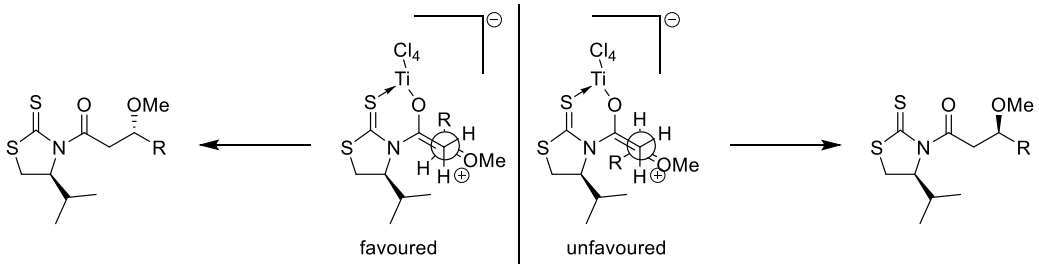
The dimethyl acetal was then ready for the penultimate key step, an acetate titanium-enolate addition to an activated acetal group (Scheme 62). This reaction is based on methodologies developed in our group on the addition of enolates to acetal compounds.[82–85] This was by far the most complex reaction in our synthetic route with a complex playoff between conversion, diastereoselectivity and deprotection of the C15 alcohol to give side-product **141**. Lower temperatures favoured high selectivity and minimised deprotection but to the detriment of conversion; similarly, higher amounts of enolate and Lewis acid increased the conversion but also promoted the deprotection which was also reflected in reaction time. After extensive testing we arrived at a trade-off with a higher reaction temperature, lower enolate concentration and minimal Lewis acid quantity over a longer reaction time. This allowed us to achieve **140** in a high yield and excellent selectivity with low deprotection.



*Scheme 62: Addition of Acetate Enolate to Dimethyl Acetal **138** to Give **140**.*

Again, the synthesis of **140** was examined to convert it from a stepwise to a multi-step process by removal of purification steps and an increase of the scale. In this late stage of the synthesis la large scale was considered above 100 mg for the product **140**. The results are summarised in the following paper.

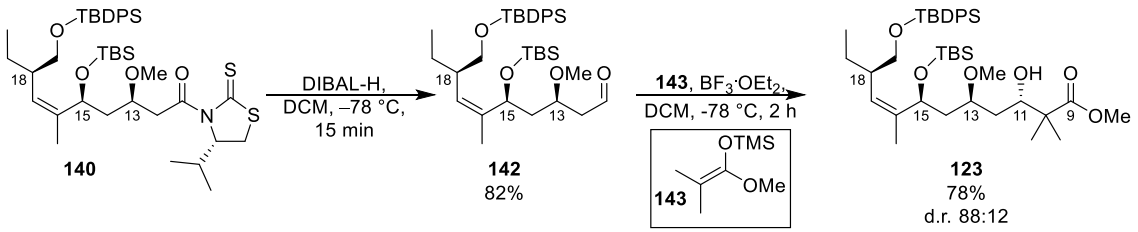
The reaction evolves in a somewhat similar manner to that of the orthoformate addition through an open transition state involving an oxocarbenium ion (Scheme 63). The approach of the acetal is restricted to the back face of the enolate but can take two geometries which are responsible for the major and minor isomers. Due to the complexity of the acetal and the lack of an alkyl group on the enolate the difference between the two transition states is not as high as in the orthoformate addition, but the selectivity of almost 9:1 is high considering these caveats.



Scheme 63: Transition States for the Acetate Enolate Addition to Acetal 124.

Importantly, this method not only allowed for the selective insertion of the C13 chiral centre but also removed the necessity of methylation of the alcohol, something required in every previous synthesis of Fragment **I**.[32–36,40,41,43,55,56]

The compound was then prepared for the final key step and last reaction. This was a Mukaiyama aldol addition, which required the transformation to an aldehyde. We decided on the same process as in Scheme 61 with a removal of the chiral auxiliary using DIBAL-H to give the aldehyde **142** without an additional oxidation step. This was then submitted to a Mukaiyama aldol similar to that described by Taylor in his synthesis of fragment C8–C19 (see Scheme 43 on Page 56).[41] Unlike Taylor, we used the ketene silyl derivative from a methyl ester rather than the ketene enol silyl ether from a methyl ketone, which gave us the ester product **123** instead of the ketone as in Taylors route. This furnished the fragment C9–C19 (**123**) with a high yield and excellent selectivity. The selectivity in the Mukaiyama reaction comes from substrate-controlled induction arising from the stereochemistry present in the aldehyde **142**. Evans studied substrate-controlled Mukaiyama aldol additions to β-alkoxy aldehydes to develop a model for stereocontrol which gave the *anti*-product as the major diastereoisomer,[86,87] our reaction follows this model giving the expected *anti*-aldol adduct **123**.



Scheme 64: Completion of Fragment C9–C19.

The yield of the sequential process over all 14 steps was around 8% and had thirteen chromatographic steps, our aim after the individual optimization was the removal of as many purification steps as possible to increase the yield and simplify the process. The final results can be seen in the following paper.

Organic LETTERS

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Stereoselective Synthesis of the C9−C19 Fragment of Peloruside A

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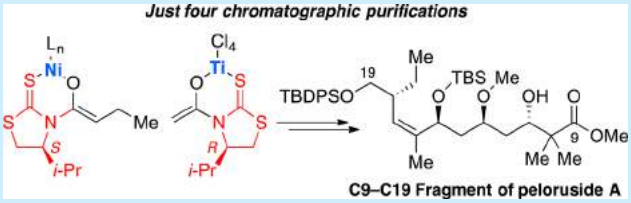
Supporting Information

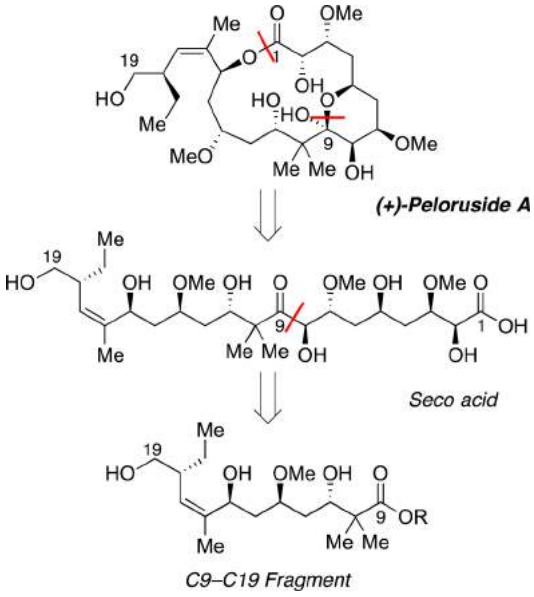
ABSTRACT: A concise synthesis of the C9−C19 fragment of peloruside A that is both highly stereoselective and efficient is described. Achieving an overall yield of 23% over 14 steps, this synthesis not only is high yielding but also involves four chromatography steps. This approach is based on the addition of metal enolates of chiral auxiliary scaffolds generated by either catalytic or stoichiometric amounts of nickel(II) or titanium(IV) Lewis acids.



(+)-Peloruside A is a polyketide macrolide that was first isolated by Northcote and co-workers in 2000 from the marine sponge *Mycale* found in Pelorus Sound, off the coast of New Zealand.[1] It displays potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng mL^{-1}.[2] In addition, peloruside A shows powerful microtubule-stabilizing activity similar to paclitaxel and is synergistic with it.[3−6] Structurally, it consists of a 16-membered lactone with an internal pyran ring and an unsaturated lateral chain, containing a total of 10 stereocenters (Scheme 1). The macrolide itself has a geminal dimethyl group and various hydroxyl and methoxy groups, while the unsaturated lateral chain contains a *Z*-olefin and a primary alcohol.

The first total synthesis of peloruside A was reported by De Brabander in 2003, confirming the absolute configuration of the natural product.[7] After this approach, other significant efforts have been directed to the total synthesis of peloruside A[8,9] or certain fragments of it.[10] More specifically, the synthesis of fragments containing the lateral chain of the macrolide has been a challenging goal due to the structural complexity.[9−11]

Scheme 1. (+)-Peloruside A and C9−C19 Fragment



In this context and considering the need for alternative routes toward such fragments, we envisaged a new and efficient approach to the C9−C19 fragment of peloruside A (Scheme 1) that could take advantage of several highly selective transformations based on chiral *N*-acyl thiazolidinethione scaffolds, developed in our group.[12−14] As seen in Scheme 2, our retrosynthetic analysis hinges on three asymmetric carbon−carbon bond forming reactions, involving the use of metal enolates of either the (*R*)- or (*S*)-enantiomer of *N*-acyl-4-isopropyl-1,3-thiazolidinethiones, and also a substrate-controlled Mukaiyama aldol reaction.[15] The use of highly effective chiral auxiliaries allows the control of reactional selectivity and also minimizes the steps needed in the synthesis by functionalization during removal of the auxiliary.[16−18] Beyond this we aimed to make the synthesis as concise and simple as possible and minimize the amount of purification processes. By doing this we would reduce both material used and time needed to carry out the synthesis, which in turn would reduce the cost and environmental impact of making the molecule.[19] In short, the aim was to create a simple and more effective synthesis of the C9−C19 fragment of peloruside A.

Our synthesis started with the first catalytic direct-type reaction applied to a peloruside A synthesis. This reaction is based on the catalytic addition of nickel(II) enolates to an oxocarbenium ion generated in situ.[14] The reaction was carried out using (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**1**)[20] as the substrate, trimethyl orthoformate as the electrophile, and a simple, robust, and commercially available $(Me_3P)_2NiCl_2$ as the precatalyst (Scheme 3); the addition of TESOTf was necessary to both activate the electrophile and

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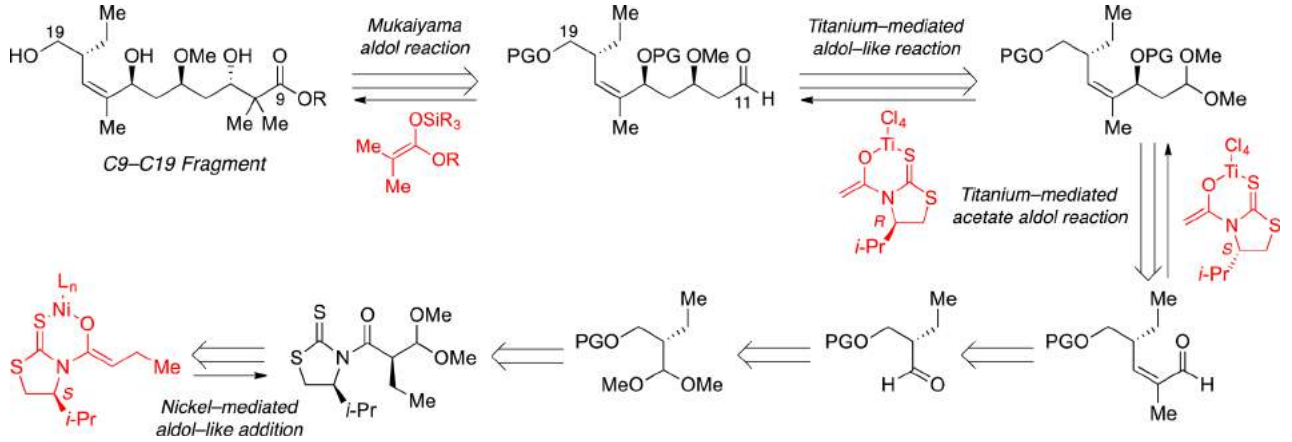
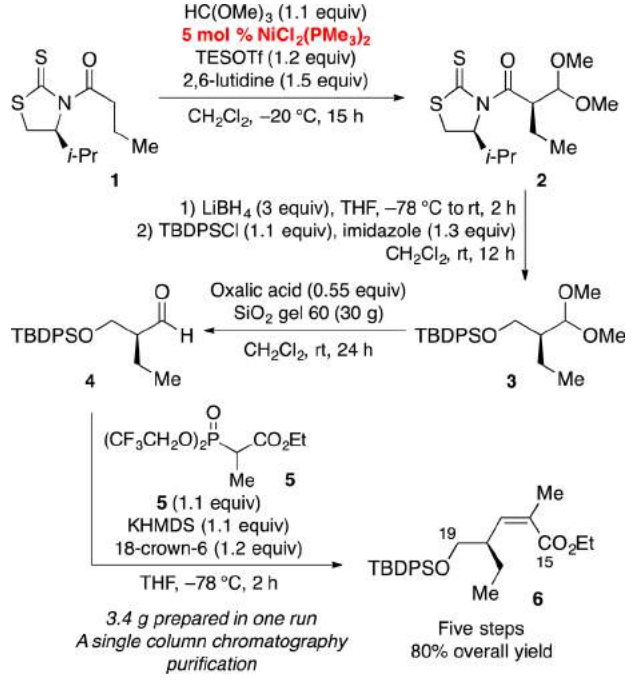
Scheme 2. Retrosynthetic Analysis of the C9−C19 Fragment



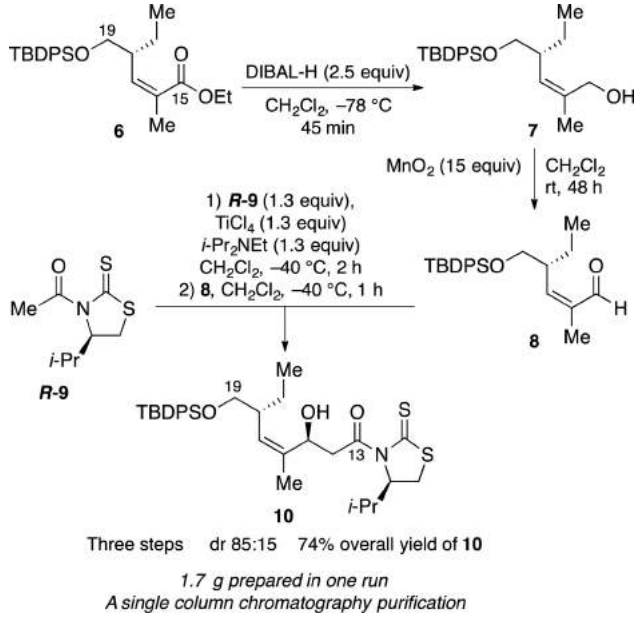
Scheme 3. Synthesis of the α,β-Unsaturated Ester 6 (C15−C19 Fragment)



create the truly active catalyst. Importantly, full conversion was achieved with only 5 mol % of $NiCl_2(PMe_3)_2$, which provided the corresponding adduct **2** as a single diastereomer with an 82% yield at a multigram scale. Removal of the chiral auxiliary with an excess of $LiBH_4$ and treatment of the resulting alcohol with TBDPSCl afforded the protected hydroxy acetal **3**. Furthermore, we were able to recover 90% of the auxiliary from this process; simple extraction in the workup allows for recycling and reuse of the chiral scaffold. Then, following a procedure described by Denmark, this acetal was converted into the aldehyde **4** using silica and oxalic acid in a simple and effective reaction.[21] Finally, the trisubstituted double bond was selectively inserted with a Still−Gennari reaction[22] using the phosphonate **5**[23] to obtain the α,β-unsaturated ester **6**. Because the aforementioned reactions proceeded efficiently and impurities were negligible, we could conduct all five reactions in sequence, with only one chromatographic purification process conducted after the Still−Gennari coupling. This led to the pure α,β-unsaturated ester **6** in a yield of 80% over five steps on a 10 mmol scale.

Continuing the synthesis, the reduction of α,β-unsaturated ester **6** with DIBAL-H[24] and the subsequent oxidation of the resultant allylic alcohol **7** with MnO_2 afforded the aldehyde **8** (Scheme 4), which served as the substrate for the next key aldol

Scheme 4. Synthesis of the Adduct 10 (C13−C19 Fragment)



reaction with the titanium(IV) enolate of (*R*)-*N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione (***R*-9**).[20] Despite the challenge of such an acetate aldol reaction,[25] the application of the experimental conditions previously developed in our group[12] afforded the desired aldol adduct **10** with an excellent 85:15 diastereomeric ratio. Furthermore, we were able to carry out this reaction in succession, purifying only after the aldol step to achieve a 74% yield of pure single diastereomer **10** (C13−C19 fragment) over three steps at 8 mmol scale.

Treatment of **10** with TBSOTf afforded protected aldol **11**, which was reduced with DIBAL-H at −78 °C to give the desired aldehyde **12** (Scheme 5). Remarkably, this process was able to stop chemoselectively at the aldehyde stage, enabling removal of the chiral auxiliary and adjustment of the oxidation state in a single step. Also notable is our recovery of the chiral

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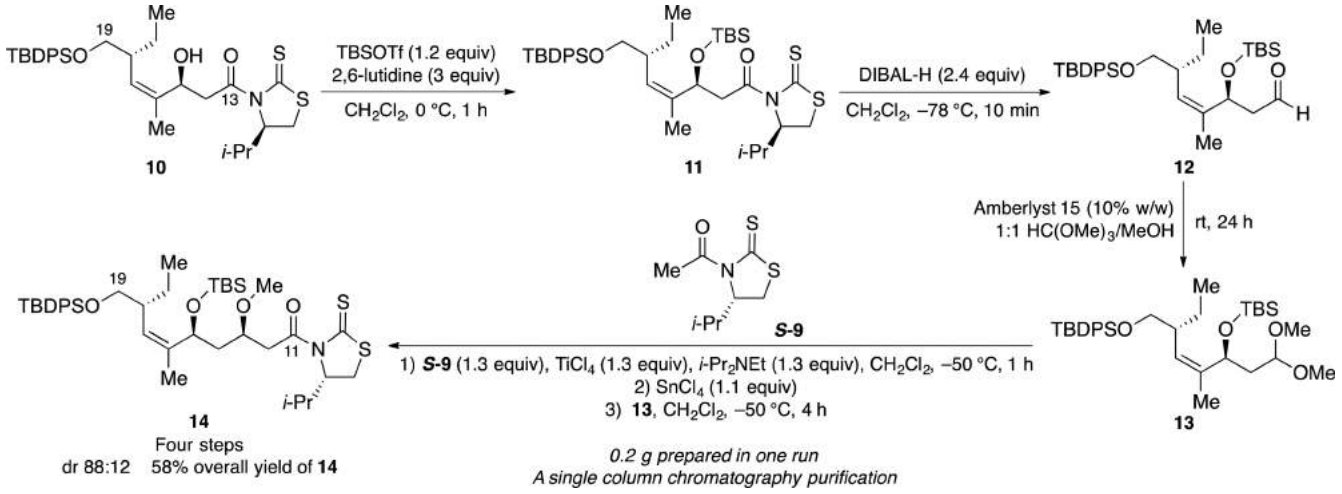
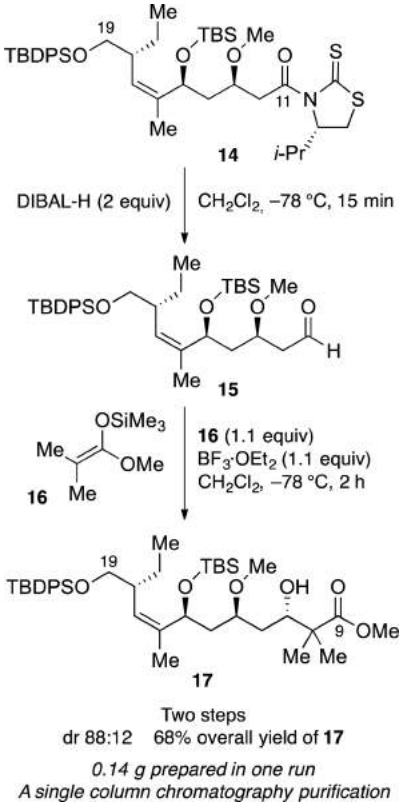
Scheme 5. Synthesis of the Adduct 14 (C11−C19 Fragment)



auxiliary in 85% purity from extraction. After various screening tests, dimethyl acetal **13** was efficiently prepared by treatment with MeOH, trimethyl orthoformate, and Amberlyst-15 without affecting the TBS protecting group. Differing from most strategies based on the stereoselective installation of the C13 hydroxyl group and subsequent methylation with energetic agents, we explored an alternative route. Indeed, we established that the Lewis acid-mediated addition of titanium enolates of *N*-acyl thiazolidinethiones to dimethyl acetals afforded *β*-methoxycarboxylic substructures stereoselectively in a single step.[13] As use of $SnCl_4$ as Lewis acid led to partial removal of the TBS protecting group, a comprehensive optimization was carried out. This was a lengthy process, balancing the maximum conversion against selectivity and the extent of deprotection of the TBS group that was occurring. Eventually, minimizing the equivalents of the enolate and the second Lewis acid, increasing the reaction time, and keeping the temperature at −50 °C afforded the desired adduct **14** (C11−C19 fragment) in a highly efficient manner. Indeed, we found that the addition of a slight excess of the titanium enolate from ***S*-9**[20] to **13** in the presence of 1.05 equiv of $SnCl_4$ (added as a 1 M solution in CH_2Cl_2) at −50 °C gave a full conversion and a selectivity of 88:12 alongside a small amount of the TBS-deprotected adduct. Again we were able to eliminate further purification processes by performing the protection, the removal of the auxiliary, the dimethyl acetal formation, and the addition in a continuous sequence, using only a single chromatographic purification at the end. This yielded 58% of a pure single diastereomer **14** over four steps.

Once again removal of the auxiliary with DIBAL-H gave the aldehyde **15** with a 92% recovery of the auxiliary. The last step involved a substrate-controlled Mukaiyama-aldol addition of silyl ketene acetal **16** to **15** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 6). The stereochemical outcome of this reaction relied heavily on the configuration of the chiral aldehyde **15**.[26] Particularly, comprehensive studies reported by Evans established that the Mukaiyama aldol addition to *β*-alkoxy aldehydes provides the corresponding *anti* aldol as the major diastereomer.[27] In accord with this model, the reaction of **15** and **16** produced a 88:12 mixture of diastereomers in a high yield. As in former sequences, we were able to run directly a two-step sequence after the removal of the chiral auxiliary to afford enantiomerically pure ester **17** in 68% yield with a single SiO_2 column purification. This final reaction concluded the synthesis

Scheme 6. Synthesis of the Ester 17 (C9−C19 Fragment)



of the C9−C19 fragment of peloruside A, and, with a methyl ester terminus, such an intermediate is suitably tailored for continuation of the total synthesis.

In conclusion, we have developed a concise synthesis of the C9−C19 fragment of peloruside A. The synthesis has been achieved in a total yield of 23% over 14 steps. Remarkably, not only have we achieved this very competitive yield compared to other attempts, but we have also been able to perform a very effective synthesis, by removing many of the purification steps, running just four chromatographic purifications over all 14 steps. The main benefit of this is a dramatic reduction of the time needed to execute the synthesis. It also permits work on a

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multigram scale. Further work is in progress to complete the total synthesis of peloruside following these ideas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01428.

Complete experimental procedures; physical and spectroscopic data for new compounds (PDF)

Copies of ^{1}H and ^{13}C spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Conclusions

Our synthetic route to the C9–C19 fragment of (+)-Peloruside A consisted of fourteen steps and gave a final overall yield of 24%. This outstanding yield for a synthetic sequence so long was owed mainly due to our approach to the purification process; from an initial sequential process with 13 chromatography steps and a combined yield of around 8% we decreased this to only four over the whole sequence. Considering there are five more elaborate key steps that introduce new stereocentres and have a possibility of producing not only other isomers but side products it is quite remarkable. This was only possible due to the optimisation of the reactions and their work-up processes, leading to full conversion and clean crude mixtures in the majority of steps. Indeed, some columns were required only to remove the minor isomer formed in a key step as the crude mixtures were surprisingly pure, even after various steps.

Although it is difficult to compare our approach to Fragment **I** with others due to the difference in the fragment size, our synthesis of the C9–C19 fragment does stand out among the current standards. The results of the synthetic routes are shown below in Table 1. The size of the fragment should be taken into account when comparing yields as the larger fragments obviously incur lower yields due to the increased steps and complexity (for this reason a percentage of the total backbone is shown). Both of Ghosh's fragments and both of Hoye's route to the same fragment are shown in the table for full comparison.

The more comparable yields were for fragments considerably smaller and containing less stereocentres than our fragment such as Hoye's 22% yield of C12–C19 over 10 steps or Evans 26% yield of C12–C19 over 9 steps (although he started from an advanced synthon which reduced the steps he needed and would reduce the yield considerably if taken into account). Therefore, our yield and synthetic sequence is one of the most efficient and innovative to date. Considering the size, both the number of steps and total yield show the efficiency of both our retrosynthetic analysis and power of both the individual reactions and our strategy of combining them.

AUTHOR	FRAGMENT	% BACKBONE([A])	STEREOCENTRES	STEPS	YIELD
TAYLOR	C8-C19	58%	5	16	16%
GHOSH	C10-C19	50%	4	15	13%
GHOSH	C11-C19	46%	4	14	20%
JACOBSEN	C11-C19	46%	4	13	3%
EVANS	C12-C19	42%	3	9	26%
HOYE	C12-C19	42%	3	8	14%
HOYE	C12-C19	42%	3	10	22%
ERMLENKO	C12-C19	42%	3	16	13%
ZHOU	C11-C19	46%	4	12	0.7%
RAGHAVAN	C9-C19	54%	5	21	0.4%
OURS	C9-C19	54%	5	14	24%

Table 1: Comparison of Our Synthetic Route to Previous Routes Described. A: Percentage Calculated from Backbone Carbons Present from Total of 24.

Our key steps also highlighted research produced in our group. The first step of the synthesis showed the synthetic viability of our alkylation of nickel(II) enolates derived from chiral *N*-acyl thiazolidinethiones. Not only was the reaction efficient, completely stereoselective, high yielding and clean enough to not require purification the product was highly important in the ensuing sequence. The auxiliary was easily removed to give the alcohol functionality required at the C19 carbon; furthermore, the introduced dimethyl acetal group was crucial in avoiding the redox sequence present in many other syntheses to give the aldehyde required for the olefination. The Still-Gennari reaction

also worked with an exceptional selectivity and yield, especially considering when used in a synthetic sequence after the four previous reactions without purification.

The Urpí-Vilarrasa acetate aldol developed earlier in our group also was shown to be highly selective, high yielding and compatible with the product being from a crude mixture of previous reactions. Considering the complexity of the reaction we only saw a drop of the selectivity to 85:15 from 94:6 when using the purified starting material but with a yield over three steps almost the same as just the aldol reaction. Again, the chiral auxiliary was essential not just for the selectivity but also was uniquely able to be removed leaving the aldehyde and not the alcohol as in many similar sequences therefore removing the need for oxidation.

Our reaction of the chiral titanium acetate enolate to the dimethyl acetal group was the most difficult of the synthesis and gave exceptional results considering the complexity of the molecule and difficulty of acetate enolate reactions. The yield over four steps was excellent especially considering the impure starting material and also methylation of the C13 oxygen was inherent in the reaction and removed an additional step. Again, the auxiliary proved key in the synthetic transformation to the aldehyde. Finally, the Mukaiyama reaction adapted by that used by Taylor in his synthesis afforded us the C9–C19 fragment.

Our aim of an efficient synthesis of the C9–C19 fragment of Peloruside A showcasing our groups methodology was more than achieved with our publication described in this Chapter.[88]

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Chapter 2: Addition of Nickel Enolates of Chiral *N*-Acyl Thiazolidinethiones to Stable Cationic Salts.

Preliminary Remarks

As seen in the introduction the use of chiral auxiliaries is a long-standing method for the stereoselective formation of new chiral centres.[1–6] Although the development of new stereoselective methodologies often focuses now on organocatalysis or chiral metal complexes, the use of chiral auxiliaries is still a staple in total synthesis due to the reliability, simplicity, easy purification and excellent stereocontrol and yields possible. Therefore, the development of a highly selective and efficient process that can compete where organocatalysis or chiral catalysis does not meet the requirement for selectivity or yield still holds a significant importance. One such example of this is the S_N1-like reaction using stable cationic substrates. In this context, the use of chiral catalysts had so far proved to be a complex process,[7–9] and the use of organocatalysis led to selectivities or yields which were only viable in a low number of substrates.[10–12]

Therefore, a methodology which can efficiently and selectively perform the general alkylation of a wide range of substrates using stable cationic substrates is a lucrative goal. One potential solution to this problem is the use of enolates derived from acylated chiral auxiliaries which would effect a high level of stereocontrol on the reaction.

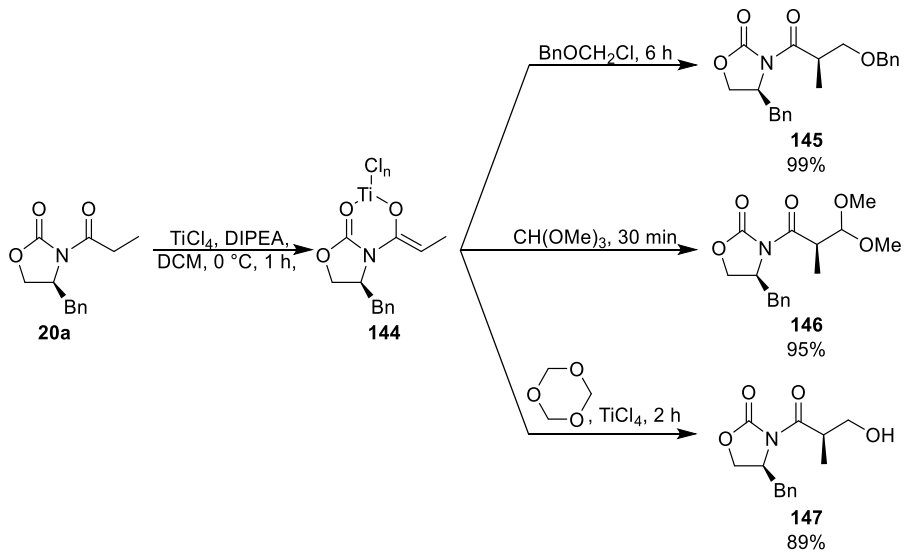
S_N1-Like Alkylation Reactions

As discussed in the introduction, the use of S_N1 and related mechanisms in stereoselective alkylation reactions is an important field in the formation of carbon-carbon bonds. Whilst there has been some exploration in Tsuji-Trost type allylation reactions using a chiral electrophilic species including combination with chiral nucleophiles,[13–22] the more relevant advances to our research involve the S_N1 alkylation reactions using chiral nucleophiles.

Two main methods are popular for this process, the most common is the use of organocatalysis, while the other is the alkylation of chiral enolate species. The use of carbocationc salts as electrophiles has largely been in non-chiral processes, but some advances in chiral organocatalytic additions and one in the selective quenching of enolates using carbocationic salts have been made. However, the field is still being actively investigated as there is still much room for improvement. The search for a universal procedure is a constant goal and many significant advances have been made in the area, especially in recent years.

Stoichiometric Reactions Using Chiral Auxiliaries

Early in the 90's Evans described various reactions of titanium enolates of *N*-acyl chiral auxiliaries (**20**) with various electrophiles in S_N1-like reactions.[23] One of the keys to this method was the initial preformation of the *Z*-enolate **144,** using $TiCl_4$/DIPEA, which was exclusively formed over the *E*-isomer (Scheme 65). This control over the enolate geometry, as explained in the general introduction, removes one of the variables and helps increase the stereocontrol of the products formed. The other, and more important, factor for the stereocontrol of the reaction is the chiral oxazolidine used as a chiral auxiliary; the chelation of the exocyclic oxygen to the titanium creates a rigidity in the structure and fixes the orientation of the enolate. The auxiliary, developed by Evans,[24] with its chiral group at the C4 position of the heterocycle blocks the approach of the electrophile to one of the faces of the chelated enolate. This steric induction created by the chiral environment leads to an exceptionally high control over the chiral centre formed upon reaction with the electrophiles.

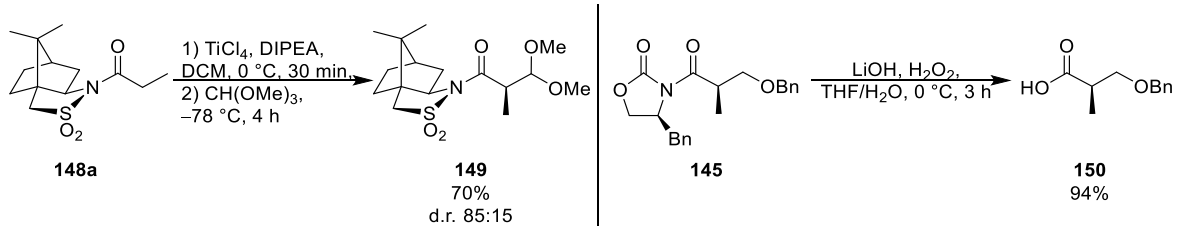


*Scheme 65: Evans' Reaction of Chiral Z-Enolate **144** with Different Electrophiles: Top: Alkyl Halide; Middle: Trimethyl Orthoformate; Bottom: Trioxane.*

The first electrophile shown to react with the enolate **144** was an alkyl halide to give product **145** in a quantitative yield in an S_N1 reaction (Scheme 65). The substitution of the chloride furnished a product with a protected β-alcohol and a new chiral centre at the α-carbon. The reaction of the enolate **144** with trimethyl orthoformate again proceeded with completestereocontrol. This time substitution of one of the methoxy groups of the electrophile furnished the dimethyl acetal product **146** with an exceptional yield. The use of trioxane as the electrophile required an additional equivalent of $TiCl_4$ as a Lewis acid activator for the electrophile, but furnished alcohol **147** in an excellent yield. This product is the deprotected analogue of **145** and therefore varying the electrophile can lead to either the protected or exposed alcohol.

The selection of the chiral auxiliary, as stated above, was essential for the selectivity of the reaction. A comparable alkylation to the above reaction with trimethyl orthoformate (Middle, Scheme 65), using an analogue of **20a** with Oppozler camphorsultam auxiliary (**148a**),[25–27] gave not only lower selectivity in the formation of dimethyl acetal **149** but also a much lower yield (Left, Scheme 66).

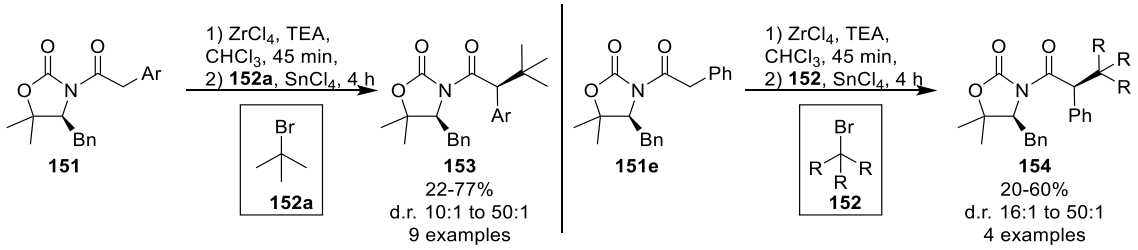
Another benefit of using the oxazolidine auxiliary was that the removal was straightforward, high yielding and also chemoselective as seen with the protected alcohol **145** being transformed to the acid **150** (Right, Scheme 66). Therefore, the correct choice of the chiral auxiliary not only is pivotal in the stereocontrol of the reaction but also in the synthesis of enantiopure synthons via removal of the auxiliary.



Scheme 66: Importance of the Correct Chiral Auxiliary: Left: Comparable Alkylation Using Oppolzer's Camphorsultam Auxiliary; Right: Removal of Oxazolidine Auxiliary.

Since the completion and publication of this chapter's work, Zakarian published a methodology based on zirconium(IV) enolates of chiral *N*-acyl oxazolidinones with tertiary bromides (Scheme 67).[28]

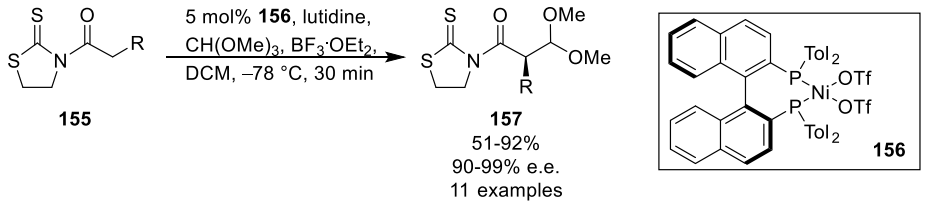
Starting from *N*-arylacetyl oxazolidinones **151**, the zirconium enolate was formed using $ZrCl_4$/TEA and the alkyl bromide **152** and an activating Lewis acid ($SnCl_4$) were then added. The reaction of different starting materials with *tert*-butyl bromide **152a** gave the products **153**/**154** in yields ranging from low to high and excellent selectivity (Left, Scheme 67). Using the phenyl starting material **151e**, different tertiary alkyl bromides **152** were also examined (Right, Scheme 67). While the results were lower in terms of yield and in most cases, selectivity compared to the **152a**, they showed the viability of the reaction with more complex alkyl bromide groups.



Scheme 67: Zakarian's Alkylation of Chiral N*-Acyl Oxazolidinones with Tertiary Bromides.*

Evans's Catalysed Asymmetric Alkylation Reaction

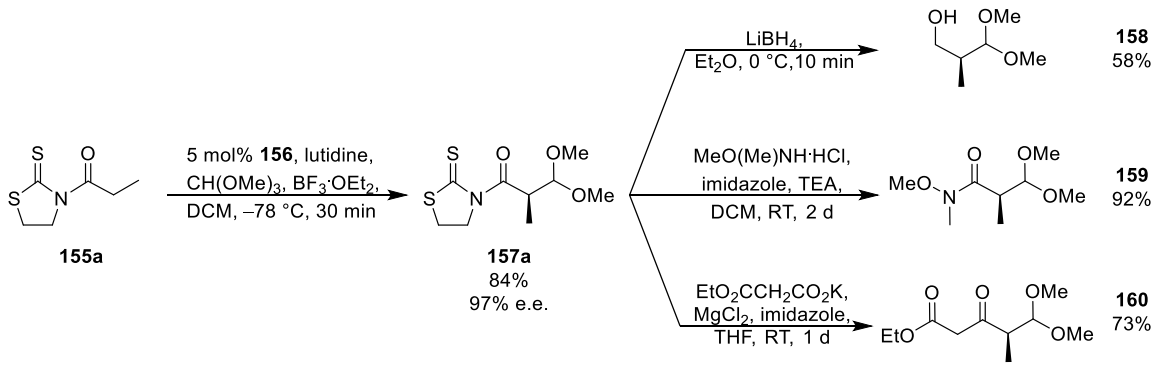
Evans also expanded his methodology to the enantioselective alkylation of achiral *N*-acyl thiazolidinethiones with orthoesters catalysed by the Tol-BINAP nickel(II) catalyst **156** (Scheme 68).[7] This reaction system the analogous dimethyl acetal product **157**, albeit in a different manner. In this case the enolate formation was catalytic and therefore the preformation required in the previous titanium mediated methodology was not required. Another difference is that the starting material was a set of achiral *N*-acyl thiazolidinethione derivatives **155**, but the main difference is the source of the chirality: in the previous methodology the source was the chiral auxiliary, in this case it is the chiral catalyst **156**. The coordination of **156** to the substrate **155** increases the acidity of the Cα hydrogens, which can be easily removed with a tertiary amine. Furthermore, the chiral diphosphine bound to the metal creates a chiral environment that determines the approach of the resultant nickel(II) enolate to the oxocarbenium intermediate.



Scheme 68: Enantioselective Orthoester Alkylation Described by Evans with a Chiral Nickel Catalyst.

The methodology was tolerant of various functional groups with varying yields (lower for more bulky substituents) and excellent enantioselectivity. The new achiral scaffold was also demonstrated to be easily removed through a range of reactions leaving various functionality (Scheme 69).

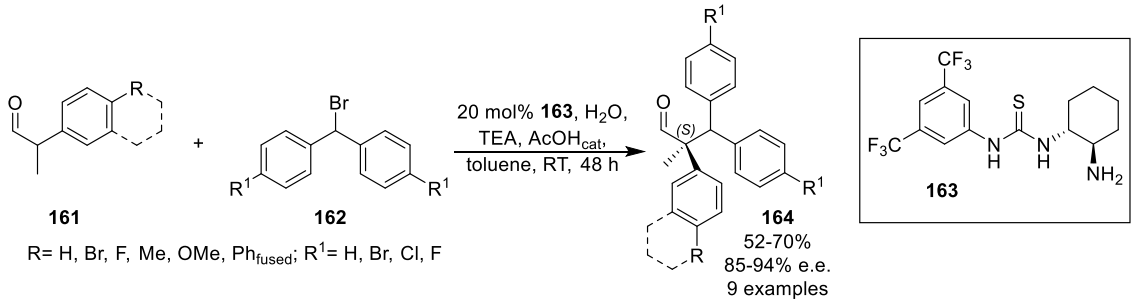
The propionate derivative of **155a** was used for the demonstration of the viability of the scaffold removal. Firstly, it was reacted in the orthoformate alkylation conditions to give **157a** in an excellent yield and enantioselectivity. This product was first reacted with lithium borohydride, removing the scaffold in reductive conditions to give alcohol **158** in a moderate yield. The removal of the scaffold in a substitution by the Weinreb salt to form amide **159** proceeded in an exceptional yield after a reaction lasting two days.[30] The reaction of potassium ethyl malonate in the conditions described by Smith afforded β-keto ester **160** in a high yield.[31] The formation of the carboxylic acid was carried out as seen in Scheme 66 and gave a moderate yield but was essential to confirm the stereochemistry.



*Scheme 69: Evans' Orthoformate Reaction of Propanoyl Starting Material **155a** and the Derivatisation of the Product **157a** Through Scaffold Removal.*

S_N1-Like Organocatalytic Reactions by Jacobsen

The use of organocatalysis in enantioselective alkylation reactions of aldehydes via an S_N1 pathway was investigated by Jacobsen using amino thiourea catalysts.[12] The substrates were a variety of α-methyl-α-aryl aldehydes as nucleophiles and diarylmethyl bromides as electrophiles (Scheme 70). As the starting material is a di-α-substituted aldehyde the resulting product is a complex, highly crowded structure with a chiral quaternary centre; due to the complexity the yields are from moderate to high but the enantiocontrol ranging from high to excellent is therefore more impressive.



*Scheme 70: Jacobsen's Use of Organocatalyst **163** in the S_N1 Alkylation Reaction of Aldehydes.*

The organocatalyst **163** had a double function in the reaction, interacting with both the nucleophile and electrophile (see Figure 20). The catalyst interacts with the aldehyde **161** forming an enamine, shown in the right of Figure 20; this forms the nucleophilic species in the reaction. On the other hand, the thiourea moiety of the catalyst interacts with the bromine of the electrophile **162** to promote its leaving through anion extraction and forming the diaryl cation shown in the left of Figure 20 (diphenyl **162o** shown). With the forming of the cationic species and the chiral nucleophile preformed, the S_N1 reaction may then take place and a new carbon-carbon bond shown by the larger dashed line is created. Catalyst dissociation to reform the aldehyde generates the final product **164** and the catalyst can enter another cycle.

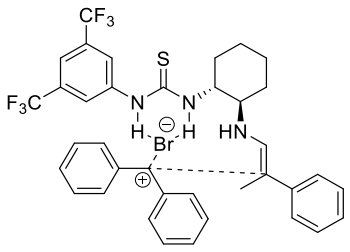
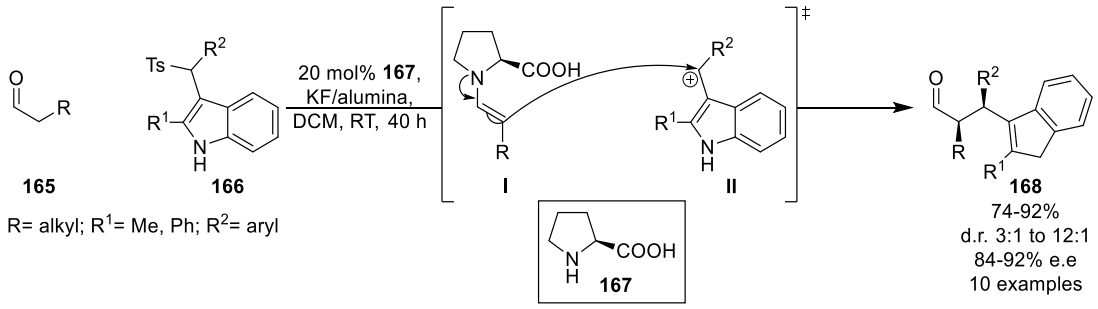


*Figure 20: Catalyst **163**'s Interaction with the Electrophile **162a** and Aldehyde **161a**. Bonds Formed/Broken in Dashed.*

S_N1-Like Organocatalytic Reactions by Melchiorre

Melchiorre has also conducted investigation in the field of organocatalytic S_N1 reactions,[42–44] and later photo-organocatalysis in S_N1-like radical processes.[45–49] The basis of his work was the use of mainly proline based organocatalysts to form chiral enamine nucleophilic species, which then react with various electrophiles in S_N1 reactions or photocatalyst promoted SET induced radical S_N1 reactions.

His initial work focussed on the proline catalysed addition to *in-situ* generated iminium ions from arylsulphonyl indoles in an S_N1 process (Scheme 71).[42] The chiral proline **167** interacts with the aldehyde **165** to form the chiral enamine species **I**, which acts as the nucleophile in the reaction. Parallelly, the indole electrophile **166** is activated by the basic alumina forming the active cationic iminium species **II** with the loss of the tosyl leaving group. The addition of the enamine to this cation followed by hydrolysis yields the products **168** and regenerates the catalytic proline species.



*Scheme 71: Melchiorre's S_N1 Alkylation of Aldehydes with Aryl Indoles Catalysed by Proline (**167**).* In-situ *Generation of Active Species **I** and **II** Shown in Centre.*

While the tolerance of the alkyl group of the aldehyde was generally high, the nature of the indole was stricter. The lack of an aryl group at the electrophilic position (R^2) was highly detrimental to the yield and selectivity, suggesting the stabilisation afforded by the inductive and resonance effects (the steric effect was limited by the use of a bicyclic alkyl structure). Tolerance of the nature of the aryl group however was high, with various substituted aryl rings performing similarly. Another key position was the R^1 group. The difference in electronic effects between methyl and phenyl had a small effect on the diasteroselectivity (8:1 for methyl, 3:1 for phenyl) and the enantioselectivity was unaffected. However, the lack of a substituent (R^1 = H) greatly reduced the selectivity, with an almost racemic ratio, which was attributed to the steric effect of the lack of substituent.

Shortly after this work Melchiorre published his findings on the γ-alkylation of enal enamines using a diaryl methanol compound in a co-catalytic S_N1 reaction.[43] This work combines the enamine forming ability of chiral quinidine derived catalysts with the Bronsted acid character of chiral BINOL derivatives (Figure 21).

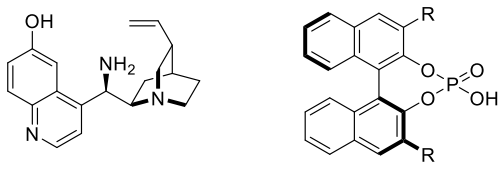
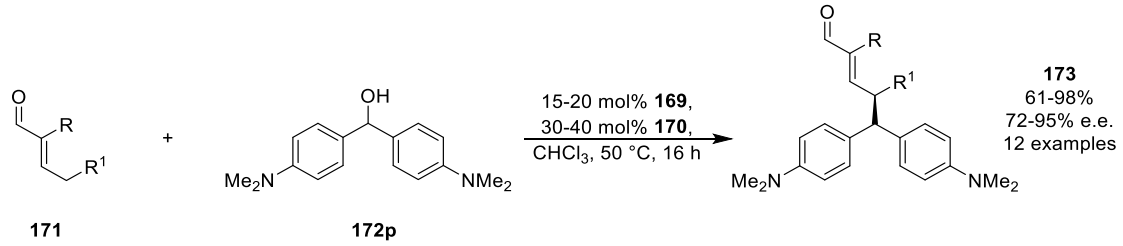


*Figure 21: Quinidine Derived Catalyst **169** and BINOL Derivatives **170** Used by Melchiorre.*

The reaction of substituted enals **171** with the benzydryl derivative **172p** was achieved through a combination of catalysts **169** and **170** (Scheme 72). The use of BINOL **170a** or its nitrobenzyl derivative **170b** was dependent on the enal substrate, whilst the normal BINOL was usually employed in the

majority of cases some cases showed **170b** could improve the selectivity of the reaction. The tolerance of the α-substituent was generally high but with a slight drop in selectivity for larger groups (e.e. with changes in R: 90% for methyl, 72% ethyl and 73% benzyl in equivalent compound and reaction conditions). Using a phenyl group was a greater detriment to the selectivity with the e.e. dropping to 45% (not shown in Scheme 72), this is probably due to the increase in α-proton acidity making it more prone to racemisation coupled with the increase in steric hinderance. The γ-substituent was more broadly tolerated with a lower decrease in the selectivity (82% minimum in e.e. over 8 compounds). The nature of the alcohol was also important, with non-stabilising cationic character affording low selectivity.



*Scheme 72: Enantioselective γ-alkylation of Enals with **172p** with Organic Co-Catalysis.*

The catalysts were both important in terms of yield and selectivity in the reaction. The protection of the alcohol as a methoxy group in the quinoline derivative **169** led to both a poorer conversion and considerably lower selectivity. Omission of the chiral Bronsted acid **170** (via TFA activation of the alcohol) led to a 20% difference in both selectivity and yield; the structural modification of the acid also had a direct effect on the selectivity. These observations could be explained by the mechanistic representation of the co-catalytic system shown in Figure 22.

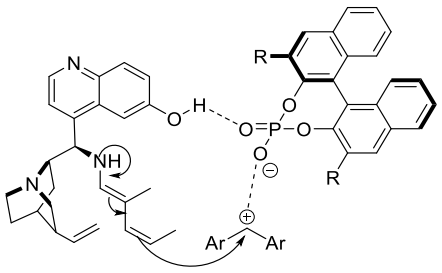
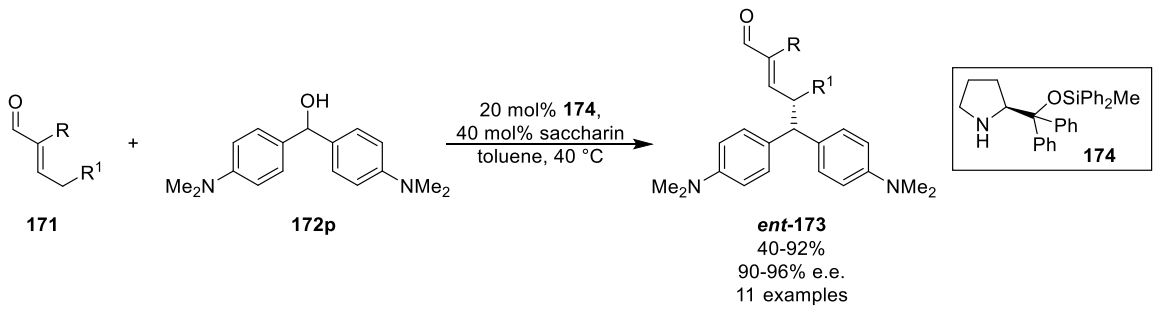


Figure 22: Mechanistic Representation of Melchiorre's Co-Catalysed S_N1 Alkylation Reaction.

The phenol group of the enamine formed by reaction of enal **171** with catalyst **169** forms a hydrogen bond linker to the BINOL catalyst **170**. The BINOL catalyst, after activating the alcohol **172p** through leaving group protonation, forms an ion pair with the resulting cationic electrophile. This creates a bridged chiral system with both the nucleophile and electrophile forced close to one another in the chiral pocket. Therefore, the attack of the nucleophile to form the carbon-carbon bond occurs in a pseudo-intramolecular fashion and could explain both the high selectivity and the dependence on the chirality of both catalysts.

The need for the secondary Bronsted acid chiral catalyst was later removed by Melchiorre's development using a proline derived organocatalyst.[44] The use of a diphenyl silyl ether derivative of proline (**174**) developed by Seebach,[50] achieved (minus one example) high yields and high to exceptional selectivity for the enantiomer of the previously synthesised product **173** (Scheme 73).[43] This high selectivity removed the need for a chiral Bronsted acid and a simpler acidic additive was used as a co-catalyst to activate the alcohol.



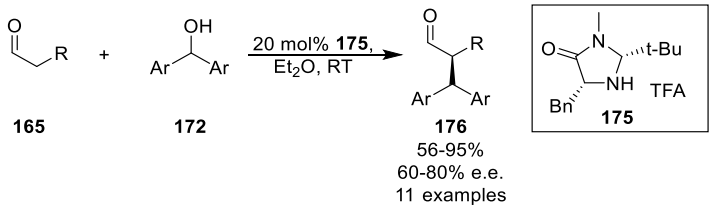
*Scheme 73: Melchiorre's S_N1 γ-Alkylation of Enals Catalysed by Proline Derivative **174**.*

S_N1-Like Organocatalytic Reactions by Cozzi

Cozzi is one of the most prolific chemists working in the field of organocatalytic S_N1-like chemistry, and has written various reviews on the topic.[51–54] His initial research was based on the alkylation of aldehydes with diarylmethyl alcohols and gradually expanded the scope to include other electrophilic species.

Alcohols as Electrophiles

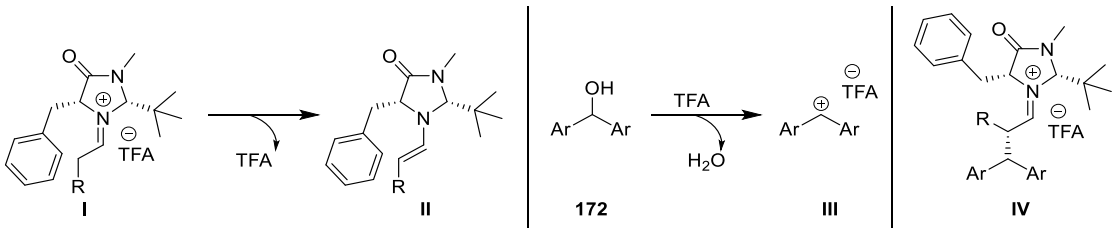
In this initial report various aliphatic aldehydes **165** were reacted with different diarylmethyl alcohols **172** to give the product **176** in low to exceptional yields with low to good enantioselectivity (Scheme 74).[10] The catalyst used to control this transformation was the MacMillan amine catalyst **175**,[55] which performed better than proline, prolinol, a derivative of prolinol (proline gave a racemic mixture and the others gave no product) and five other Macmillan catalysts. The use of the trifluoroacetic acid salt was also important, with salts of triflic acid and *p*-toluenesulphonic acid greatly decreasing the selectivity of the reaction and in fact has a crucial role in the mechanism of the reaction.



Scheme 74: Cozzi's Initial Organocatalytic S_N1 Alkylation of Aldehydes with Diarylmethyl Alcohols.

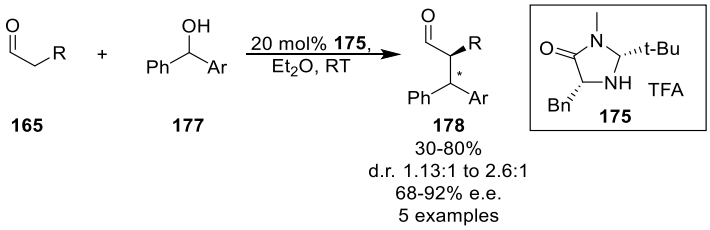
The selectivity of the reaction hinges on the configuration of the enamine formed when the catalyst **165** interacts with the aldehydes **151**. The formation of this enamine **II** is a result of the initial formation of the iminium salt **I** (Left, Scheme 75), which is then deprotonated by the trifluoroacetate anion to give the enamine **II** and expulsing trifluoracetic acid (TFA). The chiral environment provided by the tertiary butyl and benzyl groups block one face of the enamine and cause the electrophile to predominately approach from the opposing side.

The trifluoracetic acid has a double function. Once liberated upon the enamine formation, the acid then interacts with the alcohol **172** (Centre, Scheme 75). This causes the protonation of the alcohol and subsequent leaving of the water group. The resulting carbocation with the trifluoroacetate counter ion **III** then acts as the true electrophilic species in the alkylation reaction. Upon reaction of the enamine **II** with the carbocationic electrophile **III** the iminium species **IV** is initially formed (Right, Scheme 75); this species then undergoes hydrolysis to give the product **176** and the reformed catalyst **175** ready for the next catalytic cycle.



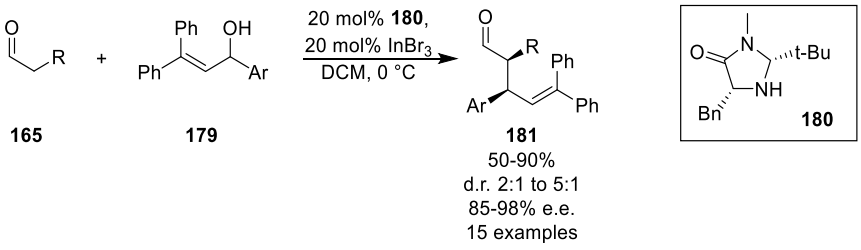
*Scheme 75: Left: Initial Iminium Ion Formed and its' Transformation to Enamine **II** Through TFA Expulsion; Centre: Activation of Alcohols 158 with the Liberated TFA to Give Activated Carbocation **III**; Right: Initial Product Upon Reaction of **II** with **III**.*

The reaction was even somewhat successful using non-symmetric diarylmethyl alcohols creating two new stereocentres with comparable enantiocontrol and low diastereoselectivites between 1:1.3 and 3:1 (Scheme 76). The alcohols used (**177**) contained phenyl as one substituent and ferroconyl or indolyl groups as the other. Whilst the selectivities were somewhat low, using an enantioenriched phenyl-ferrocenyl methyl alcohol increased selectivity and yield the maximum was a yield of almost 50% and an *anti* diastereoselectivity of just 1:1.3 with an excellent enantioselectivity. The indolyl derivative's selectivity towards the *syn* product could be increased by decreasing the temperature to -25 °C but it was at the detriment to the yield.



*Scheme 76: Cozzi's Organocatalytic SN1-Like Alkylation of Aldehydes **165** with Asymmetric Diarylmethyl Alcohols **177**.*

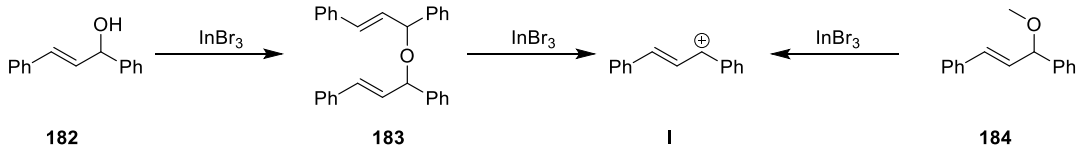
This concept was further expanded to the use of asymmetric aryl-allylic alcohols as electrophiles with the addition of an indium salt to promote the reaction (Scheme 77).[56,57] The catalyst in this case was the Macmillan amine **180** (the free form of catalyst **175**), indium(III) bromide as a Lewis acid to activate the alcohol.[56] The reaction initially gave a good enantioselectivity of 80% but an equimolar mixture of the two diastereomers using the monophenyl substituted derivative of **179**. The addition of the second phenyl group was key for the diasteroselectivity of the reaction and increased the enantioselectivity to 90%.



Scheme 77: Cozzi's S_N1-Like Alkylation of Aldehydes with Allylic Aryl Alcohols.

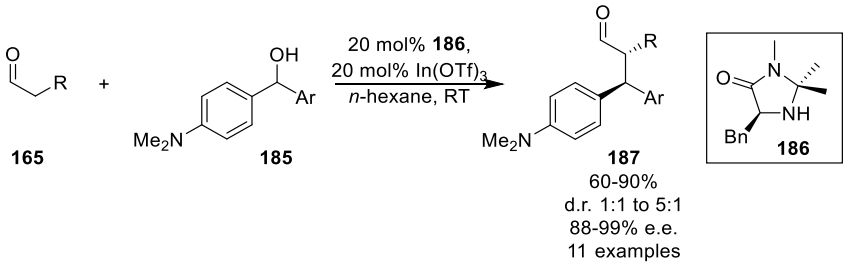
A study of the role of the indium salt was also conducted using the model electrophile substrate **182**. Upon reaction with the indium salt was shown to first form the ether species **183** which was then transformed to active carbocation **I** by Lewis acid activation (Scheme 78). This was also confirmed by the direct use of the ethers **183** and **184** in the alkylation reaction; in both cases the reaction proceeded with the same yield and selectivity as with the alcohol. This suggests the importance of the

indium salt in the Lewis acid activation of the ether compounds to the carbocationic electrophile **I** and also for the formation of the ether species from the alcohol through dimerization.



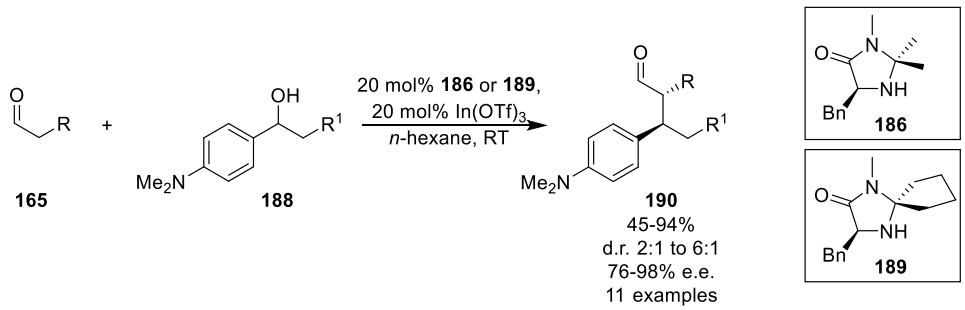
*Scheme 78: Activation of Alcohol **182** and Ether **184** with Indium Bromide to Give Carbocation **I**.*

This advance was also applied to the asymmetric diaryl alcohol type electrophiles, which gave poor results in the initial study.[10] Using amine **186** and indium salts, aldehydes **187** were isolated with selectivities ranging from 2:1 to 5:1 (Scheme 79).[58] Furthermore, the enantioselectivity was in general above 90%. The use of catalyst **180**, other indium salts (including $InBr_3$) and solvents decreased the enantioselectivity and frequently the yield also.



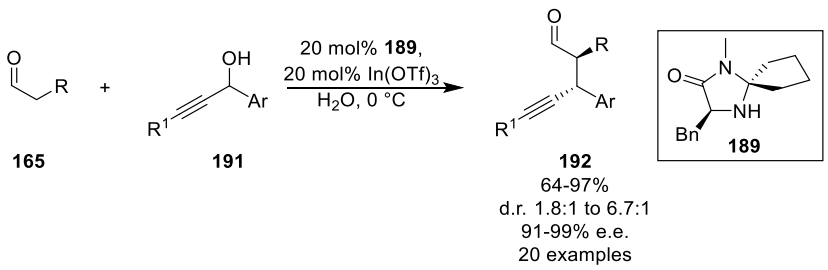
Scheme 79: Indium Salts in the Organocatalytic S_N1-Like Alkylations with Alcohols by Cozzi.

The same reaction conditions were also applied to benzylic alcohols **188** without the secondary aromatic substituent (Scheme 80).[58] This was due to the use of catalysts **186** or **189** and the *para*-dimethylaminophenyl group being sufficiently stabilizing to form the carbocationic species. Apart from one case the yields were all good to exceptional and the diastereoselectivity was moderate to high and apart form one example the enantioselectivity was over 90%.



*Scheme 80: Organocatalytic S_N1 Alkylation with Benzylic Alcohols **188** by Cozzi.*

The same strategy was also applied to propargylic alcohols **191** with high success using catalyst **189** (Scheme 81). The use of water as the solvent was essential for the selectivity and yield.[59] Various aromatic groups and substituted triple bonds in **191** were well tolerated and had little effect on the selectivity (lowest d.r. 2.1:1) or the yield of alkylated products **192**, except in the case of using indolyl groups which lowered significantly or reversed the *anti*-selectivity (d.r. 1.3:1 and 1:1.4, not shown in Scheme 81). Other aldehydes were also tolerated but with a larger decrease in the selectivity.



*Scheme 81: Alkylation of Aldehydes with Propargylic Alcohols **191** in an Organocatalytic SN1-Like Process by Cozzi.*

One thing all the previous reactions have in common is the reaction mechanism hinging on a carbocationic species generated in the reaction. If this species could be used directly it would remove the need for activation in the reaction medium and simplify the process. Therefore, Cozzi also investigated the use of carbocationic salts in the organocatalytic alkylation reactions.

Expansion to Carbocationic Salts

Insprired by his S_N1 alkylations and his work on oxidative C-H activation of electrophilic species,[10,60] Cozzi investigated the use of stable carbocationic salts as electrophiles in asymmetric alkylation reactions. For instance, electrophile (**193**) may act as an equivalent to the active species **I** formed in the reaction mixture of the previous methodology from the alcohol **165** (Figure 23), as the difference is only in the counterion and the carbocationic species is the same, the reactivity should be similar without the need for activation.

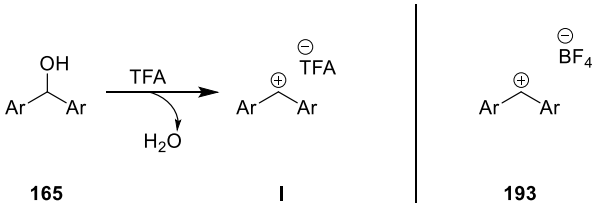
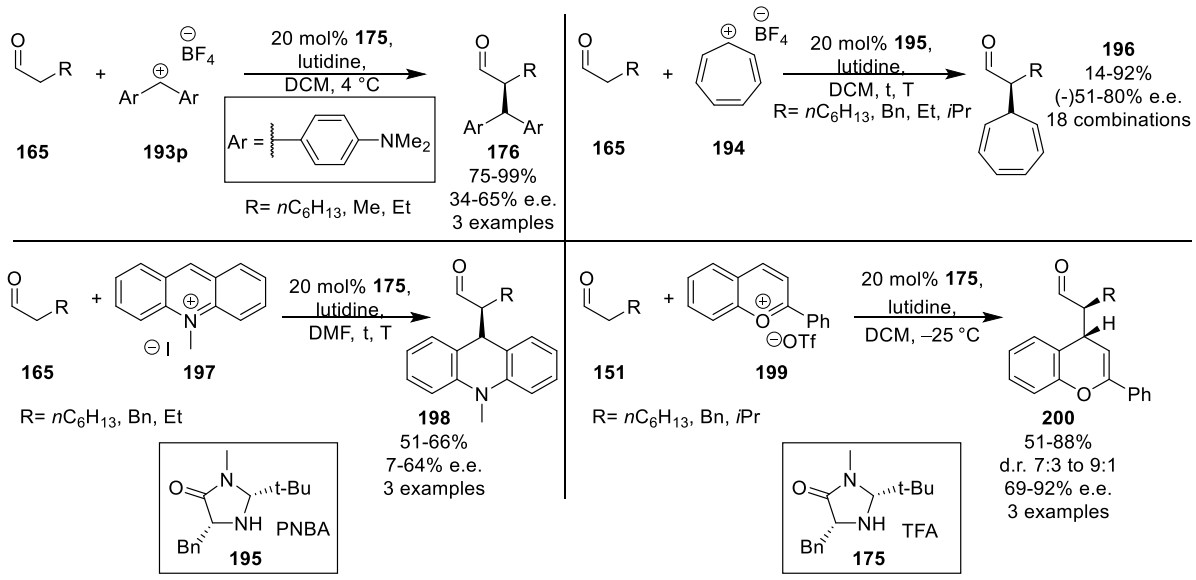


Figure 23: Left: Previous in-situ *Activation of Electrophile **165** to form the Active Species; Right: Stable Carbocationic Salt Equivalent **193**.*

The *para*-amino version of this electrophile **193p**, along with the commercially available tropylium tetrafluoroborate salt **194** and the prepared methylacridinium iodide (**197**) and flavylium triflate (**199**) salts were submitted to the organocatalytic alkylation conditions using MacMillan catalysts **175** and **195** (Scheme 82).[61]

The cationic salt derivative **193p** of the diaryl alcohol **172p**/**185p** gave the same products **176** with high to exceptional yield for the three aldehydes used (isopropyl did not give the corresponding product). However, the enantioselectivity was somewhat poor with the best case of 65% achieved with the least hindered methyl R-group, drastically dropping with subsequently larger groups (Top Left, Scheme 82). Moving to the less stabilised tropylium tetrafluoroborate electrophile **194** the results were somewhat sporadic, with the yields of the product **196** being affected by both temperature and time (Top Right, Scheme 82). The selectivity was highly dependent on the temperature with changes greatly reducing or reversing entirely the enantioselectivity of the reaction. The selection of the base also affected the selectivity with potassium carbonate reversing the selectivity of that of lutidine. More important still was the selection of the catalyst's acid component with the *para*-nitrobenzoic acid (PNBA) version **195** giving a higher selectivity than the trifluoroacetic acid (TFA) catalyst **175**.

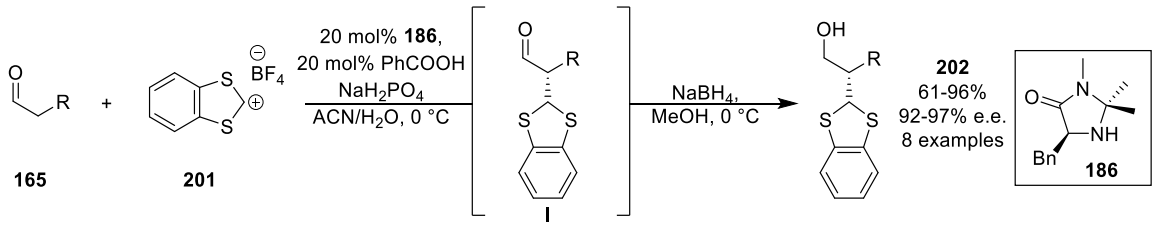


Scheme 82: Cozzi's Studies of Alkylations Using Carbocationic Salts. Top Left: Diaryl Methylium Tetrafluoroborate; Top Right: Tropylium Tetrafluoroborate; Bottom Left: Methylacridinium Iodide; Bottom Right: Flavylium Triflate.

The use of methylacridinium iodide **197** was more consistent, with the yields of **198** being moderate to good and not being affected significantly by the temperature (Bottom Left, Scheme 82). Due to the insolubility of the salt **197** the reaction was carried out in dimethylformamide. The selectivity was moderate for the ethyl and hexyl R-groups (63 and 64%), but the benzyl group gave racemic results. Using a hexafluoroantimonate counterion reduced the selectivity to 19%, highlighting the importance of the counterion choice in carbocationic electrophiles. Finally, the use of the flavylium triflate salt **199** gave the product **200** with two new stereocentres (Bottom Right, Scheme 82). Low temperatures favoured the selectivity whilst lowering the yield, with the selectivity being high to excellent with moderate to excellent yields. Notably the enantiopurity of the minor diastereomer was considerably lower than that of the major. The use of the tetrafluoroborate salt lowered the yield and selectivity significantly (13% yield, 1.1:1 d.r., 22% e.e.), reiterating the effects the counterion.

In all the cases the stereoselectivity comes, as in the previous S_N1 reactions, from enamines with one π-face blocked by the chiral groups of the organocatalyst, forcing the approach of the electrophile to the other face. In this methodology the enamine reacts directly with the carbocation, without any activation or any formal substitution, hence the S_N1-like character of the reaction. Whilst the concept was promising both the yields and selectvities had room for improvement.

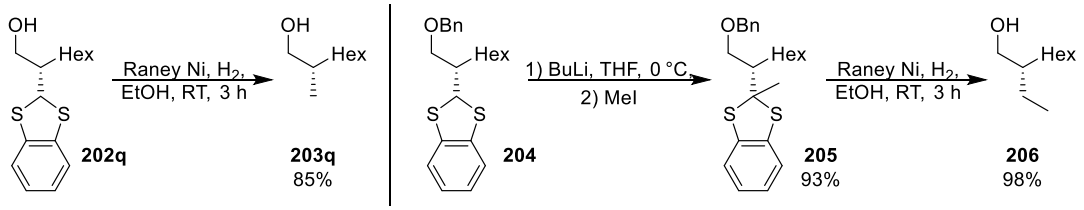
After the initial proof using a election of carbocationic salts, Cozzi moved to a new carbocation species: the benzodithiolylium ion **201**.[62,63] Whilst the initial adduct **I** was achieved, it proved to be unstable to racemisation and the direct reduction to the alcohol product **202** was necessary for reliable results (Scheme 83).[62] The MacMillan catalyst **186** was chosen after a screening of various catalysts for the higher selectivity. The solvent also had a large effect on the selectivity with water and mixtures of water giving a much larger enantioselectivity than dichloromethane. Finally, monosodium phosphate was used over organic bases to eliminate side reactions with the organic salt.



Scheme 83: Cozzi's Organocatalytic Alkylation of Aldehydes with Benzodithiolylium Tetrafluoroborate.

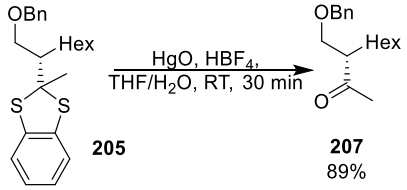
Yields ranged from good to exceptional and enantioselectivities averaging an excellent 95%. The tolerance of functional groups was broad with alkyl and aryl R-groups, protected oxygen and nitrogen groups (gave a lower yields), or nitrile groups all being tolerated with little change in the selectivity. Interestingly R-groups containing another potentially electrophilic position in form of a chloride or acetal showed no self-condensation side reactions.

One of the most inviting characteristics of using the benzodithiolyium group as an alkylating agent is its ability to be removed leaving the central carbon in the molecule. When used in the initial alkylated products **202**, upon reductive elimination with Raney nickel leaves a methyl group in place of the benzodithiolyium moiety (product **203**). This can be seen in the left of Scheme 84 using the hexyl derivative **202q** to give the deprotected **203q** in an excellent yield. Additionally, the carbon between the two sulphur atoms can be deprotonated by butyl lithium, which allows for the alkylation using alkyl halides. Using the protected alcohol **204** derived from the protection of **202q**, a methyl group was introduced using methyl iodide to give product **205** (Right, Scheme 84). When submitted to the reductive elimination conditions the group revealed is an ethyl group, giving product **206**. Incidentally the benzyl protecting group is also removed leaving once again the free alcohol. This methodology can be used to extend the revealed alkyl group and add functionality to the final products if desired.



Scheme 84: Utility of Benzodithiolyium Group: Left: Reductive Removal to Reveal Methyl Group; Right: Alkylation of Central Carbon to Change the Group Revealed by Reductive Elimination.

The intermediate **205** also opens a removal pathway not available to the initial product **202**. The oxidative removal of the benzodithiolyium group from **205** with mercury oxide and tetrafluoroboric acid gives the ketone product **207** in an excellent yield (Scheme 85).[64] In this case the alcohol remains protected giving a β-benzyloxy ketone. Again, this was repeated using the benzyl derivative of **205** and the results were comparable.

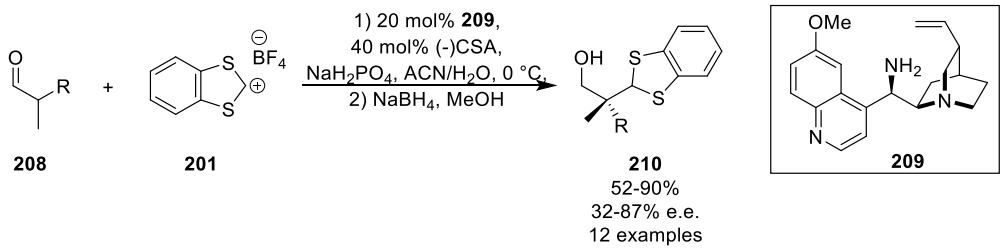


Scheme 85: Oxidative Removal of Benzodithiolyium to Leave a Ketone Product.

In all cases the manipulation and removal of the benzodithiolyium group produced no decrease in the enantiopurity of the products. The methodology is not only highly selective in the alkylation reaction

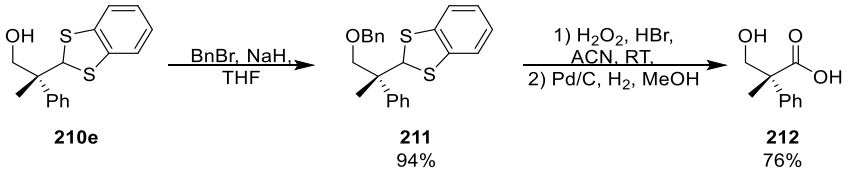
but due to the versatility of the electrophile a wide variety of enantiopure synthons can be synthesised with facile changes in either the starting material, secondary alkylation electrophile or the removal process.

The methodology was later applied to disubstituted α-methyl aldehydes **208** which presented a further challenge due to the increased steric hinderance creating quaternary centres.[66] Various organocatalysts were screened for the reaction, but the most effective was a quinidine catalyst used by Melchiorrie (**209**).[43] This catalyst, with chiral additive CSA, gave product **210** in moderate to excellent yields and selectivity ranging from poor to high (Scheme 86). Once again, the initial aldehyde adduct was unstable and direct reduction was required. The selectivity was highly dependent on the R-group, with aromatic substituents performing considerably better (68-87% e.e.) than alkyl (32-44% e.e.). The nature of the aromatic group also affected the reaction, with *ortho*-substituted groups inhibiting the reaction and *meta*-substituted groups improving the selectivity.



Scheme 86: Cozzi's Expansion of the Organocatalytic Alkylation with Benzodithiolyium Tetrafluoroborate to More Hindered Aldehydes.

Again, the benzodithiolyium group was shown to be synthetically useful, performing again the removals shown in the previous work (see Scheme 84). A different oxidative removal was also described: using hydrogen peroxide with the benzyl protected alcohol **211** gave a carboxylic acid product which on subsequent deprotection gave alcohol **212** in a high yield (Scheme 87).



Scheme 87: New Process for the Removal of Benzodithiolyium to Leave a Carboxylic Acid.

Whilst the enantioselectivity could be improved this expansion of the methodology is a meaningful advancement and represents a competitive route to highly complex enantioenriched structures.

These results show not just the viability but the potential of a methodology of alkylation using carbocationic salts as electrophiles in S_N1-like reactions. However, the selectivity achieved so far by organocatalysis is low and too variable to be used on a wide synthetic application. The conditions are also very restrictive, only being able to be used for either cyclic ketones, or aldehydes, and each type of starting material and/or electrophile requiring differing catalysts, solvents, and reaction conditions. The development of a universal methodology that can tolerate various starting materials or electrophiles with minimal change in the conditions and a sole catalyst is a lucrative endeavour. Our experience with S_N1 reactions catalysed by nickel complexes and the precedent set in organocatalysis in S_N1-like reactions led us to believe that we could combine this with the use of carbocationic salts as electrophiles in a more general methodology.

Carbocationic Salts as Electrophiles

The use of carbocationic salts as electrophiles in alkylation reactions is not a new concept in organic synthesis. In fact in the 50's and 60's Shriner, Soder, Klingsberg and Looker all published papers dealing with the use of carbocation salts as electrophiles in the S_EAr alkylation of dimethylaniline and its derivatives.[67–69] Shriner used the flavylium chlorate salt **216**, the same used by Cozzi with a different counterion, to give product **217** (Figure 24).[67] Soder used methylbenzodithiolyium chlorate **218** to give the corresponding product **219**;[68] Klingsberg used the dithiolium chlorate **220** to give **221**,[70] and finally, Looker used the tropylium tetrafluoroborate salt **194**, to give **222**.[69]

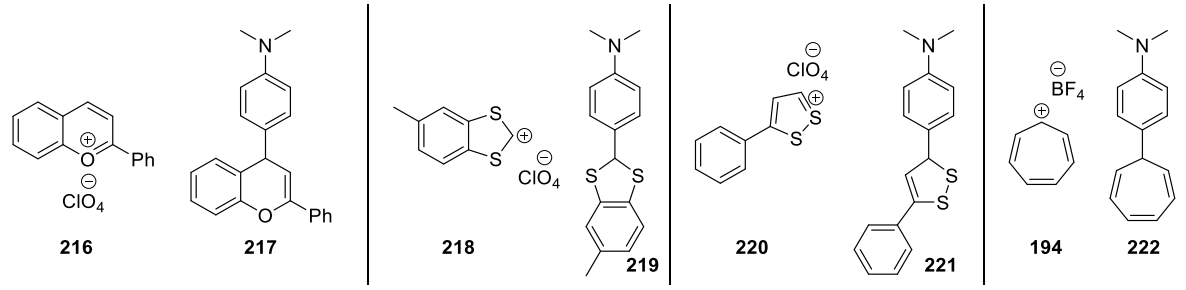
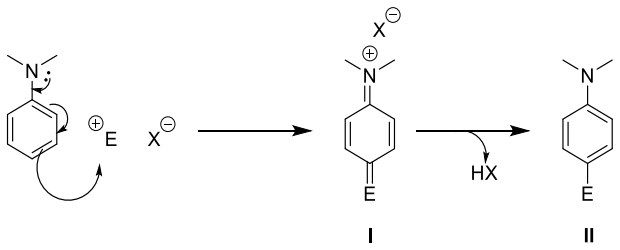


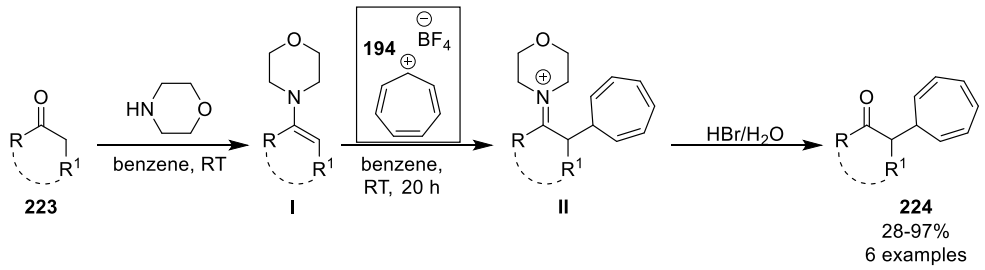
*Figure 24: Alkylation of Dimethylaniline, Electrophile and Product Shown. Left: Shriner and Flavylium Salt **216**; Centre Left: Soder and Methyl-benzodithiolyium Salt **218**; Centre Right: Klingsberg and 1,2-Dithiolium Salt **220**; Right: Looker and Tropylium Tetrafluoroborate **194**.*

Naturally, products **217**, **219**, and **221** were prepared as racemic mixtures, but it was the first proof of the viability of the use of carbocationic salts' in carbon-carbon bond forming reactions. The mechanism involved the attack of the nitrogen lone pair, which was pushed through the molecule, through the para position of the ring to the electrophile (Scheme 88). This forms an unstable intermediate **I** which is deprotonated to give the final product **II**. Looker also expanded the methodology of alkylation using tropylium tetrafluoroborate as an electrophile to the analogous reaction with phenol nucleophiles.[71]



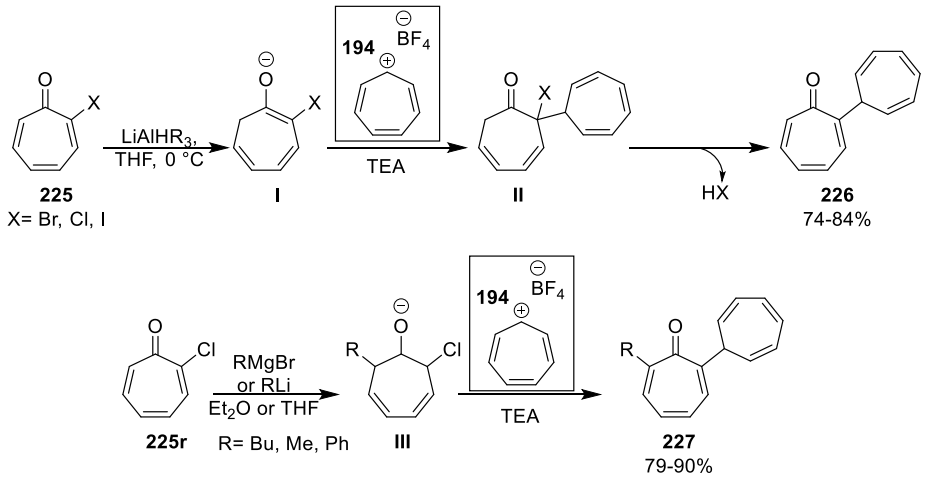
Scheme 88: Mechanism of Alkylation of Dimethylaniline with Cationic Salts.

Taking advantage of such concepts Soma later described the alkylation of ketones and propionaldehyde using the reaction of a stoichiometric preformed morpholine enamine with tropylium tetrafluoroborate **194** (Scheme 89).[72] This reaction gave an intermediate **II** which was liberated to furnish the final product **224** in yields that ranged from low to exceptional. Whilst this was a racemic procedure, it showed again the viability of using carbocationic salts in alkylation reactions. Furthermore, it laid the foundation for the later use of chiral amines in enantioselective enamine additions to carbocationic salts.



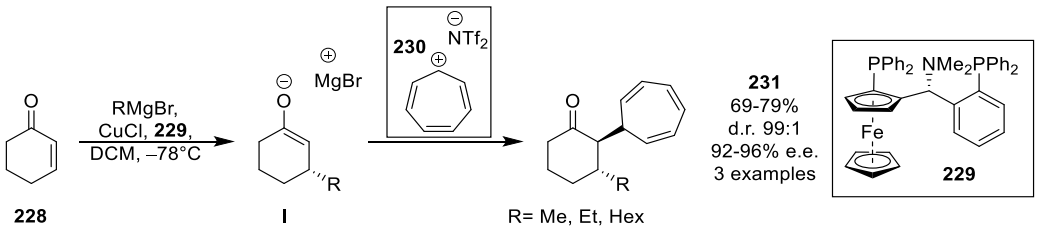
Scheme 89: Soma's Alkylation of Enamines Using Tropylium Tetrafluoroborate.

The use of tropylium tetrafluoroborate **194** for the alkylation of metal enolates was further demonstrated by Nitta.[73] As shown in Scheme 90, enolate **I** was formed from the cyclic halotropone **225** upon its reaction with a nucleophile. The first case was the use of a hydride from different lithium aluminium hydride complexes to form the intermediate **I** which was then added to the cation in triethyl amine to form the adduct **II** (Top, Scheme 90). This product then is deprotonated, returning the conjugation of the system, and expulsing the halide in an elimination step to give product **226** in high to excellent yields. The initial nucleophile was not limited to the hydride ion; either additions of Grignard or lithium carbanions to chlorotropone **225r** gave the related enolate species **III**, which was then similarly quenched with the tropylium salt to give product **227** in high to excellent yields (Bottom, Scheme 90).



*Scheme 90: Nitta's Work on the Alkylation of Metal Enolates Using Tropylium Tetrafluoroborate. Top: Enolate from Reaction of **225** with Hydride; Bottom: Formation of Enolate Through Addition of Organometallic Compound.*

The development of an asymmetric alkylation using the tropylium salt as a quenching agent was developed by Šebesta in his use of copper(I) catalysed addition of Grignard reagents to unsaturated carbonyl compounds.[75] Using cyclohexenone **228** and various Grignard reagents he performed conjugate additions catalysed by copper(I) and the chiral ligand **229** to give the chiral enolate **I** (Scheme 91). This was then reacted with the tropylium bis(trifluoromethanesulfonyl)amide salt **230** to trap the enolate and give *anti* product **231** in good to high yields with complete diasterocontrol and excellent enantiocontrol.



Scheme 91: Šebesta's Copper Catalysed Conjugate Addition with Enolate Trapping with Tropylium Cation.

The use of the bis(trifluoromethanesulfonyl)amide counterion was essential to the high yield, whilst the reaction worked with the tetrafluoroborate salt **194**, the yield was less than 20% due to the low solubility in organic solvents. A counterion exchange was performed to yield the triflic amide salt from the tetrafluoroborate salt. The reaction with acyclic enones was also investigated but gave low yields, low enantioselectivities and no π-face selectivity of the enolate quench giving an equimolar ratio of diastereomers.

The methodology was further expanded to other electrophiles with varying success (Figure 25). The reaction with diarylmethyl carbocation **193k** led to the product **232** with a low yield and diasteroselectivity but a high enantioselectivity. Using the benzodithiolyium salt **233** the results were considerably better, the yield and enantioselectivity of product **234** was high and the diastereocontrol complete. Finally, the quench with the trityl cation **235** was attempted, the reaction was conducted with the achiral 1,1'-bis(diphenylphosphino)ferrocene ligand so the product **236** was racemic. The yield of the reaction was very low and not of the expected product; instead of the addition at the central carbon the addition occurred at the *para*-position of one of the phenyl rings followed by a further rearomatisation.

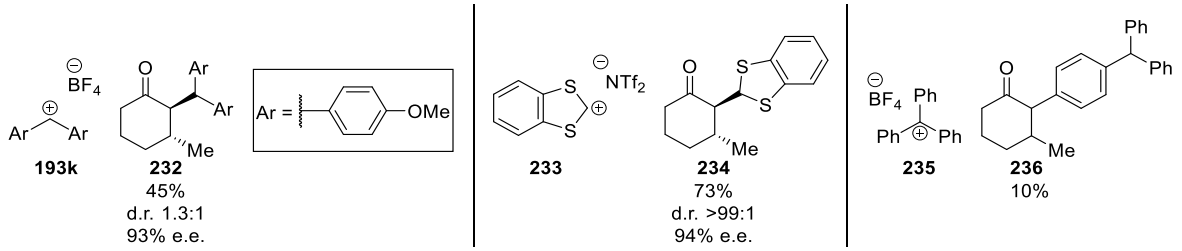
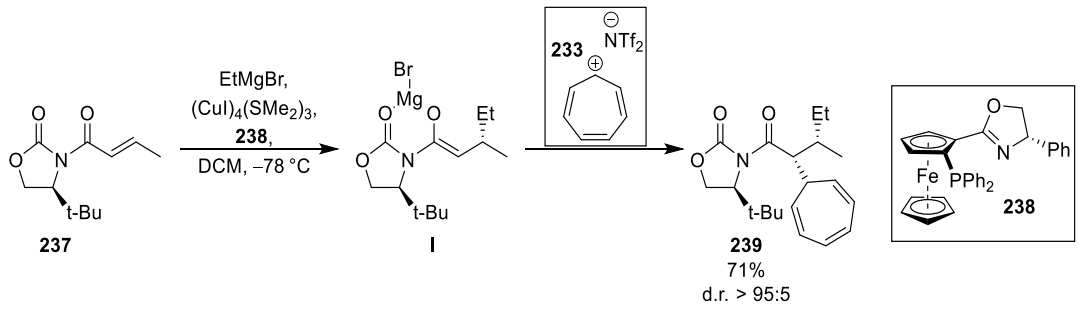


Figure 25: Expansion to Other Electrophiles by Šebesta. Left: Diarylmethylium Salt; Centre: Benzodithiolyium Salt; Right: Tritylium Salt.

Perhaps the most important reaction described by Šebesta was a copper(I) catalysed conjugate addition to *N*-enoyl oxazolidine **237** and its subsequent quench with the tropylium cationic salt to give product **239** in a good yield and excellent selectivity (Scheme 92). The chiral auxiliary controls the stereochemical outcome of the reaction and provides an excellent diastereomeric ratio of the resultant alkylated compound **239**.



Scheme 92: Šebesta's Conjugate Addition to N*-Enoyl Substrate with Cationic Salt Enolate Trapping.*

The chiral enolate **I** is similar to the enolate derived from *N*-acyl oxazolidinone compounds via deprotonation, the fact it can be highly selectively alkylated using a carbocationic salt led us to believe we could develop a methodology for the catalytic formation of chiral enolate from *N*-acyl auxiliaries and use them in a highly selective direct alkylation reaction using cationic carbenium salts.

Design of Our Approach

Our proposal for a new alkylation reaction was based on various ideas collected from the fields of S_N1 chemistry, especially those with carbocationic salts, the use of carbocations as electrophiles and our experience in the reaction of catalytically generated enolates with *in-situ* activated carbenium ions. The idea was to try and combine these fields and develop a combined methodology, which was highly selective and high yielding, for the catalytic alkylation using carbocationic salts.

Previous Work from Our Group

Our group developed a S_N1-like reaction using catalytically generated chiral nickel(II) enolates **I** from *N*-acyl thiazolidinethiones, which reacted with the oxocarbenium II produced *in situ* by treatment of trimethyl orthoformate with TESOTf (Figure 26).[76] The achiral nickel chloride complexes were activated in-situ to the triflate catalyst with triethylsilyl triflate,[77] which can then coordinate to the starting material and with the organic base, form the enolate species **I**. The triflate also acted as a Lewis acid to activate the electrophile, forming the oxocarbenium **II** through abstraction of a methoxy group.

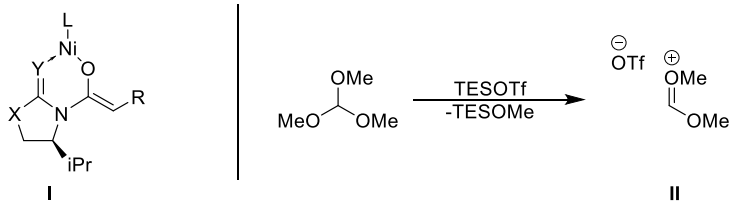
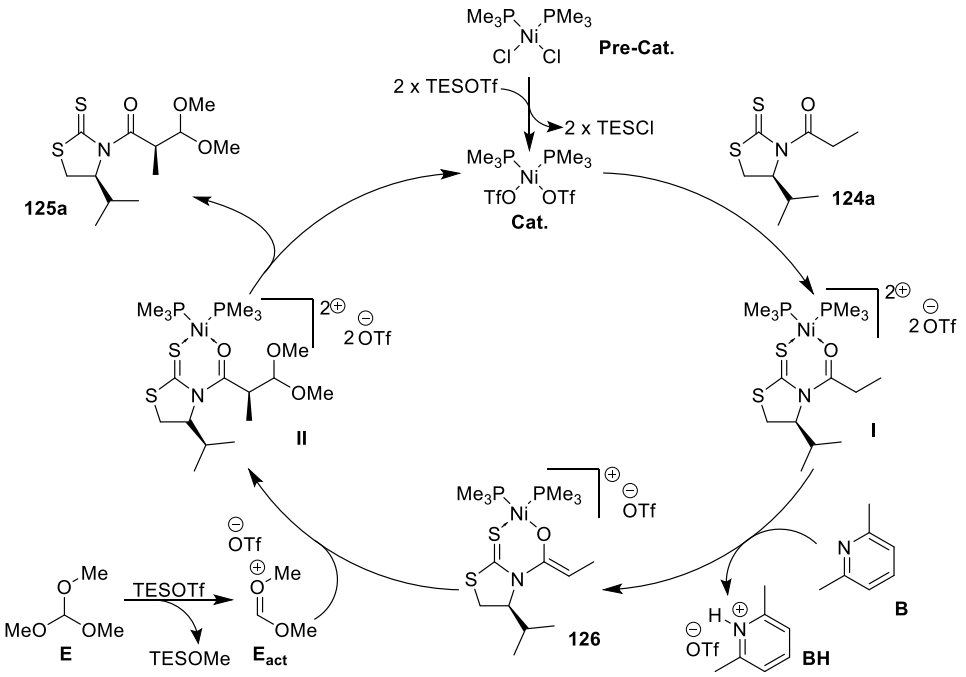


Figure 26: Left: Catalytically Generated Enolate I; Right: In-situ Activation of Trimethyl Orthoformate to Give Electrophilic Species II.

The catalytic cycle for the reaction of trimethyl orthoformate with chiral *N*-acyl thiazolidinethiones is shown below in Scheme 55. The catalyst is first introduced into the catalytic cycle by the activation of the pre-catalyst through the ligand exchange with triethylsilyl triflate. This can then interact with the starting material **124a** to form the coordinated complex **I**, which is deprotonated by the base to give the *Z*-enolate **126**. This then reacts with the activated electrophile to give the compound **II** which dissociates to give the adduct **125a** and the catalyst re-enters the cycle. The electrophile activation is also achieved through reaction with triethylsilyl triflate which, through the abstraction of a methoxy group, forms an oxocarbenium ion.



Scheme 93: Catalytic Cycle of Trimethyl Orthoformate Reaction.

The choice of the chiral auxiliary was important for the reaction to work correctly, comparing the propanoyl acyl chain the results using different auxiliaries was especially clear (Figure 27). Using the oxazolidine auxiliary, no product **240a** was found making the classical Evans auxiliary unfeasible for the reaction.[78] Moving to an oxazolidinethione auxiliary allowed the reaction to take place,[79] albeit in a moderate yield of **240a**, with complete control over the new chiral centre. Finally, using the thiazolidinethione auxiliary,[80] an excellent yield of a single diastereoisomer of **125a**.

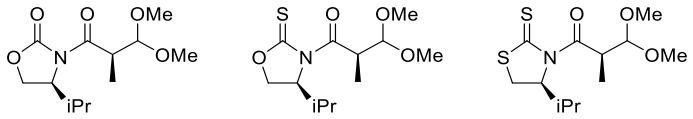
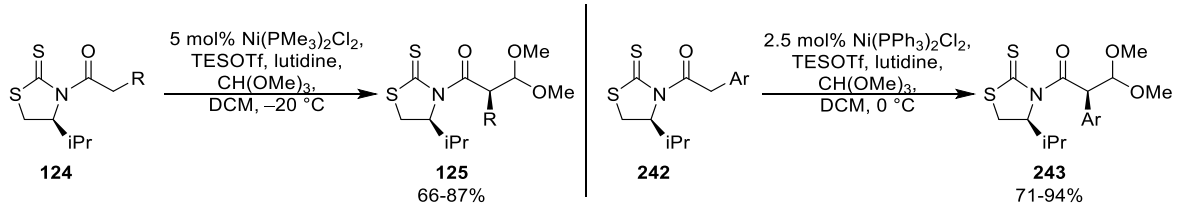


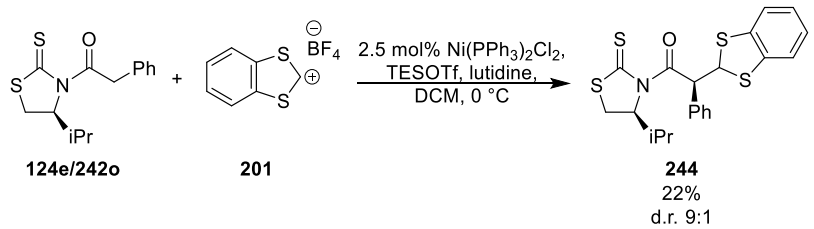
Figure 27: Products from Reaction with Different Chiral Auxiliary Starting Materials.

With the chiral auxiliary chosen the reaction was tested with two different classes of starting material with two slightly different methods of reaction. For starting materials containing an aryl group in the α-position (**242**), the triphenylphosphine derivative of the nickel(II) complex was used to give **243** in a high to exceptional yield of only one diastereoisomer (Right, Scheme 94). For those not containing an aryl group (**124**) the trimethylphosphine complex was used to give products **125** in good to excellent yields, again as a single diastereoisomer (Left, Scheme 94).



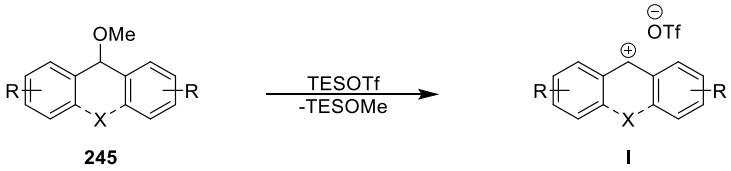
Scheme 94: Orthoformate Alkylation of N*-Acyl Thiazolidinethiones. Left: Non-Aromatic Starting Materials; Right: Aromatic Starting Materials.*

With the method applied to various starting materials with success and the activated electrophile being a carbocation, an attempt was made to conduct the direct reaction with a stable carbocationic salt. The benzodithiolyium tetrafluoroborate salt **201** was chosen due to its availability and synthetic potential. Using the α-phenyl starting material **144e**/**242o** a low yield of **244** was obtained in a 9:1 mixture of diastereomers. So it was clear further work was needed to improve the process.



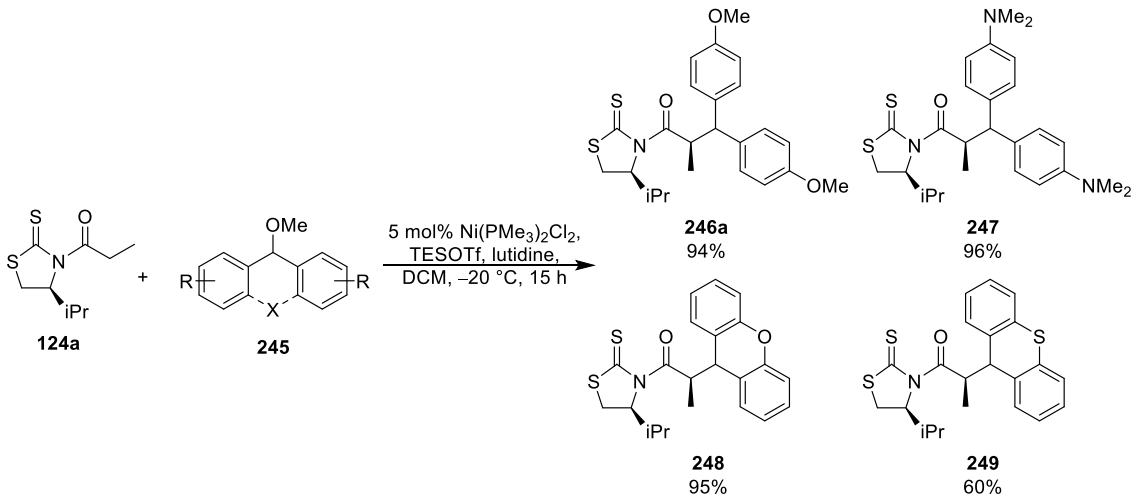
Scheme 95: Attempt at Using a Carbocationic Salt in the Alkylation Reaction.

Our group also expanded the methodology to another class of electrophile compounds: diarylmethyl methyl ethers **245**.[81] Again, these compounds were activated *in-situ* to give the true electrophilic species, in this case a carbenium ion **I** (Scheme 96). The reaction was catalysed by the trimethylphosphine nickel triflate catalyst prepared *in-situ* from the chloride salt as in the previous paper.[76]



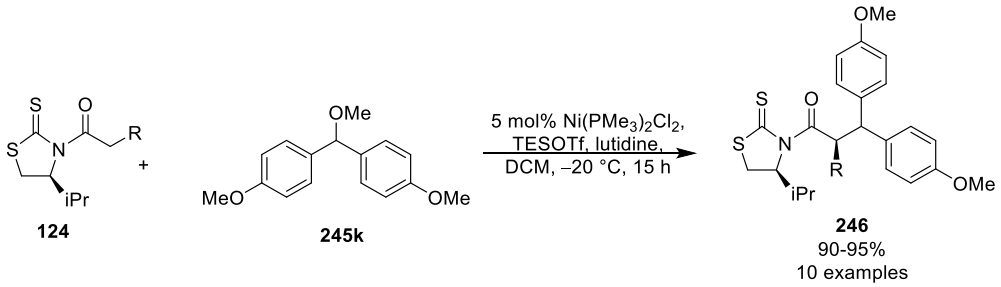
*Scheme 96: Activation of Methyl Ether **245** with Triethylsilyl Triflate.*

The reaction was initially probed with various diarylmethyl methyl ethers, with four giving good results (Scheme 97). The highly stabilising *para*-methoxy and *para*-dimethylamine substituted electrophiles both gave exceptional yields of a single diastereoisomer (**246a** and **247** respectively). Having an ether bridge at the *ortho*-position also gave an exceptional yield of one diastereoisomer of **248**. Whilst the reaction worked with a thioether bridge at the *ortho*-position and gave complete control over the new stereocentre the yield of **249** was significantly lower. The use of a *para*-methyl derivative of **245** led to the product in a very low yield of 10% (not shown); the reason for this is probably the methyl groups stabilising effect not being high enough to efficiently form the cationic species **I**. Without any stabilising groups the reaction did not occur, and no product was observed most likely due to the cation not being formed in the activation process.



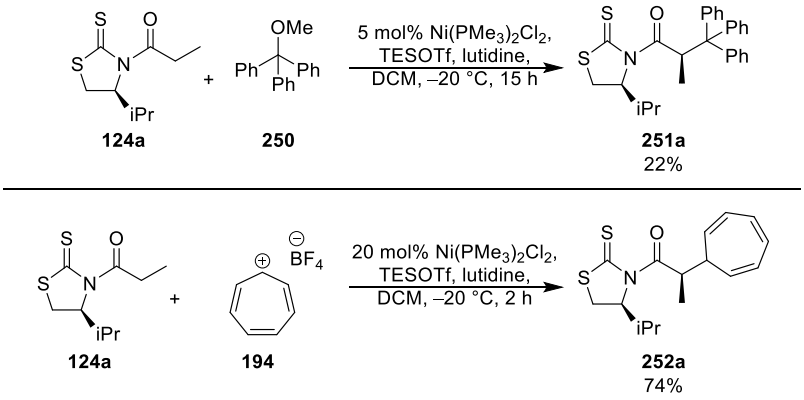
*Scheme 97: Alkylation of 124**a** with Different Diarylmethyl Methyl Ethers.*

The methodology was then expanded to different acyl chains using the *para*-methoxy electrophile **243a** with overwhelming success (Scheme 98). The minimum yield over ten different examples was 90% and, in all cases, the stereocontrol was complete. The tolerance of functional groups was also broad, with various more hindered or unsaturated chains working without problems. Protected oxygen and nitrogen groups at the α-position were also well tolerated with two examples of each being tested.



*Scheme 98: Alkylation of Different Starting Materials with Methyl Ether **245k**.*

Finally, two further electrophiles were examined. The sterically challenging trityl group was introduced using the methyl ether **243b** giving the expected product **245** in a low yield (Top, Scheme 99). The low yield was likely due to the steric complexity making the approach of the electrophile difficult; the possible alkylation at the external phenyl ring described by Šebasta was also in potential competition to the desired alkylation pathway.[75] The reaction with tropylium tetrafluoroborate (**184**) required a large catalyst loading to achieve a high yield of **246a** (Bottom, Scheme 99).The result was somewhat inconsistent, with repeated reactions not always giving the same yield. Whilst the reaction was clear proof that carbocatioinic salts could be used in the nickel-catalysed alkylation further work is needed to improve the process in terms of: yield, efficiency, reliability and the application to other substrates and cations.



Scheme 99: Application Attempts to Other Electrophiles. Top: Trityl Methyl Ether; Bottom: Tropylium Tetrafluoroborate.

Initial Results

One of the first things we found causing the unreliability of the reaction was the degradation of the tropylium salt **194** under ambient conditions (Figure 28), running the same reaction in the same conditions weeks apart gave worse results. The use of fresh reagents and the storage in the fridge under nitrogen for a maximum timeframe greatly increased the reliability of the results. We also believed that solubility of the salt in organic solvents could be an issue. To combat this we performed a counterion exchange described by Šebasta,[75] to give the triflic amide salt **230**. This however did not improve the yield of the reaction.

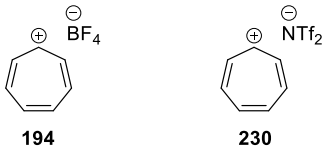


Figure 28: Tropylium Salts.

We then aimed to fully optimise all the reaction conditions and then apply the new reaction conditions to a wide range of starting materials. The different starting materials were chosen to have differing steric constraints and levels of unsaturation, various functional groups including esters and protected alcohol and amines at the α-position. One of the acyl chains that did not work despite our attempts was the benzyl protected α-alcohol, which gave low yields of the desired product.

Case of Triphenyl Methyl Salt

One of the electrophiles we had used previously that we envisaged taking advantage of was the trityl cation. Whilst previously prepared *in-situ* via Lewis acid activation the tetrafluoroborate salt is also commercially available. We saw this as a challenge as previously the maximum yield achieved of the desired adduct was 22%, and would suggest if this cationic salt would work then it would be easy to believe that in general our reaction could be applied to any carbocationic salts.

When we submitted the salt **235** to the reaction conditions, we observed three products formed in the reaction and were able to isolate them and determine their structure. The desired adduct **251a** was formed in a 25% ratio in the crude mixture, along with two products arising from the attack at the external para position of the phenyl rings (Figure 29). The initial adduct **253** was unstable, which when left over time converted mostly to the aromatised product **254**. Interestingly when submitted to the original reaction conditions without the addition of the electrophile, isolated **253** gave not only the expected stable derivative **254** but also a certain amount of **251a**.

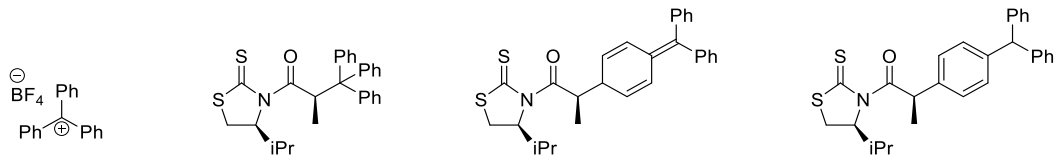
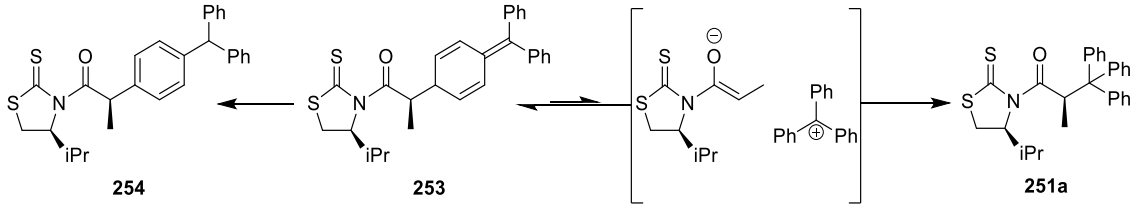


*Figure 29: Electrophile **235** and the Initial Ratio of Products Formed in its Reaction.*

The obtention of the adduct **251a** from **253** suggests that the formation of the unstable adduct **247** is reversible and the electrophile and enolate species can be reformed in the reaction (Scheme 100). This allows two possibilities: the reformation of the unstable adduct **253** or the formation of the desired adduct **251a**. Over time, due to the reversibility of the formation of the unstable adduct and the irreversible formation of **251a** (both **251a** and **254** were stable in the reaction conditions and therefore irreversible), over time the quantity of the desired product should increase. However, the product **253** could also irreversibly form the aromatic compound **254** so we aimed to investigate if time or other factors could increase the yield of the desired product **251a** to a practical level.



*Scheme 100: Reactivity of **253**, Aromatisation and Reversibility of Addition.*

In fact the reversibility of this reaction was something hinted by Cozzi in his organocatalytic alkylation of enamines with diarylmethyl alcohols.[10] In his catalytic cycle he suggested the formation of the carbon-carbon bond through the reaction of the enamine with the activated diaryl cation could potentially be reversible if the carbocations stability was high enough and of a similar electrophilicity to the enamine.

Finally, we also aimed to prove the utility of using the thiazolidinethione auxiliary by effecting its removal to leave various functional groups as enantiopure chiral synthons. With all these questions in mind we conducted a full investigation into the nickel catalysed alkylation reaction using stable carbocationic salts which is summarised in the following publication.[82]

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Diastereoselective and Catalytic α-Alkylation of Chiral *N*-Acyl Thiazolidinethiones with Stable Carbocationic Salts

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Supporting Information

ABSTRACT: Direct nickel-catalyzed alkylation of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones using a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, has been developed for tropylium and trityl tetrafluoroborate salts. The reaction provides a single diastereomer of the corresponding adducts in good to high yields, which, in turn, can be easily converted into a wide array of enantiomerically pure compounds that are difficult to obtain by other asymmetric procedures.

The stereoselective alkylation of metal enolates is one of the most significant methods to construct the carbon backbone of chiral compounds.[1] Particularly, the alkylations of lithium enolates from chiral *N*-acyl-1,3-oxazolidin-2-ones[2] or *N*-acylpseudoephedrines[3] are among the most successful and reliable approaches to the stereoselective construction of carbon−carbon bonds and have been largely employed in the synthesis of biologically active products.[4] Besides such well-established procedures, the better understanding of the structure and the reactivity of lithium enolates achieved during the last decades has revealed clues to tackle increasingly complicated challenges.[5,6] Parallel to these achievements, emphasis on asymmetric and catalytic transformations has also stimulated the development of insightful phase-transfer alkylation reactions.[7] However, different these methods may seem, they all feature the S_N2 addition of a chiral enolate to a suitable electrophile, preferentially an activated haloalkane, which restricts their scope and makes it therefore desirable to devise new approaches to prepare more elaborate or sterically hindered compounds.

In this context, methods based on an S_N1-like mechanism may be regarded as an appealing alternative. Highly enantioselective palladium- and iridium-catalyzed allylations of ketone enolates, in which the chiral cationic allyl−metal complex determines the stereochemical outcome of the addition, are proof of the synthetic potential of such an approach.[8−10] The opposite strategy, which involves the addition of a chiral nucleophile to a cationic intermediate, has also proved to be successful. Indeed, Evans demonstrated that titanium(IV) enolates could undergo reaction with orthoesters, acetals, and alkyl halides with a predisposition toward S_N1-like transformations.[11] This and subsequent contributions took advantage of heteroatom-stabilized intermediates,[12−14] but parallel transformations involving simple carbenium intermediates have also been described more recently. For instance, Jacobsen reported the enantioselective α-alkylation of aldehydes catalyzed by aminothiourea derivatives via an S_N1 pathway,[15] whereas the groups of Melchiorre[16] and Cozzi[17] have firmly established the feasibility of asymmetric organocatalytic alkylation of aldehydes through S_N1-type additions of chiral enamines to carbenium intermediates.[18] In contrast, similar procedures based on chiral metal enolates have been hardly reported, and most of them require activated carbonyl groups.[19,20]

As part of our studies aimed at the development of new catalytic and stereoselective carbon−carbon bond-forming reactions,[21] we have recently described a nickel-catalyzed alkylation of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with diarylmethyl methyl ethers, which provide the corresponding adducts in high yields and with absolute stereocontrol.[22] Considering that the reaction involves the addition of a nickel(II) enolate to a cationic intermediate generated in situ, we thus envisaged that a related procedure based on the direct addition to naked carbenium cations[23] would avoid the need to activate the electrophile, greatly simplifying the experimental procedure and attaining a more atom-economic process, and might also provide a way to introduce sterically hindered groups, a challenge that still remains elusive. Herein, we describe the direct and diastereoselective alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with tropylium and trityl carbenium salts catalyzed by a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, and subsequent conversion of the resultant adducts into enantiomerically pure derivatives (Scheme 1).

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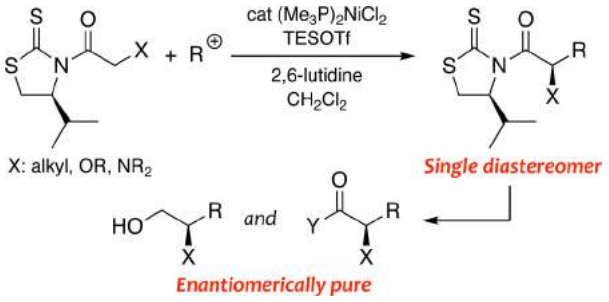
Scheme 1. Synthesis of Enantiomerically Pure Compounds by Direct and Stereoselective α-Alkylation of Chiral *N*-Acyl Thiazolidinethiones Catalyzed by a Nickel(II) Complex

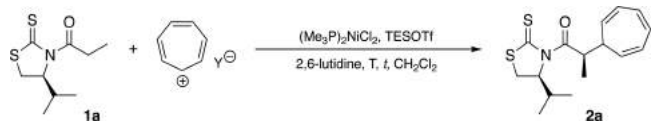


Applying small changes to the conditions previously employed[21,22] where the electrophile required activation, we initially assessed the addition of (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1a**) to the stable tropylium cation, a model for naked carbenium ions, promoted by $(Me_3P)_2NiCl_2$ in the presence of 2,6-lutidine. Remarkably, this nickel(II) complex is structurally simple, robust, and can be handled without any special care; furthermore, this is easily activated in the reaction mixture by TESOTf to form the true catalyst, $(Me_3P)_2Ni(OTf)_2$. Preliminary experiments using tropylium tetrafluoroborate, $[C_7H_7]$ BF_4,[24] indicated that the addition was not affected significantly by the quantity of the electrophile, whereas, on the contrary, an increase of the reaction temperature had a detrimental influence on the conversion (compare entries 1−5 in Table 1). Then, we focused on the effect of the reaction time. We were pleased to observe that a single diastereomer of adduct **2a** was isolated in an 83% yield after 4 h (entry 6 in Table 1); further increases of the reaction time had little effect on the conversion (compare entries 6−8 in Table 1). Finally, reducing the catalyst loading to 5 mol % afforded **2a** with a slightly lower isolated yield than with double the catalyst (entries 9 and 10 in Table 1), but pushing the catalyst loading further down to 2.5 mol % produced a sharp decrease in the conversion (entries 11 and 12 in Table 1). As the poor solubility of the tropylium tetrafluoroborate raised some concerns, we also evaluated parallel additions of **1a** to more soluble tropylium bis(trifluorosulfonyl)amide, $[C_7H_7]$ NTf_2.[19a] The results were comparable to those previously obtained (entries 13 and 14 in Table 1), which proved that the use of $[C_7H_7]$ NTf_2 instead of less soluble but commercially available $[C_7H_7]$ BF_4 had no advantage even lowering the conversion slightly.

Once we had established the optimal conditions for the alkylation of **1a**, we proceeded to analyze the scope of the reaction by varying the side chain of the *N*-acyl thiazolidinethione and testing compatibility of the reaction with a large variety of functional groups. Remarkably, just one diastereomer was observed for all the screened substrates shown in Scheme 2. Increasing the steric bulk of X from **1a** (X = Me) to **1d** (X = *i*-Pr) induced a slight decrease of the yield, and alkylated products **2a** and **2d** were isolated in 83 and 68% yield, respectively. Lengthening and adding unsaturation in **1e** and **1f** or an ester group in **1g** had little effect on the yield, and the corresponding adducts **2e−g** were isolated in yields up to 81%. Even hetero-substituted enolates from **1h** and **1i** afforded the α-aza and α-oxy derivatives **2h** and **2i** in reasonably good yields. Moreover, X-ray diffraction analyses of crystalline adducts **2d** and **2h** firmly established the configuration of the new Cα-stereocenter (see Supporting Information).[25] All together, these achievements demonstrate that the nickel(II)-mediated direct catalytic alkylation of a broad array of *N*-acyl thiazolidinethiones **1**, with the naked tropylium carbenium ion, is a highly stereoselective procedure that permits you to obtain a single diastereomer of the corresponding adducts **2** in moderate to good yields under simple experimental conditions.

Taking advantage of the easy removal of the chiral scaffold,[26] we next converted adduct **2f** into various enantiomerically pure derivatives under mild experimental conditions, as represented in Scheme 3. Thereby, reduction of **2f** with $NaBH_4$ afforded alcohol **3f** in an 86% yield. In turn, ester **4f**, thioester **5f**, and morpholine amide **6f** were isolated in yields of 82−90% through treatment of **2f** with methanol, dodecanethiol, and morpholine, respectively. Finally, the thiazolidinethione was

Table 1. Direct and Catalytic α-Alkylation of *N*-Propanoyl Thiazolidinethione 1a with Tropylium Salts



entry	$(Me_3P)_2NiCl_2$ (mol %)	electrophile	equiv	*T* (°C)	*t* (h)	conversion[a] (yield)[b] (%)
1	10	$[C_7H_7]$ BF_4	1.1	−20	2	69
2	10	$[C_7H_7]$ BF_4	1.3	−20	2	73
3	10	$[C_7H_7]$ BF_4	1.5	−20	2	70
4	10	$[C_7H_7]$ BF_4	1.1	0	2	48
5	10	$[C_7H_7]$ BF_4	1.5	0	2	43
6	10	$[C_7H_7]$ BF_4	1.1	−20	4	88 (83)
7	10	$[C_7H_7]$ BF_4	1.5	−20	6	88
8	10	$[C_7H_7]$ BF_4	1.1	−20	15	84
9	5	$[C_7H_7]$ BF_4	1.1	−20	4	77 (71)
10	5	$[C_7H_7]$ BF_4	1.1	−20	15	81
11	2.5	$[C_7H_7]$ BF_4	1.1	−20	4	39
12	2.5	$[C_7H_7]$ BF_4	1.1	−20	15	43
13	10	$[C_7H_7]$ NTf_2	1.1	−20	2	63
14	10	$[C_7H_7]$ NTf_2	1.5	−20	2	58

[a]Established by ^1H NMR analysis of the reaction mixtures. [b]Isolated yield after chromatographic purification.

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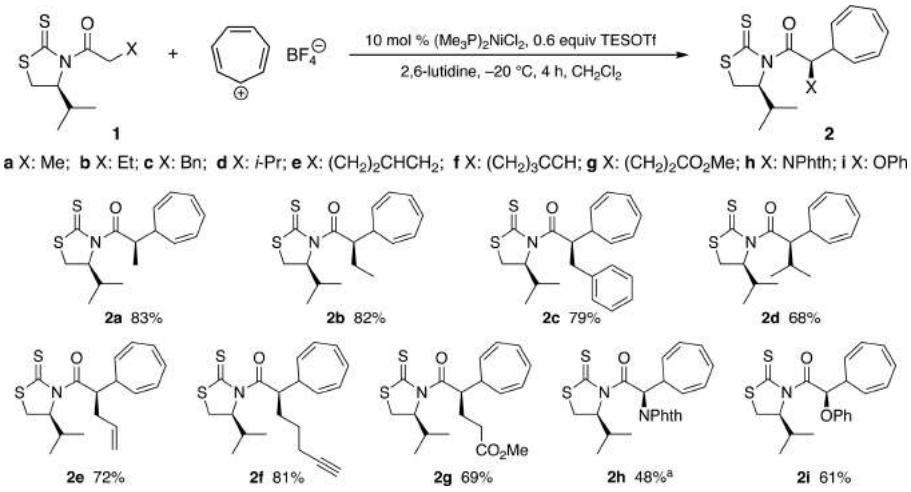
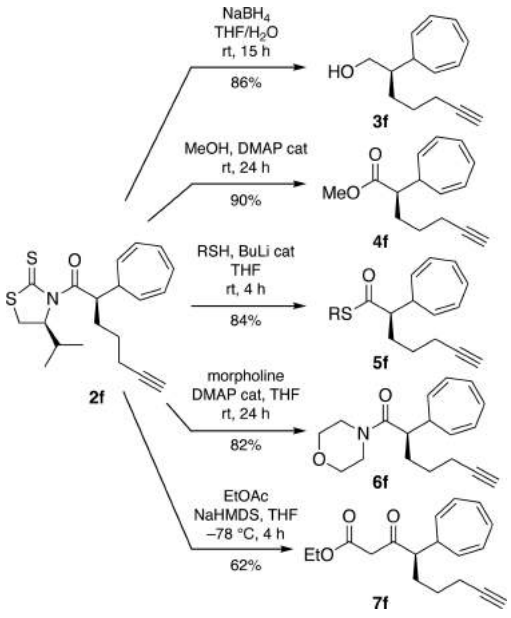
Scheme 2. Direct and Catalytic α-Alkylation of *N*-Acyl Thiazolidinethiones 1 with $[C_7H_7]$ BF_4



[a]20 mol % of catalyst was used.

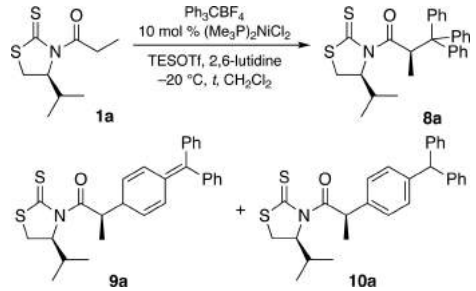
Scheme 3. Removal of the Chiral Auxiliary



displaced by the sodium enolate of ethyl acetate to deliver β-keto ester **7f** in a 62% yield. Noticeably, the conjugated triene from the tropylium cation did not undergo any rearrangement during the alkylation step or the removal of the chiral auxiliary. Indeed, derivatives **3f**–**7f** were all obtained, keeping intact the conjugated triene and the terminal triple bond, which highlights the synthetic potential of the overall procedure to prepare enantiomerically pure compounds containing a tropylium group. These sorts of intermediates may be used in the total synthesis of xanthanolides,[27] a large group of natural products whose structure contains a fused seven/five bicyclic system and features a remarkable range of biological properties.[28]

Finally, we moved to tackle a more challenging alkylating agent such as the trityl cation. The trityl group is commonly used to protect alcohols,[29] but it has rarely been employed in the stereoselective construction of carbon–carbon bonds because of its bulkiness, which makes it non-amenable to current alkylation methods. Thus, we envisaged that the experimental procedure optimized for tropylium tetrafluoroborate might be used to alkylate **1a** with trityl tetrafluoroborate, Ph_3CBF_4. Initial experiments were disappointing, with the desired alkylated adduct **8a** only isolated in low and somewhat variable yields. However, a careful analysis of the reaction mixtures showed that most of the starting material **1a** disappeared to produce **8a** and two other products, **9a** and **10a**. As shown in Table 2, these do not come from the addition

Table 2. Direct and Catalytic Alkylation of *N*-Propanoyl Thiazolidinethione 1a with Trityl Tetrafluoroborate



entry	t (h)	ratio[a] **8a**/**9a**/**10a**	yield of **8a**[b] (%)
1	4	25:60:15	22
2	15	45:30:25	40
3	30	65:10:25	57

[a]Established by ^{1}H NMR analysis of the reaction mixtures. [b]Isolated yield after chromatographic purification.

to the central carbon but to one of the phenyl groups. Indeed, **9a** contains a fully conjugated system that results directly from the nucleophilic attack of the enolate to the *para* position of a phenyl group. In turn, this undergoes a rearrangement to form **10a** to fully recover the aromatic character of the phenyl groups. As summarized in Table 2, the composition of the mixture changed dramatically with time, so the simple stirring of the reaction mixture for 30 h permitted the isolation of the desired adduct **8a** in a 57% yield. Further extensions of the reaction time did not increase this yield significantly.

Interestingly, submission of **9a** to the initial reaction conditions without any cation afforded the alkylated adduct **8a** and the fully aromatic compound **10a**. This proves that the changes in the composition of the mixtures summarized in

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Scheme 4. S_N1 Alkylation of 1a with a Trityl Salt Catalyzed by a Nickel(II) Complex

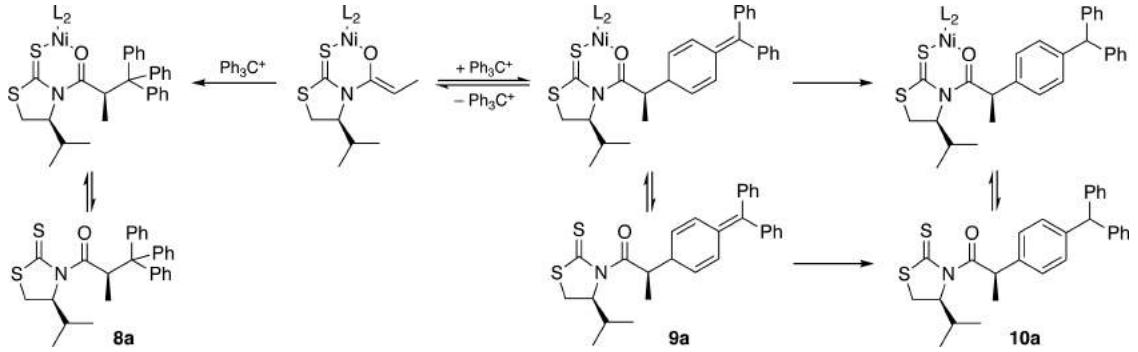

Table 2 are due to the reactivity of **9a**. Indeed, the central ring in **9a** tends to recover the aromatic character through a simple rearrangement, which produces **10a**, or by decomposing back into trityl cation and the nickel(II) enolate, which can eventually react to give **8a**. Therefore, the addition of the enolate to the *para* position to form **9a** is a reversible step, which is rare and only possible due to the stability of the trityl cation. The entire mechanism represented in Scheme 4 accounts for these results and also suggests that the nickel(II)-mediated alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones can be applied to a large array of carbenium salts irrespective of their bulk provided that the reaction conditions are suitably tuned to the structure of the electrophile.

In conclusion, catalytic amounts of a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, activated in situ with TESOTf, trigger a direct and completely diastereoselective alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with carbenium salts. The reaction is broadly tolerant of functionality and gives good yields in most cases with 10 mol % of nickel(II) complex. Furthermore, the straightforward removal of the chiral auxiliary under mild conditions provides concise access to a wide array of enantiomerically pure compounds that are difficult to prepare by other asymmetric procedures.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified, when necessary, according to standard procedures. All commercial reagents were used as received. Column chromatography was carried out under low-pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Analytical thin-layer chromatographies (TLC) were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or *p*-anisaldehyde. R_f values are approximate. Melting points were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected. Specific rotations ($[\alpha]$) were determined at 589 nm and at 20 °C on a PerkinElmer 241 MC polarimeter. IR spectra (attenuated total reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer, and only the more representative frequencies (ν) are reported. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR); data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (and their corresponding combinations) with coupling constants measured in Hz; when necessary, 2D techniques (COSY and HSQC) were also used to assist with structure elucidation. High-resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer with a TOF analyzer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

Preparation of *N*-Acyl Thiazolidinethiones. As previously reported, *N*-acyl thiazolidinethiones **1** were prepared by acylation of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione.[22,30]

*(S)-N-(6-Heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (**1f**).* A solution of 6-heptynoic acid (693 mg, 5.5 mmol) in CH_2Cl_2 (5 mL) was added via cannula to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (805 mg, 5.0 mmol), EDC·HCl (1.15 g, 6.0 mmol), and DMAP (31 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resultant mixture was stirred at room temperature for 8 h, diluted in CH_2Cl_2 (20 mL), and washed with 2 M HCl (20 mL), 2 M NaOH (20 mL), and brine (20 mL). The organic phase was then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (70:30 CH_2Cl_2/hexanes) to afford 1.229 g (91% yield) of (*S*)-*N*-(6-heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (**1f**) as a yellow oil. R_f 0.50 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +345.5 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3234, 2955, 2867, 1689, 1461, 1363, 1255, 1144, 1030, 631 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (1H, ddd, *J* = 8.0, 6.2, 1.2 Hz), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz), 3.38, (1H, ddd, *J* = 17.2, 8.5, 6.0 Hz), 3.17 (1H, ddd, *J* = 17.2, 8.5, 6.3 Hz), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz), 2.42–2.29 (1H, m), 2.22 (2H, td, *J* = 7.1, 2.7 Hz), 1.95 (1H, t, *J* = 2.7 Hz), 1.90–1.70 (2H, m), 1.65–1.55 (2H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.6 (C), 84.0 (C), 71.6 (CH), 68.6 (CH), 37.7 (CH_2), 30.8 (CH_2), 30.4 (CH), 27.8 (CH_2), 23.9 (CH_2), 19.0 (CH_3), 18.3 (CH_3), 17.7 (CH_2). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{13}H_{20}NOS_2$ 270.0981; found 270.0974.

*(S)-4-Isopropyl-N-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione (**1i**).* A 2.5 M solution of *n*-BuLi in hexanes (4.4 mL, 11.0 mmol) was added dropwise to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (1.61 g, 10.0 mmol) in THF (7 mL) at −78 °C. The resultant mixture was stirred for 15 min, and 2-phenoxyacetyl chloride (1.8 mL, 13.0 mmol) was carefully added. The reaction mixture was stirred for 5 min at −78 °C and 1.5 h at room temperature, cooled to 0 °C, and quenched with saturated NH_4Cl (2 mL) and water (5 mL). This mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with 2 M NaOH (3 × 10 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (50:50 hexanes/CH_2Cl_2) to afford 2.80 g (9.5 mmol, 95% yield) of (*S*)-4-isopropyl-*N*-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione (**1i**) as a yellow solid. Mp 80–83 °C. R_f 0.35 (50:50 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ +235.1 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 1701, 1594, 1492, 1363, 1239, 1166, 1084, 1036, 751, 688 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–6.90 (5H, m), 5.59 (1H, d, *J* = 17.4 Hz), 5.49 (1H, d, *J* = 17.4 Hz), 5.20 (1H, ddd, *J* = 8.1, 6.1, 1.1 Hz), 3.64 (1H, dd, *J* = 11.6, 8.1 Hz), 3.12 (1H, dd, *J* = 11.6, 1.1 Hz), 2.46–2.35 (1H, m), 1.09 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 169.2 (C), 157.7 (C), 129.6 (CH), 121.6 (CH), 114.8 (CH), 71.5 (CH), 69.7 (CH_2), 31.5 (CH_2), 30.8 (CH), 19.0 (CH_3), 17.6 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{14}H_{18}NO_2S_2$ 296.0773, found 296.0786.

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General Procedure for the Alkylation of 1. Solid $(Me_3P)_2NiCl_2$ (14.2 mg, 50 μmol, 10 mol %) was added to a solution of thioimide **1** (0.5 mmol) and tropylium tetrafluoroborate (98 mg, 0.55 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The resulting dark red suspension was purged with N_2 and then cooled to −20 °C. Next, TESOTf (68 μL, 0.3 mmol) was added followed by 2,6-lutidine (88 μL, 0.75 mmol) after 4 min. The resultant mixture was stirred at −20 °C for 4 h. The reaction was quenched with saturated NH_4Cl (1.2 mL) and diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. ^1H NMR analysis of the crude product showed the presence of a single diastereomer of the corresponding alkylation product **2**. The crude was purified by flash column chromatography to afford the desired alkylated product **2**.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2a**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione **1a** (108 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 128 mg (0.42 mmol, 83% yield) of **2a** as a yellow oil. R_f 0.70 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +225.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3011, 2959, 2925, 2870, 1683, 1457, 1360, 1253, 1231, 1145, cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.25−6.17 (2H, m), 5.32 (2H, dt, *J* = 9.4, 5.7 Hz), 5.21 (1H, ddd, *J* = 8.1, 5.9, 1.2 Hz), 5.09 (1H, dq, *J* = 8.4, 6.9 Hz), 3.47 (1H, dd, *J* = 11.5, 8.1 Hz), 2.98 (1H, dd, *J* = 11.5, 1.2 Hz), 2.23 (1H, dtt, *J* = 8.4, 6.1, 1.2 Hz), 1.27 (3H, d, *J* = 6.9 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 0.97 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 176.9 (C), 131.0 (CH), 130.6 (CH), 125.4 (CH), 125.0 (CH), 124.6 (CH), 122.6 (CH), 71.9 (CH), 42.0 (CH), 39.6 (CH), 30.8 (CH), 29.7 (CH_2), 19.2 (CH_3), 17.6 (CH_3), 15.1 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{16}H_{22}NOS_2$ 308.1137, found 308.1139.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)butanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2b**).* It was prepared according to the general procedure from (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione **1b** (116 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 132 mg (0.41 mmol, 82% yield) of **2b** as a yellow oil. R_f 0.80 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +324.8 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2958, 2929, 2869, 1682, 1454, 1359, 1305, 1115, 1090, 1030, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.23−6.16 (2H, m), 5.41−5.38 (1H, m), 5.32−5.28 (1H, m), 5.21−5.18 (2H, m), 3.47 (1H, dd, *J* = 11.5, 7.9 Hz), 3.01 (1H, dd, *J* = 11.5, 1.0 Hz), 2.40−2.30 (1H, m), 2.11 (1H, dtt, *J* = 8.8, 6.0, 1.3 Hz), 1.87−1.75 (2H, m), 1.06 (3H, d, *J* = 6.9 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 176.4 (C), 131.0 (CH), 130.6 (CH), 125.2 (CH), 125.0 (CH), 124.4 (CH), 122.7 (CH), 72.0 (CH), 45.8 (CH), 41.2 (CH), 30.8 (CH), 30.6 (CH_2), 23.8 (CH_2), 19.2 (CH_3), 17.9 (CH_3), 11.2 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{17}H_{24}NOS_2$ 322.1294, found 322.1282.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2c**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(3-phenylpropanoyl)-1,3-thiazolidine-2-thione **1c** (146 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 151 mg (0.39 mmol, 79% yield) of **2c** as a yellow oil. R_f 0.80 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +415.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2961, 2872, 1685, 1362, 1251, 1147, 1036, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.21 (5H, m), 6.71−6.69 (2H, m), 6.30−6.26 (1H, m), 6.22−6.18 (1H, m), 5.65−5.55 (2H, m), 5.41 (1H, dd, *J* = 9.4, 5.8 Hz), 4.51 (1H, t, *J* = 7.2 Hz), 3.27 (1H, dd, *J* = 13.2, 4.8 Hz), 2.74 (1H, dd, *J* = 13.2, 11.3 Hz), 2.64 (1H, d, *J* = 11.2 Hz), 2.50 (1H, dd, *J* = 11.2, 7.2 Hz), 2.30−2.15 (1H, m), 2.09 (1H, dt, *J* = 10.0, 5.9 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 204.1 (C), 176.4 (C), 138.5 (C), 131.2 (CH), 130.7 (CH), 128.7 (CH), 128.5 (CH), 126.6 (CH), 125.4 (CH), 125.1 (CH), 123.9 (CH), 122.6 (CH), 72.1 (CH), 46.2 (CH), 42.5 (CH), 39.1 (CH_2), 31.2 (CH_2), 30.5 (CH), 19.2 (CH_3), 18.3 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{22}H_{26}NOS_2$ 384.1450, found 384.1441.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-3-methylbutanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2d**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(3-methylbutanoyl)-1,3-thiazolidine-2-thione (122 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 118 mg (0.35 mmol, 70% yield) of 2d as a yellow solid. Mp 89−91 °C. R_f 0.70 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +488.8 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 2869, 1688, 1463, 1337, 1248, 1229, 1147, 1115, 1020, 700, 684 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.64 (2H, m), 6.22−6.16 (2H, m), 5.51 (1H, dd, *J* = 9.3, 5.9 Hz), 5.32−5.26 (2H, m), 5.14−5.09 (1H, m), 3.47 (1H, dd, *J* = 11.5, 7.6 Hz), 3.04 (1H, dd, *J* = 11.5, 0.8 Hz), 2.47−2.35 (1H, m), 2.33−2.20 (1H, m), 2.05−1.98 (1H, m), 1.09 (3H, d, *J* = 6.8 Hz), 1.01 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.9 (C), 175.9 (C), 130.9 (CH), 130.5 (CH), 124.7 (CH), 124.6 (CH), 123.6 (CH), 122.8 (CH), 72.1 (CH), 48.9 (CH), 40.4 (CH), 31.2 (CH_2), 30.8 (CH), 30.6 (CH), 20.6 (CH_3), 19.3 (CH_3), 19.0 (CH_3), 18.2 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{18}H_{26}NOS_2$ 336.1450, found 336.1454.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-4-pentenoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2e**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(4-pentenoyl)-1,3-thiazolidine-2-thione **1e** (123 mg, 0.50 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 131 mg (0.36 mmol, 72% yield) of **2e** as a yellow oil. R_f 0.60 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +297.6 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3005, 2958, 2926, 2869, 1682, 1356, 1245, 1144, 1087, 1030, 912, 836, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.62 (2H, m), 6.26−6.16 (2H, m), 5.80 (1H, dddd, *J* = 17.1, 10.2, 8.4, 5.9 Hz), 5.43 (1H, dd, *J* = 9.4, 5.9 Hz), 5.34−5.27 (2H, m), 5.09−5.00 (3H, m), 3.43 (1H, dd, *J* = 11.4, 7.8 Hz), 2.99 (1H, dd, *J* = 11.4, 0.9 Hz), 2.57 (1H, dddt, *J* = 14.1, 5.9, 4.3, 1.6 Hz), 2.46−2.42 (1H, m), 2.40−2.30 (1H, m), 2.20−2.13 (1H, m), 1.05 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.5 (C), 175.8 (C), 134.9 (CH), 131.1 (CH), 130.6 (CH), 125.4 (CH), 125.1 (CH), 124.2 (CH), 122.5 (CH), 117.1 (CH_2), 72.2 (CH), 44.4 (CH), 41.3 (CH), 35.7 (CH_2), 30.9 (CH_2), 30.8 (CH), 19.2 (CH_3), 18.0 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{18}H_{24}NOS_2$ 334.1294, found 334.1296.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2f**).* It was prepared according to the general procedure from (*S*)-*N*-(6-heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (135 mg, 0.50 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 155 mg (0.41 mmol, 82% yield) of **2f** as a yellow oil. R_f 0.60 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +292.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3290, 3012, 2958, 2926, 2863, 1682, 1467, 1359, 1235, 1144, 1090, 1023, 738, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.24−6.17 (2H, m), 5.48−5.31 (1H, m), 5.34−5.29 (1H, m), 5.27−5.22 (1H, m), 5.22 (1H, ddd, *J* = 7.9, 4.3, 1.2 Hz), 3.49 (1H, dd, *J* = 11.5, 7.9 Hz), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz), 2.40−2.27 (1H, dq, *J* = 13.6, 6.8 Hz), 2.20 (2H, td, *J* = 7.0, 2.6 Hz), 2.11 (1H, dtt, *J* = 8.4, 5.9, 1.3 Hz), 1.97−1.94 (1H, m), 1.91−1.87 (2H, m), 1.56−1.46 (2H, m), 1.04 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 176.1 (C), 131.1 (CH), 130.7 (CH), 125.3 (CH), 125.1 (CH), 124.1 (CH), 122.4 (CH), 83.7 (C), 72.0 (CH), 68.8 (CH), 44.1 (CH), 41.5 (CH), 30.8 (CH), 30.4 (CH_2), 29.5 (CH_2), 25.8 (CH_2), 19.2 (CH_3), 18.5 (CH_2), 17.8 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{20}H_{26}NOS_2$ 360.1450, found 360.1455.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-4-methoxycarbonylbutanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2g**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(4-methoxycarbonylbutanoyl)-1,3-thiazolidine-2-thione **1g** (144 mg, 0.50 mmol). Purification of the crude product by column chromatography (80:20 hexanes/EtOAc) afforded 131 mg (0.35 mmol, 69% yield) of **2g** as a yellow oil. R_f 0.40 (80:20 hexanes/EtOAc). $[\alpha]_D^{20}$ +221.9 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2958, 2869, 1729, 1435, 1359, 1239, 1090, 1030, 697 cm^{-1}. ^1H NMR

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($CDCl_3$, 400 MHz) δ 6.70−6.60 (2H, m), 6.25−6.15 (2H, m), 5.40 (1H, dd, J = 9.4, 5.9 Hz), 5.32 (1H, dd, J = 9.4, 6.1 Hz), 5.27 (1H, td, J = 9.5, 4.3 Hz), 5.20 (1H, ddd, J = 7.7, 6.3, 1.0 Hz), 3.67 (3H, s), 3.54 (1H, dd, J = 11.4, 7.9 Hz), 3.00 (1H, dd, J = 11.4, 1.1 Hz), 2.40−2.25 (3H, m), 2.20−2.05 (3H, m), 1.04 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 175.7 (C), 173.3 (C), 131.1 (CH), 130.7 (CH), 125.5 (CH), 125.2 (CH), 123.8 (CH), 122.1 (CH), 72.0 (CH), 51.7 (CH_3), 43.5 (CH), 41.4 (CH), 31.3 (CH_2), 30.7 (CH), 30.4 (CH_2), 25.4 (CH_2), 19.2 (CH_3), 17.9 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{19}H_{26}NO_3S_2$ 380.1349, found 380.1357.

(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-N,N-phthaloyl-2-aminoacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2h**). It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(*N*,*N*-phthaloyl-2-aminoacetyl)-1,3-thiazolidine-2-thione **1h** (348 mg, 1.0 mmol), $(Me_3P)_2NiCl_2$ (56.4 mg, 0.20 mmol, 20 mol %), tropylium tetrafluoroborate (196 mg, 1.10 mmol), TESOTf (115 μL, 0.50 mmol), and 2,6-lutidine (175 μL, 1.5 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 4 h at −20 °C. Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 209 mg (0.48 mmol, 48% yield) of **2h** as a yellow solid. Mp 134−138 °C. R_f 0.40 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +253.2 (c 1.00, $CHCl_3$). IR (ATR) ν 2958, 1770, 1707, 1467, 1375, 1261, 1163, 716, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.84 (2H, m), 7.76−7.74 (2H, m), 6.71−6.64 (2H, m), 6.42 (1H, d, J = 8.1 Hz), 6.23−6.26 (1H, m), 6.20−6.16 (1H, m), 5.61−5.57 (1H, m) 5.33−5.29 (1H, m), 4.82 (1H, ddd, J = 7.5, 6.3, 0.9 Hz), 3.40 (1H, dd, J = 11.2, 7.5 Hz), 2.98 (1H, dd, J = 11.2, 0.9 Hz), 2.75 (1H, dtt, J = 8.1, 6.2, 1.1 Hz), 2.52−2.40 (1H, m), 1.05 (3H, d, J = 6.9 Hz), 1.03 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 201.8 (C), 169.5 (C), 167.7 (C), 134.5 (CH), 131.1 (CH), 131.0 (CH), 130.9 (CH), 126.2 (CH), 124.6 (CH), 123.6 (CH), 123.4 (CH), 120.6 (CH), 74.2 (CH), 54.2 (CH), 41.5 (CH), 32.2 (CH_2), 31.2 (CH), 19.2 (CH_3), 18.0 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{23}H_{23}N_2O_3S_2$ 439.1145, found 439.1128.

(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-2-phenoxyacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2i**). It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione **1i** (148 mg, 0.50 mmol). Purification of the crude product by column chromatography (60:40 CH_2Cl_2/hexanes) afforded 118 mg (0.31 mmol, 61% yield) of **2i** as a yellow oil. R_f 0.65 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +69.3 (c 1.00, $CHCl_3$). IR (ATR) ν 3025, 2955, 2870, 1698, 1597, 1587, 1489, 1363, 1236, 1157, 1084, 748, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.27 (2H, m, 2H), 7.18 (1H, d, J = 2.7 Hz), 7.02−6.96 (1H, m), 6.95−6.90 (2H, m), 6.72−6.62 (2H, m), 6.31−6.23 (2H, m), 5.74 (1H, dd, J = 9.5, 5.6 Hz), 5.42 (1H, dd, J = 9.4, 5.4 Hz), 5.30 (1H, ddd, J = 8.8, 5.4, 1.6 Hz), 3.52 (1H, dd, J = 11.6, 8.8 Hz), 3.01 (1H, dd, J = 11.6, 1.6 Hz), 2.49−2.42 (1H, m), 2.26−2.13 (1H, m), 0.91 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.0 (C), 171.1 (C), 157.7 (C), 131.0 (CH), 130.8 (CH), 129.7 (CH), 125.5 (CH), 125.4 (CH), 122.1 (CH), 121.7 (CH), 120.0 (CH), 115.2 (CH), 76.1 (CH), 71.7 (CH), 41.7 (CH), 30.7 (CH), 30.2 (CH_2), 19.0 (CH_3), 17.0 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{21}H_{24}NO_2S_2$ 386.1243, found 386.1247.

Removal of the Chiral Auxiliary. *(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptyn-1-ol* (**3f**). A mixture of **2f** (180 mg, 0.5 mmol) and $NaBH_4$ (94.5 mg, 2.5 mmol) in THF/H_2O (10 mL/0.1 mL) was stirred for 15 h at room temperature. The mixture was diluted in Et_2O (20 mL) and washed with 1 M NaOH (3 × 20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (CH_2Cl_2) afforded 87 mg (86% yield) of pure alcohol **3f** as a colorless oil. R_f 0.25 (CH_2Cl_2). $[\alpha]_D^{20}$ +10.1 (c 1.00, $CHCl_3$). IR (ATR) ν 3364 (br), 3294, 3009, 2923, 2866, 1027, 734, 701, 628 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69−6.65 (2H, m), 6.26−6.19 (2H, m), 5.35−5.28 (2H, m), 3.80 (2H, t, J = 5.2 Hz), 2.25−2.20 (2H, m), 1.96 (1H, t, J = 2.7 Hz), 1.90−1.82 (1H, m), 1.76−1.54 (5H, m), 1.23 (1H, t, J = 5.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 130.9 (CH), 130.7 (CH), 125.1 (2 × CH), 123.7 (CH), 123.6 (CH), 84.4 (C), 68.6 (CH), 63.4 (CH_2), 41.6 (CH), 40.4 (CH), 27.9 (CH_2), 26.1 (CH_2), 18.7 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{14}H_{19}O$ 203.1430, found 203.1436.

Acidification of the aqueous layer using HCl (until pH 1) and subsequent extraction with CH_2Cl_2 (3 × 20 mL) gave 67 mg (84%) of recovered chiral thiazolidinethione.

Methyl (R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoate (**4f**). A solution of **2f** (180 mg, 0.5 mmol) and DMAP (25 mg, 0.2 mmol) in MeOH (5 mL) was stirred for 24 h at room temperature. The solvent was removed, and the resulting crude mixture was dissolved in Et_2O (20 mL). The ethereal solution was washed with 1 M NaOH (3 × 20 mL) and H_2O (20 mL), and the organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (50:50 hexanes/CH_2Cl_2) yielded 103 mg (90% yield) of ester **4f** as a colorless oil. R_f 0.60 (50:50 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ +24.2 (c 1.00, $CHCl_3$). IR (ATR) ν 3291, 3009, 2945, 2863, 1729, 1432, 1194, 1154, 702, 635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69−6.63 (2H, m), 6.25−6.17 (2H, m), 5.31−5.23 (2H, m), 3.71 (3H, s), 2.72 (1H, td, J = 9.7, 4.2 Hz), 2.21 (2H, td, J = 7.0, 2.7 Hz), 1.96 (1H, t, J = 2.7 Hz), 1.95−1.91 (1H, m), 1.87−1.73 (2H, m), 1.56−1.46 (2H, m). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.3 (C), 131.1 (CH), 130.8 (CH), 125.4 (CH), 125.3 (CH), 123.1 (CH), 122.9 (CH), 83.8 (C), 68.7 (CH), 51.6 (CH_3), 46.9 (CH), 41.3 (CH), 29.3 (CH_2), 26.2 (CH_2), 18.2 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{15}H_{19}O_2$ 231.1380, found 231.1381.

Acidification of the aqueous layer using HCl (until pH 1) and extraction with CH_2Cl_2 (3 × 20 mL) gave 71 mg (89%) of recovered chiral thiazolidinethione.

S-Dodecyl (R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynethioate (**5f**). A 2.5 M solution of *n*-BuLi in hexanes (60 μL, 0.15 mmol) was added to a solution of dodecanethiol (360 μL, 1.5 mmol) in THF (3 mL) at 0 °C. The reaction was left 15 min before a solution of **2f** (180 mg, 0.5 mmol) in THF (2 mL) was added dropwise. The resultant mixture was stirred for 15 min at 0 °C and for 4 h at room temperature. The mixture was then diluted in H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (from 90:10 hexanes/CH_2Cl_2 to CH_2Cl_2) to afford 64 mg (80%) of recovered chiral auxiliary and 168 mg (84% yield) of thioester **5f** as a colorless oil. R_f 0.55 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +19.5 (c 1.00, $CHCl_3$). IR (ATR) ν 3307, 3018, 2920, 2851, 1679, 1454, 964, 742, 698, 628 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.62 (2H, m), 6.27−6.15 (2H, m), 5.35 (1H, dd, J = 9.5, 6.0 Hz), 5.27 (1H, dd, J = 9.5, 6.0 Hz), 2.90 (2H, t, J = 7.3 Hz), 2.95−2.83 (1H, m), 2.26−2.16 (2H, m), 2.01−1.97 (1H, m), 1.96 (1H, t, J = 2.7 Hz), 1.91−1.75 (2H, m), 1.66−1.46 (4H, m), 1.41−1.21 (18H, m), 0.88 (3H, t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.1 (C), 131.1 (CH), 130.8 (CH), 125.4 (CH), 125.3 (CH), 123.0 (CH), 122.5 (CH), 83.7 (C), 68.7 (CH), 55.1 (CH), 41.7 (CH), 31.9 (CH_2), 29.9 (CH_2), 29.6 (3 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 18.3 (CH_2) 14.1 (CH_3). HRMS (+ESI): m/z calcd for $[M + NH_4]^+$ $C_{26}H_{44}NOS$ 418.3138, found 418.3138.

N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoyl]morpholine (**6f**). Morpholine (130 μL, 1.5 mmol) was added dropwise to a solution of **2f** (180 mg, 0.5 mmol) and DMAP (50 mg, 0.4 mmol) in THF (10 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 24 h. The volatiles were removed to leave a crude mixture that was purified by column chromatography (from 50:50 hexanes/CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH) to afford 63 mg (79%) of recovered chiral auxiliary and 116 mg (82% yield) of amide **6f** as a yellowish oil. R_f 0.50 (97.5:2.5 CH_2Cl_2/MeOH). $[\alpha]_D^{20}$ +2.0 (c 1.00, $CHCl_3$). IR (ATR) ν 3288, 3012, 2918, 2854, 1625, 1429, 1223, 1112, 1027, 701, 641 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66−6.56 (m, 2H), 6.26 (1H, dd, J = 9.7, 5.5 Hz), 6.20 (1H, dd, J = 9.7, 4.8 Hz), 5.40 (1H, dd, J = 9.5, 7.2 Hz), 5.32 (1H, dd, J = 9.5, 7.0 Hz), 3.70−3.61 (6H, m), 3.49−3.43 (2H, m), 2.87 (1H, td, J = 9.6, 4.1 Hz), 2.55 (1H, dt, J = 9.6, 7.0 Hz), 2.19−2.12 (2H, m), 1.95 (1H, t, J = 2.6 Hz), 1.84−1.69 (2H, m), 1.56−1.44 (1H, m), 1.41−1.30 (1H, m). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.2 (C), 130.8 (CH), 130.5 (CH),

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125.9 (CH), 125.6 (CH), 124.5 (CH), 123.9 (CH), 83.9 (C), 68.7 (CH), 67.2 (CH_2), 66.9 (CH_2), 46.4 (CH_2), 42.2 (CH_2), 41.5 (CH), 39.8 (CH), 29.9 (CH_2), 26.1 (CH_2), 18.5 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{18}H_{24}NO_2$ 286.1802, found 286.1803.

*Ethyl (R)-4-(2,4,6-Cycloheptatrien-1-yl)-3-oxo-8-nonynoate (**7f**).* A solution of EtOAc (0.1 mL, 1.0 mmol) and 1 M NaHMDS in THF (1 mL, 1.0 mmol) in THF (2.5 mL) was stirred for 1 h at −78 °C. A solution of **2f** (180 mg, 0.5 mmol) in THF (2.5 mL) was then added, and the resultant mixture was stirred for 4 h at −78 °C. The reaction was quenched with NH_4Cl (5 mL). The mixture was diluted with EtOAc (20 mL), washed with H_2O (20 mL), 1 M NaOH (2 × 20 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (from 50:50 to 40:60 hexanes/CH_2Cl_2) of the residue yielded 88 mg (62% yield) of a ≈70:30 keto/enol mixture of β-keto ester **7f** as a colorless oil. R_f 0.45 (CH_2Cl_2). $[\alpha]_D^{20}$ +34.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3291, 2980, 2933, 2863, 1742, 1704, 1641, 1622, 1492, 1226, 1144, 1207, 698, 634 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 12.12 (1H, s, *enol*), 6.71−6.63 (2H, m), 6.29−6.16 (2H, m), 5.32−5.18 (2H, m), 5.04 (1H, s, *enol*), 4.20 (2H, q, J = 7.0 Hz, *enol*), 4.18 (2H, q, J = 7.1 Hz), 3.46 (1H, d, J = 15.6 Hz), 3.38 (1H, d, J = 15.6 Hz), 2.94 (1H, td, J = 9.3, 4.3 Hz), 2.41−2.35 (1H, m, *enol*), 2.20 (2H, td, J = 7.0, 2.6 Hz), 2.06 (1H, dt, J = 9.3, 6.3 Hz), 1.96 (1H, t, J = 2.6 Hz), 1.90−1.79 (2H, m), 1.78−1.71 (1H, m, *enol*), 1.60−1.41 (2H, m), 1.31 (3H, t, J = 7.1 Hz, *enol*), 1.27 (3H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ *keto* 205.2 (C), 166.9 (C), 131.0 (CH), 130.9 (CH), 125.8 (CH), 125.7 (CH), 123.1 (CH), 122.0 (CH), 83.6 (C), 68.9 (CH), 61.3 (CH_2), 53.2(CH_2), 48.4 (CH), 40.1 (CH), 28.1 (CH_2), 25.6 (CH_2), 18.3 (CH_2), 14.1 (CH_3); *enol* 178.8 (C), 172.4 (C), 131.0 (CH), 130.7 (CH), 125.3 (CH), 125.0 (CH), 123.6 (CH), 123.3 (CH), 91.3 (CH), 84.0 (C), 68.6 (CH), 60.1 (CH_2), 47.0 (CH), 41.4 (CH), 29.4 (CH_2), 26.0 (CH_2), 18.3 (CH_2), 14.2 (CH_3). HRMS (+ESI): m/z calcd for $[M + NH_4]^+$ $C_{18}H_{26}NO_3$ 304.1907, found 304.1906.

Acidification of the aqueous layer using HCl (until pH 1) and extraction with CH_2Cl_2 (3 × 20 mL) afforded 68 mg (85%) of recovered chiral thiazolidinethione.

Coupling with Trityl Cation. Solid $(Me_3P)_2NiCl_2$ (28.2 mg, 0.1 mmol, 10 mol %) was added to a solution of **1a** (217 mg, 1.0 mmol) and trityl tetrafluoroborate (396 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) at room temperature, and the resulting dark red suspension was cooled to −20 °C. Then, TESOTf (140 μL, 0.6 mmol) was added followed by 2,6-lutidine (180 μL, 1.5 mmol) after 4 min. The reaction mixture was stirred at −20 °C for 30 h.

The reaction was quenched with saturated NH_4Cl (2 mL) and diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. ^1H NMR analysis of the crude product showed a full conversion and a ≈65:10:25 **8a**/**9a**/**10a** mixture. This was then directly purified by column chromatography (60:40 hexanes/CH_2Cl_2) to yield 261 mg (0.57 mmol, 57% yield) of the alkylated adduct **8a** and 92 mg (0.20 mmol, 20% yield) of **10a**.

*(S)-4-Isopropyl-N-[(R)-2-(triphenylmethyl)propanoyl]-1,3-thiazolidine-2-thione (**8a**).* Yellow solid. Mp 190−192 °C. R_f 0.50 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +185.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2962, 2836, 1697, 1707, 1488, 1362, 1241, 1134 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54−7.03 (16H, m), 5.07 (1H, ddd, J = 8.2, 5.3, 0.9 Hz), 3.32 (1H, dd, J = 11.5, 8.2 Hz), 2.90 (1H, dd, J = 11.5, 0.9 Hz), 2.10−2.00 (1H, m), 1.10 (3H, d, J = 7.2 Hz), 1.04 (3H, d, J = 6.9 Hz), 0.83 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.7 (C), 175.2 (C), 144.0 (C), 128.7 (CH), 127.7 (CH), 126.9 (CH) 72.2 (CH), 60.5 (C), 42.7 (CH), 30.7 (CH), 28.4 (CH_2), 19.0 (CH_3), 17.4 (CH_3), 16.6 (CH_3). HRMS (+ESI): m/z calcd for $C_{28}H_{30}NOS_2$ $[M + H]^+$ 460.1763; found 460.1767.

*(S)-N-[(R)-2-(4-Diphenylmethylene-2,5-cyclohexadien-1-yl)-propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**9a**).* Yellowish and unstable solid. R_f 0.50 (60:40 CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.23 (6H, m), 7.20−7.14 (4H, m), 6.66−6.54 (2H, m), 5.80−5.67 (2H, m), 5.34−5.29 (1H, m), 4.66 (1H, qd, J = 6.8, 3.4 Hz), 3.91−3.81 (1H, m), 3.51 (1H, dd, J = 11.5, 8.2 Hz), 3.00 (1H, dd, J = 11.5, 1.3 Hz), 2.38−2.22 (1H, m), 1.07 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 175.3 (C), 141.8 (C), 141.7 (C), 138.5 (C), 130.7 (CH), 130.4 (CH), 129.2 (CH), 128.8 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 71.7 (CH), 42.1 (CH), 40.8 (CH_2), 30.9 (CH), 30.1 (CH), 19.0 (CH_3), 17.7 (CH_3), 12.1 (CH_3).

*(S)-N-[(R)-2-(4-Benzhydrylphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**10a**).* Thick yellow oil. R_f 0.50 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +112.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 1689, 1591, 1350, 1245, 1147, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.03 (14H, m), 5.95 (1H, q, J = 6.9 Hz), 5.51 (1H, s), 5.19−5.09 (1H, m), 3.38 (1H, dd, J = 11.4, 8.7 Hz), 2.97 (1H, dd, J = 11.4, 3.5 Hz), 2.07−1.96 (1H, m), 1.50 (3H, d, J = 6.9 Hz), 0.83 (3H, d, J = 7.0 Hz), 0.63 (3H, d, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 176.9 (C), 143.8 (C), 142.9 (C), 137.9 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.3 (CH), 126.3 (CH), 72.2 (CH), 56.5 (CH), 44.6 (CH), 30.0 (CH_2), 28.9 (CH), 19.3 (CH_3), 19.0 (CH_3), 16.0 (CH_3). HRMS (+ESI): m/z calcd for $C_{28}H_{30}NOS_2$ $[M + H]^+$ 460.1763; found 460.1751.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00657.

Copies of ^1H and ^{13}C NMR for unreported *N*-acyl thiazoldinethiones **1f** and **1i** and compounds **2**−**10** (PDF)

X-ray data for **2d** (CIF)

X-ray data for **2h** (CIF)

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Notes

The authors declare no competing financial interest.

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Conclusions

Our new methodology was a large improvement over our previous attempts using carbocationic salts as electrophiles in the nickel(II) catalysed alkylation reaction of chiral *N*-acyl thiazolidinethiones. We achieved a similar yield with a quarter of the catalyst by the optimisation of all of the reaction conditions and improvements in the storage and handling of the salt reagent (Previous: 74% with 20 mol%, New: 71% using 5 mol%). Furthermore, with an optimal catalyst loading of 10 mol% we achieved full conversion and an excellent yield.

We achieved a wide application to various starting materials with different functional groups. Both steric hindrance and levels of unsaturation were well tolerated, with methyl, ethyl, isopropyl, benzyl, double and triple bonds or ester containing R-groups all giving yields over 68% with most being around 80% and the lowest being the sterically hindered isopropyl group. Even heteroatoms in the α-position were well tolerated in the α-position giving α-hydroxy and α-amino carboxylic acid equivalents with slightly lower yields. The *O*-phenyl group gave a yield of 61% and the phthalimide derivative required double the catalyst loading to achieve a 48% yield due to the electronic and steric complexity of the protecting group of the amine.

The chiral auxiliary was easily removed and gave excellent yields of enantiopure synthons and a high level of chiral auxiliary recovery. Unlike many similar procedures, we did not use the simplest derivative (the methyl substituent **246a**) for these tests, rather we used the more sterically demanding side chain containing a terminal triple bond to give a more representative proof of the utility. Reduction with borohydride or displacement by alcohol, thiol or amino nucleophiles all gave excellent yields of the corresponding alcohol, ester, thioester and amide compounds without complications. Furthermore, the displacement by the sodium enolate of ethyl acetate led to the β-keto ester with a slightly lower yield due to partial Claisen reaction of the enolate producing a small amount of ethanol in the reaction leading to a proportion of the ethyl ester product.

Finally, we were able to apply the methodology to another sterically hindered carbocationic salt with the trityl cation. Whilst the initial results were rather modest and similar to those reported by Šebasta in the quenching of a metal enolate formed by conjugate addition by trityl tetrafluoroborate,[75] we were able to considerably improve them. We achieved a final yield of 57% of the desired adduct **245** and 20% of the phenylmethyl diphenyl adduct **248**. The increase of the yield of the desired adduct was possible due to the discovery of a reversible carbon-carbon bond formation.

Our method gave only single diastereomers of the products, which can be easily transformed into a variety of enantiopure chiral synthons. Both the selectivity and the range of enantiomerically pure available intermediates are an improvement on existing organocatalytic methods, which in general have lower enantioselectivity and are limited to aldehyde, ketone or alcohol products. Furthermore, our methodology is widely universal with a large range of starting materials and proceeds with complete stereocontrol and excellent yields in the majority of cases. The application to other cationic salts was also demonstrated by using the notoriously difficult trityl cation; with this milestone achieved cations between the simple tropylium and the complex trityl cation should also prove successful considering they present a less difficult challenge. Salts such as diarylmethyl, benzodithiolyium, and acridinium cations used in the organocatalytic processes should therefore also be applicable in our methodology.

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Chapter 3: New Methodologies for the Catalytic and Enantioselective C-C Bond Forming Reactions with Chiral Nickel Complexes

A New Enantioselective Reaction and its Application to a Short Total Synthesis

The development of new asymmetric C–C bond forming reactions is a central pillar in the field of organic chemistry, especially in the construction of the carbon skeleton of natural products. One of the most prevalent methods for this is the use of metal enolates,[1] which traditionally require their stoichiometric formation. One downside of such a process is the low atom economy;[2] since the stoichiometric strong base or Lewis acid/tertiary amine required for the enolization are not incorporated into the final which can be regarded as a large waste in the process. Any move to use either the Lewis acid, the base or ideally both in a catalytic capacity, would greatly decrease the atom economy cost of the reaction.

Another drawback of many of the more traditional techniques is the source of the chirality. In most cases the source is stoichiometric: a chiral starting material; a chiral Lewis or Brønsted acid; a chiral electrophile or some chiral additive, all having been used in stoichiometric quantities. This gives an equimolar transfer of chirality, one chiral molecule lending its chirality to another, either inter- or intramolecularly. If the source of chirality could also come from a sub-stoichiometric source, then one molecule's chirality could imprint its chirality on various molecules giving a higher rate of transfer of chirality.

One solution exists for both of the aforementioned problems: chiral metal catalysis. A chiral metal complex that can catalytically form a chiral metal enolate species provides a sub-stoichiometric source of the nucleophilic enolate species and also the chirality. This would increase significantly the atom economy of the reaction and the chirality transfer efficiency. However, due to the products being formed potentially containing inseparable mixtures of enantiomers, instead of the separable diastereoisomers when chiral starting materials or reagents are used, the requirements are stricter. As the enantiomers cannot be separated by traditional methods the enantiomerical purity of the products has to be a much higher level; lower selectivity regarding other separable isomers can be acceptable. Therefore, a method with an excellent enantioselectivity is required to be synthetically useful and high diastereoselectivity is also desirable but less restricting due to the option of separation.

Chiral Metal Complexes in Asymmetric Alkylations and Related Reactions of Enolates

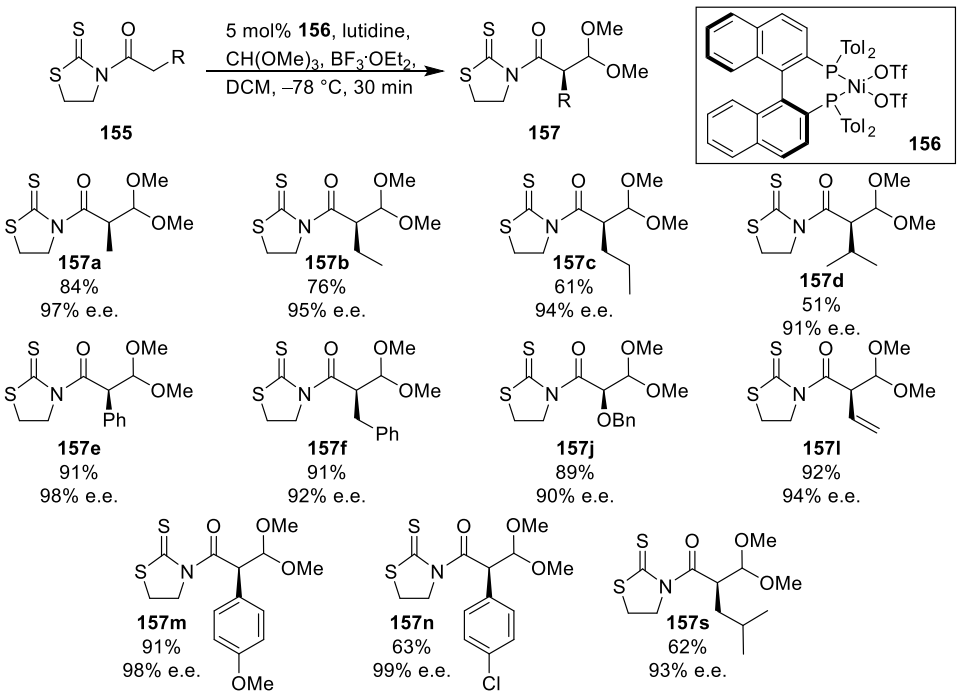
In spite of its extreme value, the use of chiral metal enolates arising from achiral substrates and chiral metal complexes and their use as nucleophiles in alkylation reactions is an area that so far has yielded few results. Currently the methodology available for the alkylation of chiral enolates is limited to chiral substrates or the use of chiral auxiliaries, or the equivalent alternative in organocatalysis. However, methodologies using a catalytically formed chiral enolate from an achiral substrate would represent a large advance in the field. While few examples currently exist, they demonstrate the viability of such reactions and also the desire to find more examples. Also, related reactions of enolates with chiral metal complexes with other electrophiles lend further support to the cause.

Evans' Asymmetric Orthoformate Addition

One of the most important advances in this field was the orthoformate reaction described by Evans using a chiral nickel complex to catalytically form the enolate species.[3] This was briefly discussed in Chapter 2. However, here it holds even more importance due to the achiral starting material and chiral metal complex used. The achiral starting materials were *N*-acyl thiazolidinethiones **155** (Scheme 101), similar to the chiral auxiliaries developed by Nagao and widely employed by our group in carbon-

carbon bond forming reactions.[4–11] These substrates were then combined with: the catalytic species **156**, the organic base lutidine, boron trifluoride as a Lewis acid, and finally trimethyl orthoformate in a direct reaction to give compound **157** (Scheme 101).

The scope of the reaction was large with generally excellent yields and selectivities. The longer the chain the lower the yield of the adduct obtained with the move from **157a** to **157c** slowly eroding the yield and partly the selectivity. Steric hindrance in the form of branching was also tolerated but again with decreases in the yield and selectivity. Adding two methyl groups at the terminal position was proof of this: comparing **157a** with **157d** and **157b** with **157s** we see a decrease of 33% and 14% in the yield respectively and a decrease of 6% and 2% in the enantioselectivity. Adding unsaturation was well tolerated with allylic product **157l** and benzyl product **157f** obtained in exceptional yields and excellent selectivity. The presence of an α-aryl substituent was beneficial for the selectivity with the highest enantioselectivity being achieved with products **157e,m,n** and the yield only being affected when using an electron-poor aromatic ring (**157n**). Finally, α-benzyloxy derivative **157j** was also achieved with similar results.



*Scheme 101: Evans' Orthoformate Reaction Scope Catalysed by Chiral Nickel Complex **140**.*

The chiral catalyst was based on the Tol-BINAP ligand developed by Noyori in asymmetric hydrogenations (Left, Figure 30).[12] This was then combined with nickel(II) chloride and the chlorides exchanged with triflate ligands carefully in a glovebox to give the catalyst **156** (Right, Figure 30). The requirement of a **glovebox** was necessary due to the instability of the catalyst to air and moisture, which also made crucial the weighing and handling of the catalyst in a glovebox and the use of low temperatures in the reaction. Due to this the reaction was highly sensitive and is possibly why it was not investigated further.

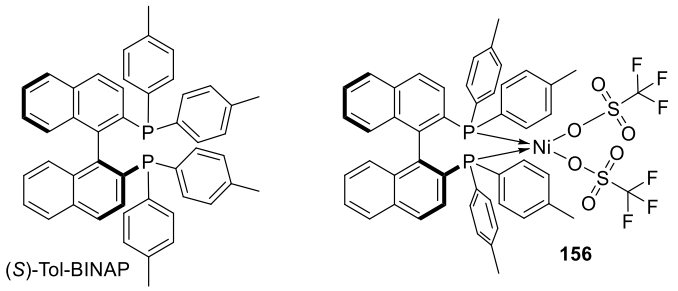
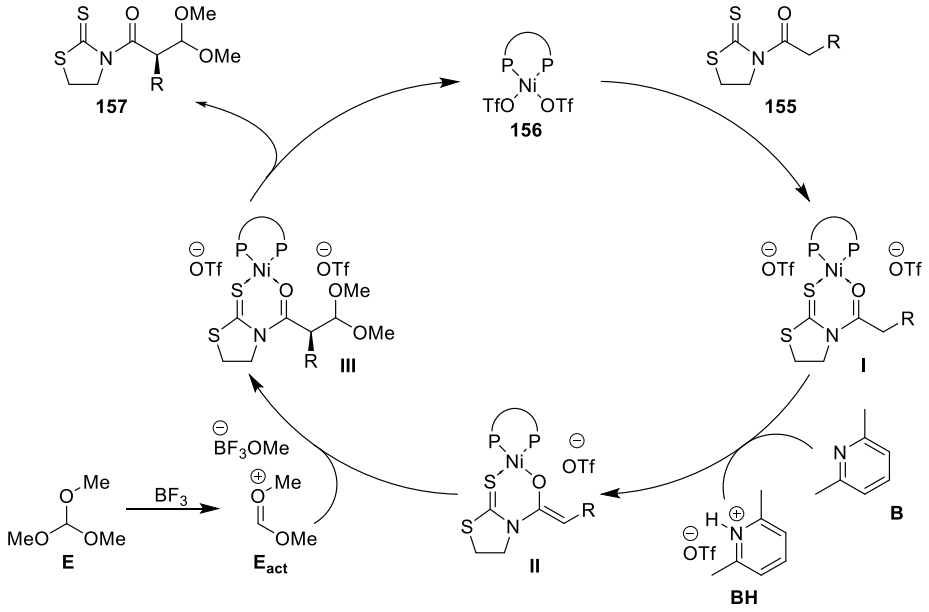


*Figure 30: Left: Tol-BINAP Ligand; Right: Nickel Catalyst **156**.*

This catalytic species performs the double function of promoting the enolate formation and creating the chiral environment for the substrate. The first step of the mechanism is the association of **156** with the starting material **155** to form the coordinated complex **I** (Scheme 102). This association increases the acidity of the α-proton, making deprotonation easier and able to be carried out by a weaker organic base, namely 2,6-lutidine **B**. This then forms exclusively the *Z*-enolate species **II** with the appropriate chiral environment, which effectively blocks one π-face of the enolate causing the electrophile to approach for the opposite side. The trimethyl orthoformate electrophile **E** was activated *in-situ* by the boron Lewis acid to form the oxocarbenium intermediate $\mathbf{E_{act}}$ through abstraction of one of the methoxy groups. This then approaches the enolate from the less sterically hindered π-face of the C=C bond and forms the carbon-carbon bond to give the adduct **III**. Dissociation of **III** finally produces **157** with the new stereocentre and regenerates **156** to continue to the catalytic cycle.



*Scheme 102: Catalytic Cycle and Mechanism Proposed by Evans Illustrated with the Methyl Substrate **155a**.*

The achiral scaffold also acts as an activated ester species, allowing it to be easily displaced by various nucleophilic species to provide a variety of derivatives. Thus, the scaffold is not only the structural platform that makes the reaction possible but also gives a versatility to the products other methods do not. Examples of such transformations are shown in Scheme 69 (see Chapter 2). Therefore, in one step the scaffold can be removed and recovered and simultaneously a functional group manipulation is performed.

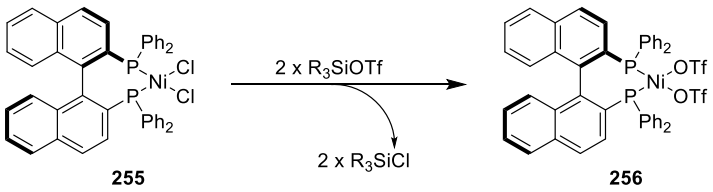
Whilst the methodology was generally very promising with high yields and selectivity of the products, there was still room for improvement in both. Furthermore, the instability and sensitivity of the catalyst species made further investigation less appealing. However, the potential of a similar procedure that addressed these issues and expanded the scope would be an attractive improvement which could be more widely used.

Asymmetric Halogenation by Sodeoka Using Chiral Metal Enolates

Sodeoka used various chiral catalysts, based on either palladium,[13–17] or nickel complexes,[18,19] to perform enantioselective halogenation reactions. Whilst not a carbon-carbon bond forming alkylation reaction the research was highly relevant to ours due to the substrates and catalysts used, especially her later report on chiral metal enolates derived from *N*-acyl oxazolidinones and oxazolidinethiones. Such a catalytic generation of a chiral enolate species from an achiral substrate and its direct reaction with an electrophilic species inspired part of our research.

Activation of Pre-Catalyst In-Situ

One of the biggest effects Sodeoka's research had on our group's investigation was the activation of a chiral nickel chloride species to the corresponding nickel(II) triflate active catalyst species. This resolved the main problem of Evans' orthoformate reaction of the unstable nickel triflate catalytic species; the use of a bench stable nickel chloride analogue which is then activated *in-situ* gets around the instability of the triflate species. This was achieved by using pre-catalyst **255** (nickel chloride complexed to the BINAP ligand) and trialkylsilyl triflates to perform a ligand exchange to give the nickel triflate catalyst **256** (Scheme 103).[19] Triethylsilyl triflate was found to work better than the methyl counterpart.



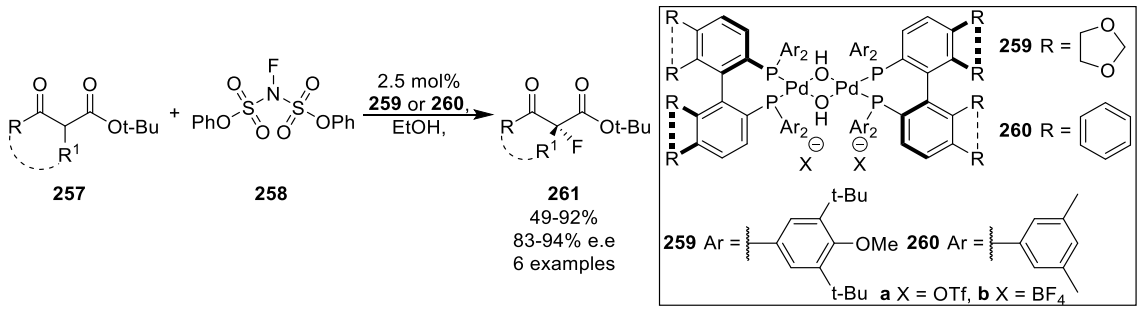
Scheme 103: Sodeoka's Activation of Ni[(R)-BINAP]Cl_2 Catalyst with Silyl Triflate.

Our group took advantage of this advance to activate achiral nickel chloride complexes to form active catalytic species in our reactions of nickel enolates of chiral *N*-acyl thiazolidinethiones with various electrophiles (see Chapter 1 and 2).[5–11] We hoped to one again use this finding to create chiral nickel chloride pre-catalysts which could be activated *in-situ* to form the active catalytic species. One other important observation made by Sodeoka was the use of the trialkylsilyl triflates. This opened another reaction pathway without the catalyst, which inherently was non-selective.[19] This was possible due to the silyl ether being able to be formed and reacting with the electrophile. This was contained by lower temperatures, low excesses of triflate and was solvent dependent. While not necessarily a problem it was something to keep in mind that could be a possible source of enantioselectivity degradation.

Palladium Enolates in Enantioselective Fluorinations

Sodeoka's initial results on enantioselective fluorination reactions were based on the reaction of enolates of β-keto esters, formed from a palladium chiral catalyst, with an electrophilic fluorine source (Scheme 104).[13] The presence of the ester group makes the α-proton more acidic whereas the sterically hindered Cα-tertiary center makes these substrates challenging. Said enolate was formed using one of a selection of four dimeric palladium catalysts either with DTBM-SEHPHOS ligands (**259**) or dimethyl-BINAP ligands (**260**) with either triflate (**a**) or fluoroborate (**b**) counterions. The enolate

was then reacted with NFSI (**258**) to give the product **261** in low to excellent yields with high to excellent enantioselectivity.

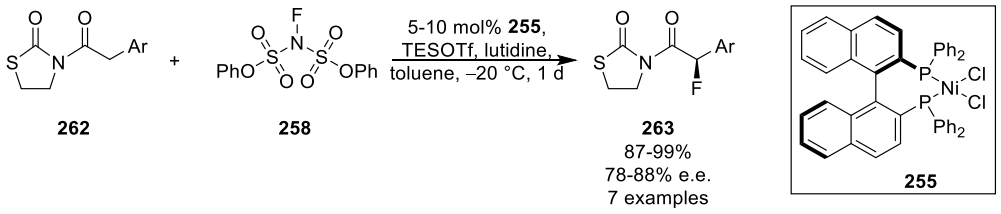


Scheme 104: Sodeoka's Enantioselective Fluorination of β-Keto Esters.

Nickel Enolates in the Enantioselective Halogenation of Oxazolidinones and Thiazolidinones

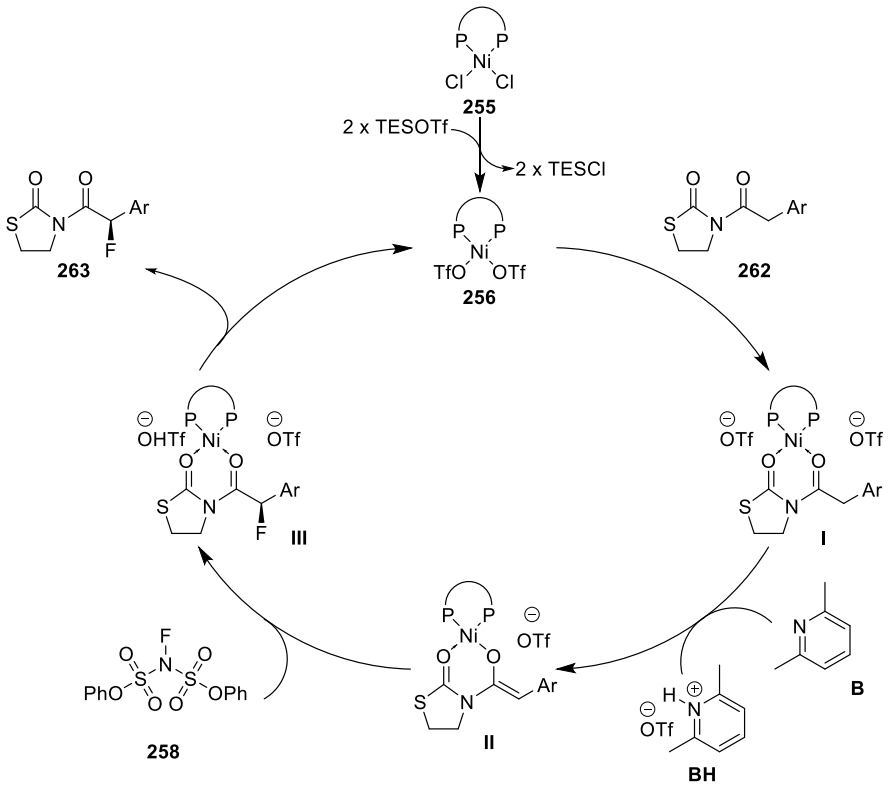
One solution for the lack in selectivity in the fluorination of adducts without a tertiary carbon at the α-position first came in the form of *N*-acyl thiazolidinones. These achiral substrate with two Cα-hydrogens and the possibility of double reaction were investigated as a solution for the over-fluorination and low selectivity previously seen by substrates lacking a secondary α-substituent.[19]

The *N*-arylacetyl thiazolidinones **262** were reacted with NSFI (**258**) in the presence of the nickel-BINAP complex **255** and triethylsilyl triflate (Scheme 105). The fluorinated adducts **263** were obtained in excellent to exceptional yields with good to high enantioselectivity. As shown in Scheme 103, the nickel(II) complex was activated to the catalytic species by chloride/triflate ligand exchange. The triflate Lewis acid also activated the fluorinating agent **258** and making it more electrophilic therefore promoting the reaction. The *N*-propanoyl counterpart was also attempted in the reaction conditions, but both a poor yield of 15% and enantioselectivity of 11% was achieved. This suggested that the aromatic group was necessary for the reaction to proceed correctly and was attributed to the acidity of the α-proton affecting enolate formation. Due to the lower selectivity a favourable aromatic-aromatic interaction between the substrate and catalyst should not be ruled out either. This reaction shows a considerable advance in the fluorination of substrates containing only one group in the α-position; Sodeoka also demonstrated the ease of removal of the scaffold allowing different functionalisation and recovery of the scaffold.



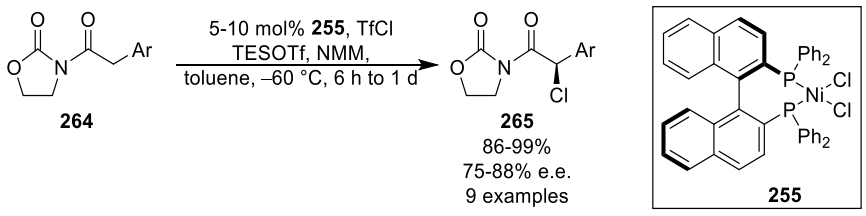
Scheme 105: Sodeoka's Fluorination of Thiazolidinones Catalysed by a Chiral Nickel Catalyst.

The proposed catalytic cycle for the reaction is shown in Scheme 106. It is somewhat similar to that described by Evans (see Scheme 102).[3] The first stage is the activation of the pre-catalyst species **255** to the active catalyst **256** through the ligand exchange. This then interacts with the starting material **262** to form the coordinated complex **I**. Deprotonation with lutidine (**B**) then leads to the *Z*-enolate species **II** which reacts with the electrophile **258** to form the fluorinated adduct **III**. The ligands bound to the nickel(II) centre block one π-face of the enolate and force the electrophile to approach from the other face. The adduct **III** then undergoes dissociation of the catalyst to give the chiral product **263** and reforms the catalytic species **256** and complete the catalytic cycle.



Scheme 106: Mechanism for the Fluorination Reaction by Sodeoka.

With a methodology for the enantioselective fluorination of α-aryl substrates developed, Sodeoka then moved to expand the scope to other halogenating compounds, namely in the use of chlorinating agents to perform selective chlorination reactions.[18] After testing different chlorine sources triflic chloride was shown to have the best results in terms of selectivity. In this case the use of the oxazolidinone scaffold was necessary as the thiazolidinone scaffold gave an inseparable mixture of the product and starting material. Therefore, starting material **264** was successfully chlorinated to give the product **265** in excellent to exceptional yields with high to good enantioselectivity (Scheme 107); the chiral nickel-BINAP complex **255** was used to form the catalyst, which then formed the enolate species and controlled the stereochemistry as in the previous fluorination reaction. A change from the lutidine base to *N*-methylmorpholine and the lowering of the temperate to –60 °C were key in increasing the enantioselectivity of the reaction. The yields for the reaction were more consistent but except for the simplest case of a phenyl substrate the catalyst loading was required to be 10 mol%.



Scheme 107: Sodeoka's Chlorination of Oxazolidinones.

These reactions, although not alkylation reactions, lend significant insights into the use of chiral enolates in enantioselective nucleophilic S_N1-like reactions. Furthermore, the use of silyl triflates to activate nickel(II) chloride complexes *in-situ* was a cornerstone of some of our previous methodology using nickel complexes. Finally, the use of achiral acylated scaffolds in halogenation reactions with its

parallels to our proposed enantioselective alkylation reactions gave us belief the methodology not only had potential but was viable.

Precedent from Our Group and Design of Our New Alkylation Reaction

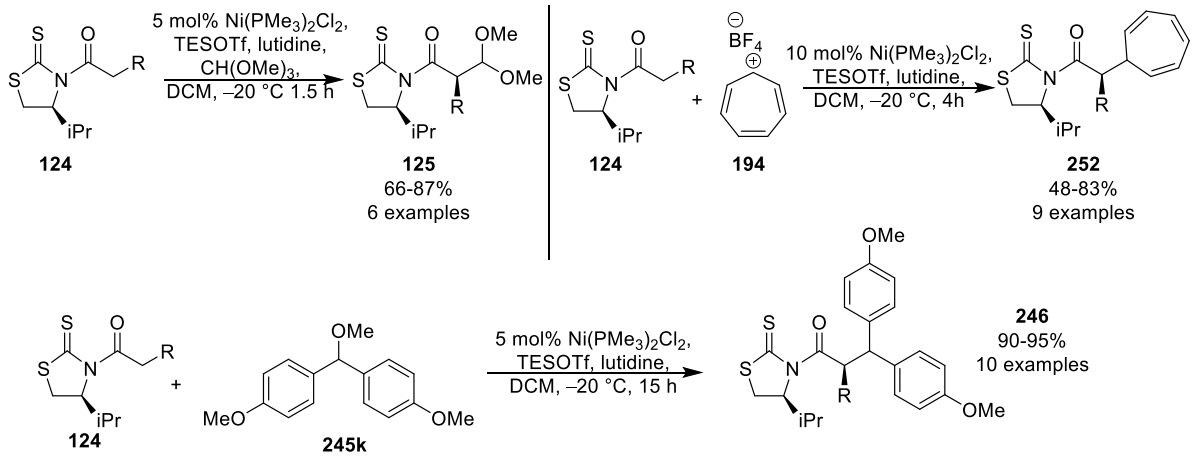
Our group for many years has been working to develop new stereoselective alkylation methodologies. More recently, we have been focused on the use of chiral enolates derived from chiral *N*-acyl thiazolidinethiones (Scheme 108).[5–10] The enolate was promoted by an achiral nickel(II) catalyst, which was generated *in-situ* from the chloride complex using triethylsilyl triflate following Sodeoka's methodology.[19]

Alkylation Methodologies Based on Chiral Thiazolidinethiones

The initial reaction studied in the group was based on the enantioselective addition of trimethyl orthoformate to chiral *N*-acyl thiazolidinethiones, catalysed by a nickel (II) complex (Top Left, Scheme 108).[5] Using the chiral auxiliary substrate **124** it was possible to exert complete control over the configuration of the products **125**. The putative catalyst was an achiral nickel(II) triflate: $Ni(PMe_3)_2(OTf)_2$, that was generated *in-situ* from the corresponding chloride. The silyl triflate complex acted both to activate the catalytic species and the electrophile to form the required oxocarbenium ion. We also succeeded applying the methodology to the synthesis of a fragment of Peloruside A as discussed in Chapter 1.[7]

In Chapter 2 a new methodology for the alkylation of chiral enolates with stable carbocationic salts was presented (Top Right, Scheme 108).[9] Again the use of the chiral *N*-acyl thiazolidinethiones **124** with $Ni(PMe_3)_2Cl_2$ and triethylsilyl triflate was key to the reaction with the chiral auxiliary imparting the stereocontrol and the catalyst activating the α-position to form the enolate through coordination. Although moderate yields were achieved for the challenging phthalimide substrate the other products **252** were obtained with good to excellent yields. Due to the use of a carbocationic salt the activation of the electrophile was not necessary and the quantity of triflate could be significantly reduced.

The use of diarylmethyl ethers as electrophiles in a related alkylation reaction with acylated chiral thiazolidinethiones, $Ni(PMe_3)_2Cl_2$ and triethylsilyl triflate was also assessed (Bottom, Scheme 108).[6] The methyl ethers were activated *in-situ* by the triflate reagent to form diaryl carbenium intermediates. The *N*-acyl thiazolidinethiones **125** were again used, giving exceptional yields of **246** as a single diastereoisomer. Other diaryl methyl ethers were also used with general success in the reaction, with weakly or non-activated aromatic rings being the limit of the methodology.



Scheme 108: Stereoselective Reactions Based on Chiral N-Acyl Thiazolidinethiones: Top Left: Orthoformate Addition; Top Right: Stable Cationic Salt Addition; Bottom: Reaction with Diarylmethyl Ethers.

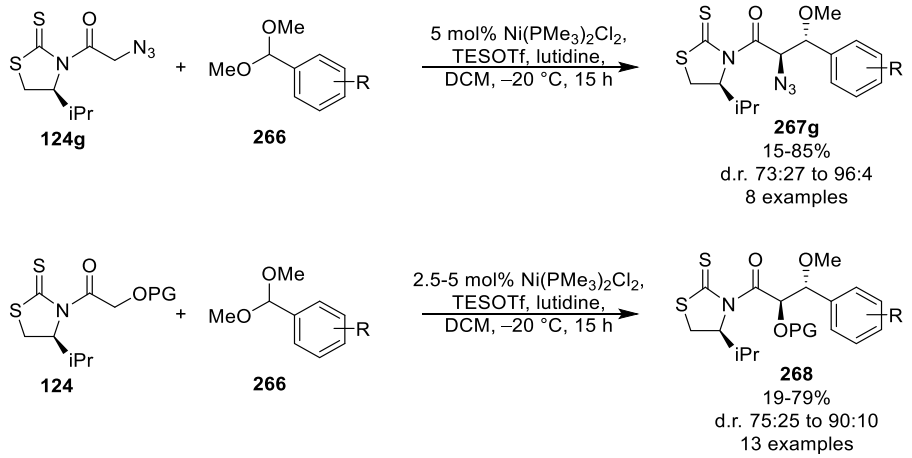
All three methodologies gave complete control over the new α-stereocentre due to the chiral auxiliary blocking one π-face of the formed enolate via the steric effects of the isopropyl group at the C4 position. The achiral nickel complex coordinated to the 1,3-carbonyl-thionyl group making the α-proton more acidic and easily deprotonated by the weak amine base to form the enolate; after reaction it then dissociated to reform the catalytic species. We then planned to merge these concepts using a chiral nickel complex to form the enolate from acylated achiral scaffolds containing a 1,3-carbonyl/thionyl structure. The catalyst would also be activated, according to our methodology adapted from Sodeoka,[19] from the chloride complex with silyl triflate reagents. The electrophiles either contained already or were activated *in-situ* to give carbenium or oxocarbenium intermediates that react with the enolate species. As all the reagents are present in the initial reaction vessel or are activated upon the reaction start, the reactions are therefore direct reactions, which do not require preformation of either the enolate or the electrophile species.

Chiral Auxiliary Based Enolates in Reactions with Dialkyl Acetals

Our group has also developed methodologies for the reaction of nickel(II) enolates generated catalytically from *N*-acyl thiazolidinethiones to dialkyl acetals; first with azidoacetyl substrates and later with various protected hydroxyacetyl substrates.[8,11] The methodology was applied to the synthesis of peptides containing an *anti* β-hydroxy tyrosine structure.[10]

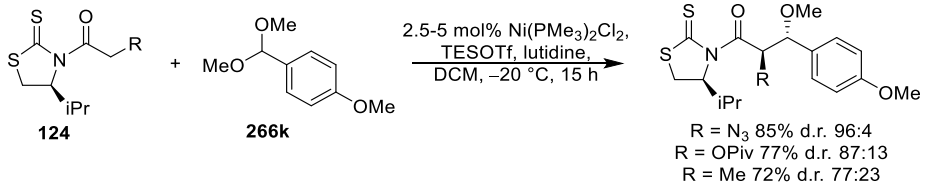
After trialling different protecting groups for α-aminoacetyl derivatives in the reaction of dialkyl acetals with nickel (II) enolates, the azide group was found to be the most selective for the *anti*-product.[8] The azido substrate **124g** was reacted with various dimethyl acetals **266** to give the adducts **267** in varied yields and diastereoselectivites ranging from good to excellent (Top, Scheme 109). The nature of the aromatic group of the acetal was important both for the selectivity and the yield. Non-activated benzyl and deactivated *m*-methoxy or *p*-chloro derivatives gave lower yields even with higher catalyst loadings (15-57% with either 10 or 20 mol% catalyst). The selectivity was also lower for the benzyl and the *m*-methoxy benzyl derivatives (77:23 and 73:27 respectively). The other acetals gave products with yields of over 73% and selectivities of 82:18. Other alkyl acetals such as allyl or benzyl acetals were also tolerated with little change in the yield or selectivity. Acetals formed from cobalted propanaldehyde derivatives were also used as electrophiles and bar one case gave complete stereocontrol of the reaction.

Later this methodology was expanded to substrates containing a protected alcohol at the α-position.[11] Therefore, the glycolate derivatives of **124** were reacted with dimethyl acetals **266** to give the α-hydroxy-β-methoxy products **268** in varied yields with good to high diastereoselectivites, with all results being slightly lower than the corresponding result for the azido derivatives (Bottom, Scheme 109). The best protecting group in terms of both selectivity and yield was the pivalic group, with the benzyl and benzoyl groups performing only slightly lower; silyl protecting groups and the methyl ether gave comparable selectivity but with much lower yields. Other dialkyl acetals again proved to be widely interchangeable with allyl and benzyl acetals just slightly lower yields and selectivity. Again α,β-unsaturated acetals were used but in this case the selectivity, whilst higher than the aryl electrophiles, was not absolute.



Scheme 109: Reaction of N-Acyl Thiazolidinethiones with Dimethyl Acetals. Top: N-Azidoacetyl Derivatives; Bottom: Protected N-Hydroxyacetyl Derivatives.

The use of simple alkyl chains was also investigated; unfortunately, the selectivity and yield were lower still than the glycolate derivatives and were synthetically useless and were not investigated to the extent of the heteroatom derivatives (Scheme 110).[20] The highest selectivity seen was using the *p*-anisaldehyde dimethyl acetal which gave a selectivity of around 3:1, whereas other acetals gave results closer to 60:40. For this reason the project was shelved.



Scheme 110: Reaction of Chiral N*-Acyl Thiazolidinethiones with Dimethyl Acetal* ***268a****.*

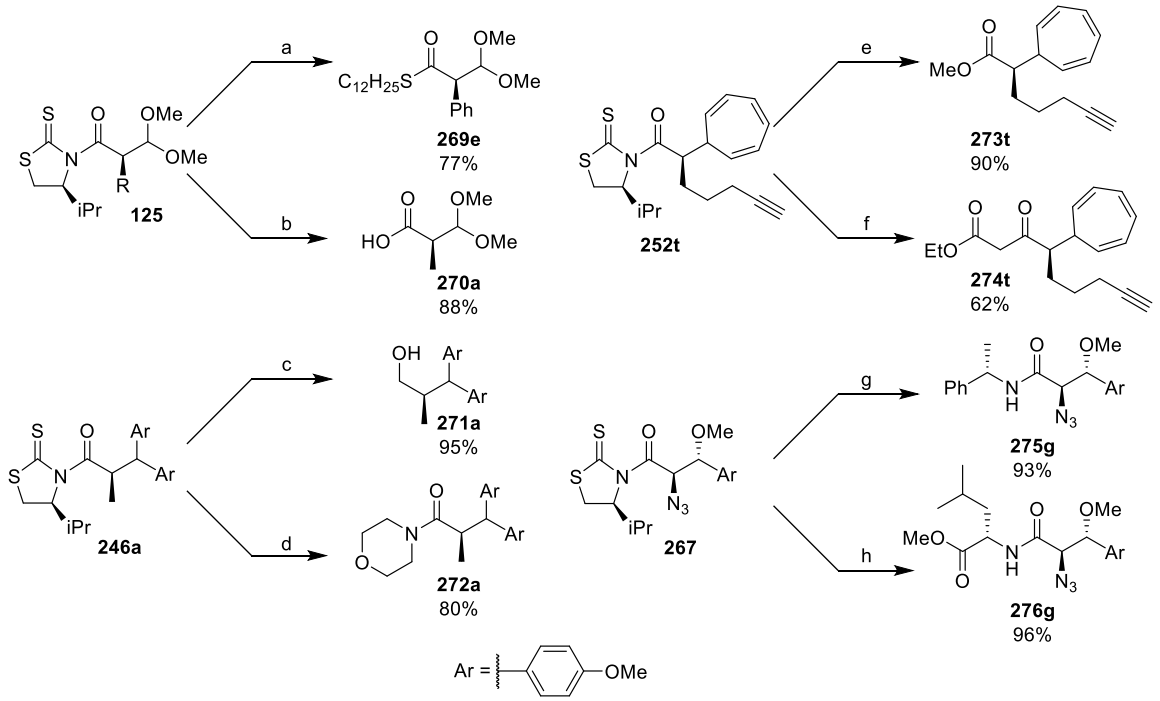
The use of chiral auxiliaries to control the stereochemistry of two newly formed stereocentres through the reaction of nickel(II) enolates and acetal electrophiles was primarily successful with yields and selectivities in general from good to excellent. However, it also highlighted the additional complexity implied with regard to controlling just one stereocentre, something we had achieved extensively.

Chiral Auxiliary Removal

Over the different methodologies developed using chiral thiazolidinethiones in alkylation reactions we have described various methods for the removal and recovery of the auxiliary leaving various functionality in its place.[5,6,8,9] This was one of the most important factors in offsetting the economy cost of using a chiral auxiliary, if it can be recovered and reused then it is no longer a waste product, and if it can remove a step/steps by furnishing a desired functionality then it can also shorten synthetic sequences.

We have therefore developed various ways of removing the auxiliary; an example of each is shown in Scheme 111. In the initial reaction of orthoformate two removals were described to leave two functional groups: a carboxylic acid **270a** and a thioester **269e**.[5] Nucleophilic displacement with the thiol using the phenyl adduct **125e** gave way to the thioester and hydrolysis of the methyl adduct **125a** with lithium hydroxide provided the acid. For the diarylmethyl ether reaction two new removals were introduced with the alcohol product **271a** and the morpholine amide product **272a** being made.[6] The alcohol was made via reduction with lithium borohydride and the amide through nucleophilic displacement with morpholine. The alkylation with stable carbocationic salts yielded another two new

removal strategies leaving an ester group in **273t** and a β-keto ester **274t**.[9] Displacement of the auxiliary with methanol gave the methyl ester product and the reaction of the sodium enolate of ethyl acetate gave the β-keto ester product. Finally, the reaction of dimethyl acetals yielded two new amide derivatives: one derived from a chiral amine (**275g**) and one from an amino ester (**276g**).[8] Both products were obtained by the nucleophilic displacement of the auxiliary (which acts as a coupling agent) with the chiral amine or ester derivative of the amino acid leucine.



a: $C_{12}H_{25}SH$, BuLi, THF, 0 °C, 45 min; b: LiOH, THF/H_2O, 0 °C, 5 h; c: $LiBH_4$, THF, –78 °C to RT, 15 h; d: morpholine, TEA, DMAP, DCM, RT, 15 h; e: MeOH, DMAP, RT, 24 h; f: EtOAc, NaHMDS, THF, –78 °C, 4 h; g: (*S*)-α-methylbenzylamine, DCM, RT, 4 h, h: HCl·HLeuOMe, DIPEA, THF, RT, 4 h.

Scheme 111: Removals of the Chiral Auxiliary from Our Different Methodologies.

In all cases the yields were high to exceptional with most being above 80%. This showed the utility of the chiral auxiliary and proved the variety of functionality that can be imparted when they are removed. In developing our new methodology with achiral scaffolds, this consideration remained as important and one of our aims was to find a scaffold that could be as easily, if not more so, removed as the chiral auxiliaries.

New Enantioselective Reactions

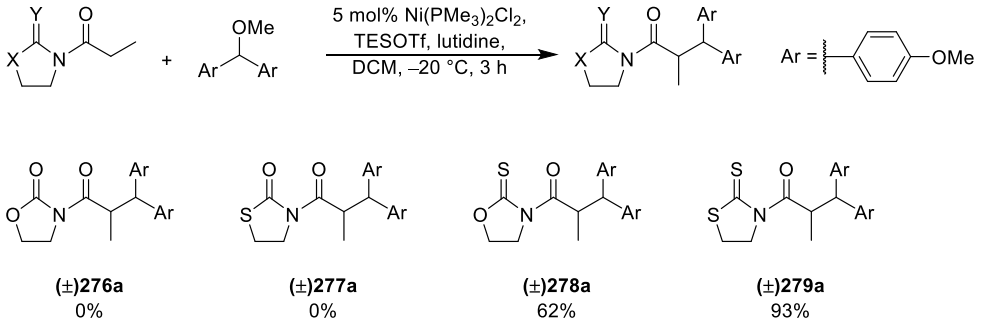
Keeping in mind the abovementioned precedents, we envisaged that moving from the source of stereocontrol from the chiral auxiliary to a chiral complex might increase the synthetic potential of the method. Thus, we launched a comprehensive assessment of new enantioselective carbon–carbon bond forming reactions based on the reactivity of nickel(II) enolates arising from achiral *N*-acyl heterocycles (the heterocycle is usually named as *scaffold*) formed catalytically from a chiral nickel(II) complex.

Development of a New Achiral Scaffold

In the initial stages of our development we realised the choice of the achiral scaffold was key; in former studies using chiral auxiliaries and titanium or nickel enolates the nature of the heteroatoms proved to be crucial to both the yield and selectivity of varying reactions.[21,22] We believed this would translate to the related achiral scaffolds. Evans used the achiral analogue of the thiazolidinethione auxiliaries

we have experience with in his orthoformate alkylation reaction;[3] Sodeoka used both oxazolidinone and thiazolidinone scaffolds in her enantioselective halogenation reactions.[18,23] Therefore we first examined the four possible combinations of sulphur and oxygen heteroatoms in the five-membered scaffold.

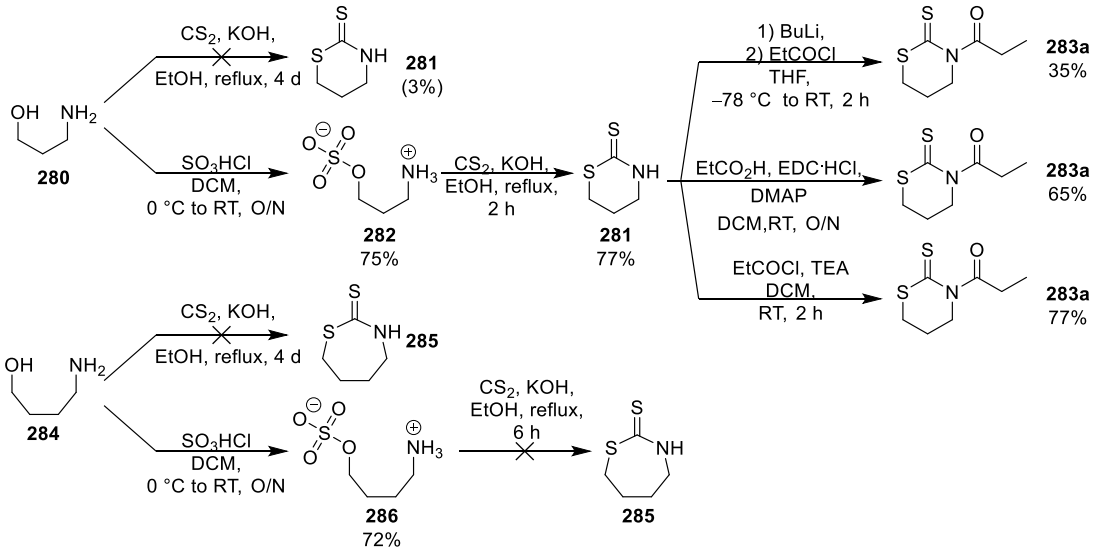
As expected from our previous experience with chiral auxiliaries, scaffolds containing an exocyclic oxygen atom did not provide a suitable platform for the reaction and no product was observed when reacted with the diarylmethyl ether electrophile chosen for the optimisation reactions (Scheme 112). The two derivatives with exocyclic sulphur atoms both facilitated the reaction, with the thiazolidinethione giving the higher yield in the same conditions over the oxazolidinethione.



Scheme 112: Testing of Different Achiral 5-Membered Scaffolds.

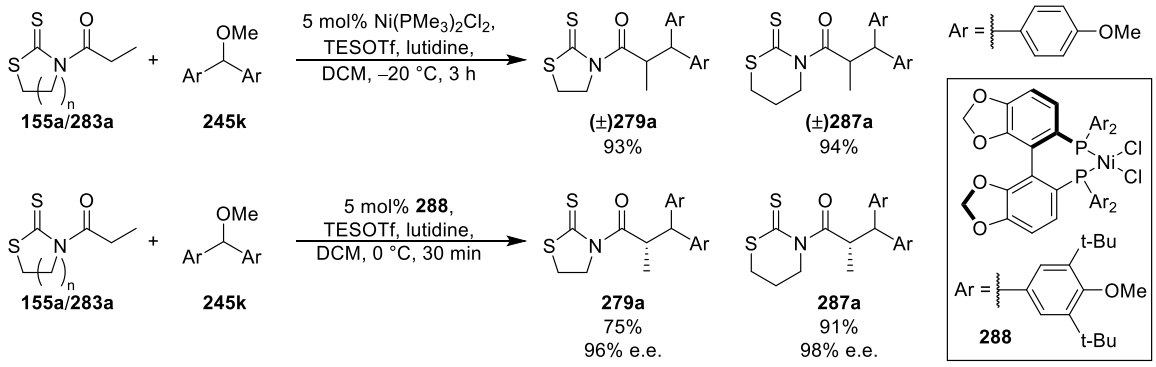
With the combination of two sulphur atoms clearly giving better results, we then moved to examine new achiral scaffolds containing dithiocarbamate cores. We initially investigated increasing the ring size to examine the effects on the yield and selectivity of the reaction. We aimed to make both the six- and seven-membered derivates. The method we normally utilised for the formation of thiazolidinethione chiral auxiliaries was the reaction of the amino alcohol with and excess of carbon disulphide in basic conditions at reflux.[24] This however did not work for either of the amino alcohols **280** or **284** with minimal yields of six-membered **281** and no trace of the seven-membered **285** found after four day reaction times (Scheme 113). We therefore attempted a procedure described by Wipf and optimised by Okamoto and Miyashita that involves first forming the hydrogen sulphates **282**/**286**. Gratifyingly, both substrates were obtained in high yields.[25,26] Next, attempts at their cyclisation was then made using a similar methodology adapted for use with the hydrogen sulphate compounds. The six-membered scaffold **281** was isolated initially in a high yield but unfortunately, the seven-membered analogue **285** was not observed even after longer reaction times.

Once obtained, the new thiazinanethione scaffold **281** was then acylated using the standard conditions for the acylation of the thiazolidinethione auxiliaries, which was using butyl lithium to deprotonate the nitrogen atom and then subsequent reaction with the acyl chloride.[24] This led to the acylated product **283a** but with low yields (Scheme 113). We also examined a coupling procedure using the carboxylic acid and coupling agent EDC which had proven successful previously;[9] this improved the results and gave the product in a good yield. Finally, we examined milder acylation conditions using the acyl chloride and triethylamine as a base; this gave the best results and provided the product **283a** in a high yield. The synthetic route to the product **283a** was therefore the transformation of the amino alcohol to the hydrogen sulphate and its subsequent cyclisation followed by acylation with the acyl chloride and triethylamine, which was submitted to optimisation to improve the yields. The option of using the carboxylic acid and a coupling agent is also a good alternative for acyl groups that do not have the acid chloride readily available with the yield being only marginally lower.



Scheme 113: Initial Results in the Synthesis and Acylation of Six-Membered Scaffold and Attempted Synthesis of Seven-Membered Scaffold.

With the six-membered scaffold prepared, we then investigated whether it had any beneficial effect over the five-membered analogue in terms of yield but also in terms of selectivity. After an examination of different catalysts, we determined that the DTBM-SEGPHOS ligand was the most selective. The results of the acylated scaffolds in the alkylation reaction with both the achiral and chiral pre-catalyst **288** are shown below in Scheme 114. Whilst the difference between the two is minimal using the achiral catalyst the difference is clear when using the chiral DTBM-SEGPHOS catalyst. The yield is significantly higher for the six-membered analogue; furthermore, the selectivity was also higher, a trend shown across all catalysts tested. Hence, we concluded that the best scaffold to conduct the alkylation reactions was the six-membered thiazinanethione and the optimisation of the reactions conditions was conducted using the compound **283a**.

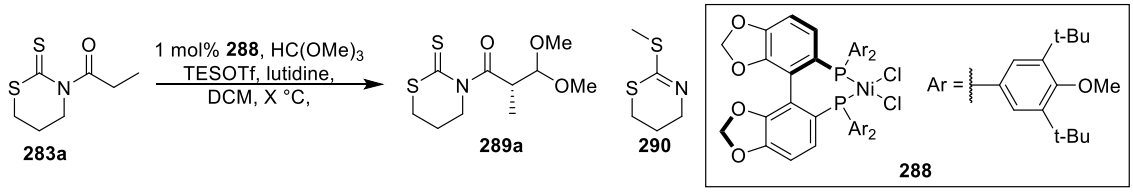


Scheme 114: Comparison of Five-Membered and Six-Membered Scaffolds in the Alkylation Reaction.

Other Electrophiles

We also sought to expand the methodology to other electrophiles to make it more of a universal procedure. The first we turned our attention to was the trimethyl orthoformate electrophile used by Evans in his alkylation reaction.[3] In our optimised conditions for the related alkylation reaction with diarylmethyl ethers we observed a low yield of product **289a** (46%); upon further examination we observed the formation of a side-product **290** arising from the nucleophilic character of the exocyclic sulphur atom attacking the activated electrophile (Table 2). The initial ratio of the products was 50:50, we believed reducing the temperature would decrease this background reaction and favour the

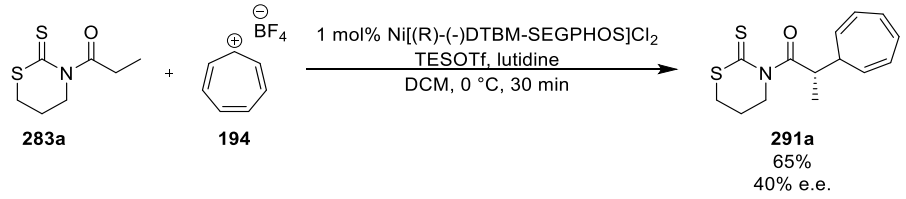
catalysed alkylation reaction. Indeed, reducing the temperature by twenty degrees saw a shift to a 75:25 ratio in favour of the desired product and reduction by a further twenty degrees abolished its formation entirely. The final results using this electrophile can be seen in the following paper.



ENTRY	TEMPERATURE (X °C)	289a/290
1	0	50:50
2	-20	75:25
3	-40	100:0

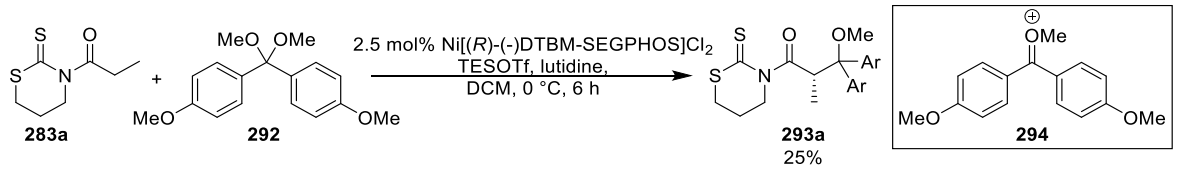
Table 2: Effect of Temperature on the Formation of a Side-Product in the Orthoformate Alkylation.

In Chapter 2 we a reaction of nickel(II) enolates with stable carbocationic salts, so we took advantage of this knowledge and used this class of electrophile with our new conditions. For tropylium tetrafluoroborate **194** we tested the established protocol, which furnished the expected product **291a** in a good yield albeit with a low enantioselectivity (Scheme 115). The low enantioselectivity is most likely due to a background reaction which does not involve the chiral catalyst and is most likely promoted by the silyl triflate Lewis acid and therefore racemic which erodes the overall selectivity. To counter this, we decided to optimise the reaction conditions, mainly the catalyst loading, the results of which can be seen in the following paper.



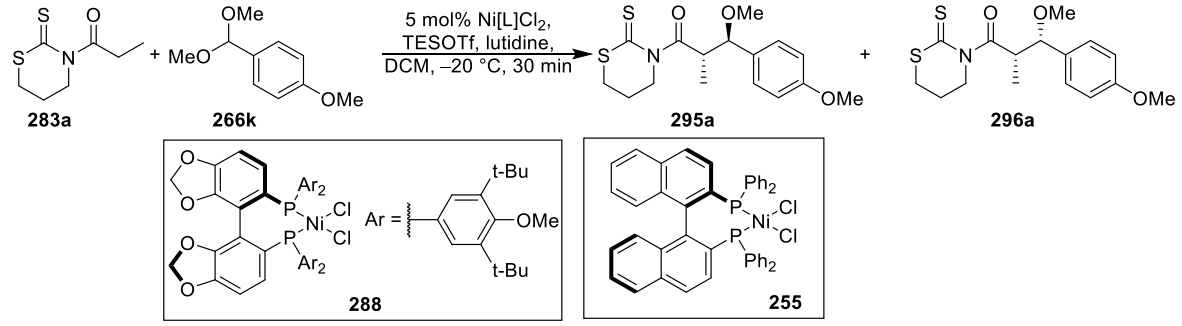
Scheme 115: Initial Results with Tropylium Tetrafluoroborate.

We also trialled a new class of electrophile which presented an additional challenge: dimethyl ketal substrates (**292**), related to the diarylmethyl ethers used in the initial optimisation but with an additional methoxy group (derived from a ketone instead of an alcohol). This means the activated electrophile would be the oxocarbenium cation **294** (Scheme 116), similar to that seen with the orthoformate electrophile and more hindered than the corresponding carbenium ion arising from the activation of the diarylmethyl ethers. In the initial reaction conditions (1 mol% catalyst) only traces of the product **293a** were observed and the catalyst loading had to be increased to 2.5 mol% to achieve the product in a reasonable quantity (Scheme 116). Again, we ran optimisation of the reaction conditions changing both the catalyst loading and the reaction time to see if increasing either or both could increase the yield; the final results can be found in the following paper.



Scheme 116: Initial Results with Diaryl Methyl Ketal.

When performing the reaction with the achiral nickel complex and the dimethyl acetal compound **266k** to form the racemate (±)**295a** at –20 °C, we observed a promising initial selectivity towards the *anti*-product of 72:28 (Entry 1, Table 3). We then tested the reaction with different chiral catalysts. The BINAP ligand gave predominately the *anti*-product **295a** with excellent enantioselectivity but with a selectivity over the *syn*-adduct of 60:40 (Entry 2, Table 3). Interestingly, the DTBM-SEGPHOS ligand provided the *syn*-product **296a** as the major diastereoisomer with a ratio of 70:30 (Entry 3, Table 3). We speculated that this reversal in selectivity is due to the sheer bulk of the DTBM-SEGPHOS catalyst blocking more effectively and a larger area of the enolate π-face. Also having a possible effect is the narrower bite angle of the SEGPHOS over the BINAP family (dihedral angle θ: 65.5 for SEGPHOS, 74.5° for BINAP).[27] This then caused the acetal to approach in a specific manner in the transition state reducing steric clashing.



Entry	Nickel Complex	Ratio *Anti*/*Syn*	e.e.
1	$Ni(PMe_3)_2Cl_2$	72:28	0%
2	Ni[(*R*)-BINAP]Cl_2 (**249**)	60:40	98%
3	Ni[(*R*)-(-)DTBM-SEGPHOS]Cl_2 (**290**)	30:70	>99%

Table 3: Reaction with Acetals Catalysed by Different Catalysts.

Unfortunately, adduct **296a** proved difficult to separate from its diastereoisomer **295a** but the results in the selectivity are promising. In fact, this warrants further investigation in a project dealing with the addition of chiral nickel(II) enolates to oxocarbenium intermediates from acetals.

Limitations of our Methodology

We achieved wide success in the expansion to other electrophiles and starting materials, but our method failed in a few cases. These marked the limit of the methodology for varied reasons. Some were due to unwanted side-reactions, others for problems in activation or degradation of products or reagents. Following is a summary of some of the most relevant cases we found to be incompatible with our methodology and the reasons why.

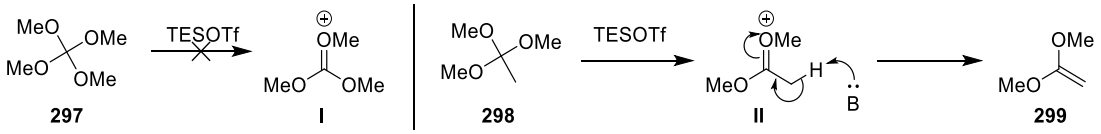
Other Methoxy Derivatives

With the success of trimethyl orthoformate, diarylmethyl ethers and diarylmethyl ketals, we also investigated other methoxy containing groups that could potentially be activated *In-situ* to form oxocarbenium or carbenium ions. We looked at two reagents closely related to trimethyl orthoformate: tetramethyl orthocarbonate **297** containing an additional methoxy group, and trimethyl orthoacetate **298** containing a methyl group instead of a hydrogen (Scheme 117). Unfortunately, both compounds did not work in the reaction conditions because of problems in the activation of the electrophile.

The presence of the activated oxocarbenium ion **I** was not observed in the reaction mixture from tetramethyl orthocarbonate **297** and upon work-up the unaltered reagent was recovered (Left, Scheme 117). This suggests that the triethylsilyl triflate was not sufficient to activate the electrophile

and therefore the reaction could not proceed. Even at higher temperatures the activated compound was not observed.

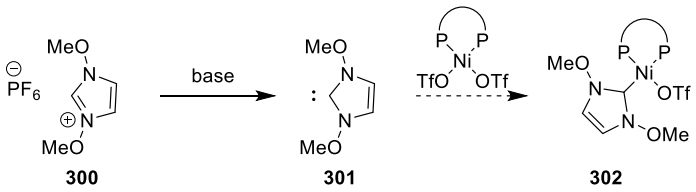
For the orthoacetate reagent **298** the activation took place to give the active compound **II** but due to the methyl group next to the oxocarbenium ion it makes it ripe for deprotonation (Right, Scheme 117). In fact, we observed the product **299** arising from the deprotonation of the activated compound **II** by lutidine and the only compound related to the electrophile isolated was the elimination product.



Scheme 117: Activation Attempts of Tetramethyl Orthocarbonate and Trimethyl Orthoacetate.

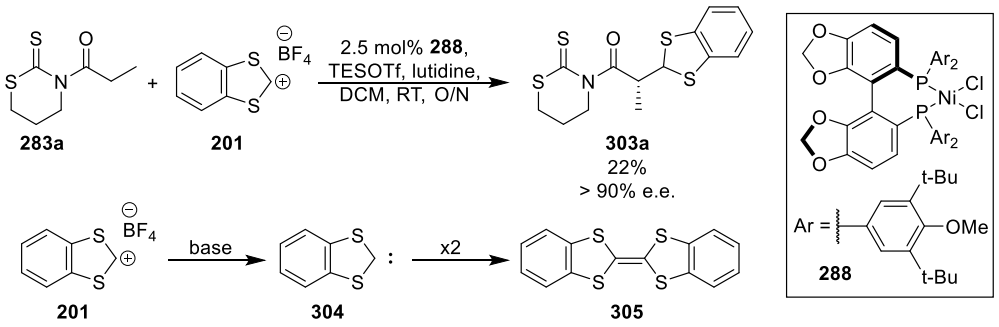
Other Carbocationic Salts

Following from the success of the reaction with the tropylium cation, we investigated different classes of carbocationic salts for their incorporation into our enantioselective reaction. One of the initial cations we trialled was the dimethoxyimidazolium salt **300** (Scheme 118). We observed upon submission to the reaction conditions a fast auto-quench of the reaction, so no desired product was observed and we recovered the acylated starting material intact. Heterocyclic imidazolium salts have been shown to form carbene compounds upon the reaction with base;[28] thus we believe this was happening and the reaction of **300** and lutidine in the reaction mixture triggered the formation of the *N*-heterocyclic carbene (NHC) **301**. These carbene species have been noted to react with nickel-phosphine species in complexation reactions.[29] Therefore we assumed the formation of **301** led to reaction with the catalyst to form the complex **302** which does not catalyse the reaction.



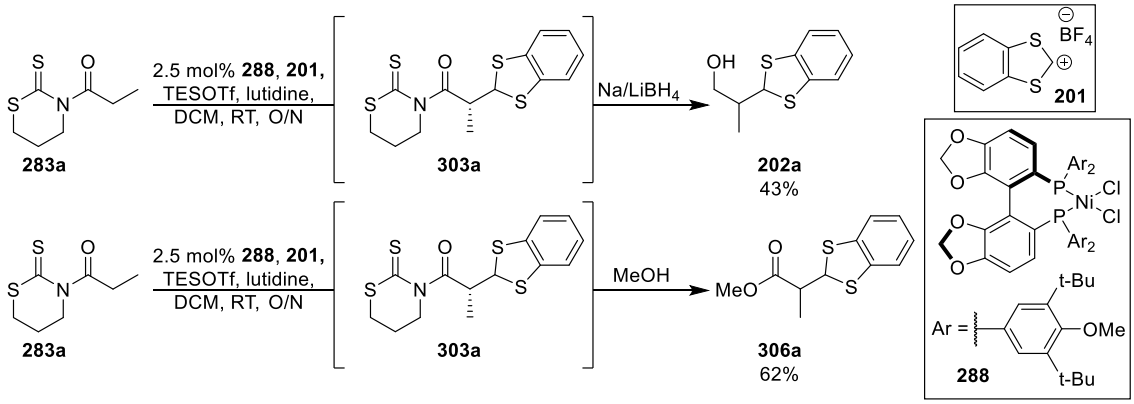
Scheme 118: Formation of Carbene Species from Imidazolium Salts and their Presumed Reaction with the Catalytic Species.

The other cationic species we attempted to use in our methodology to little success was the benzodithiolylium salt popularised by Cozzi as an electrophile in organocatalytic alkylation reactions and discussed in Chapter 2.[30] We initially had problems from a background reaction arising from the formation of carbene **304** from the cationic salt **201** and the lutidine base in the reaction; this species then dimerised to form the tetrathiofulvalene **305** (Scheme 119). Although we were able to optimise the reaction conditions to achieve full conversion to product **303a**, which proved to be unstable and was only isolated in yields below 30%. The isolated product degraded even under nitrogen atmosphere and at lower temperatures, making characterisation difficult. The enantioselectivity appeared to be generally above 90%.



Scheme 119: Initial Results with the Benzodithiolylium Cation and its Side Reaction with Base.

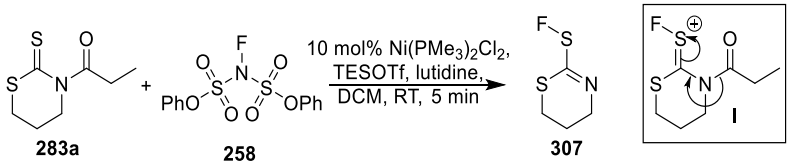
To counter the problem of the instability of the adduct **303a** we looked to the work of Cozzi for inspiration: he performed a direct reduction of the initial aldehyde adducts due to racemisation and instability to form the alcohol.[30] We therefore performed the alkylation reaction and used either sodium or lithium borohydride as a quenching reagent to form the alcohol product **202a** *in-situ* from the product **303a** (Top, Scheme 120). This improved the yield by a factor of two, but the product obtained was almost racemic. We attributed this to the racemisation of the initial adduct during the reduction process, especially as it passes through the easily racemised aldehyde substrate. We therefore tried quenching with methanol to form the methyl ester **306a** but this product, although isolated in a higher yield was also racemic or with low enantioselectivity. Due to the complexity of the electrophile and the problems with instability or racemisation we stopped investigation into its use in our reaction.



Scheme 120: Quench Attempts to Isolate Stable Products in Higher Yields.

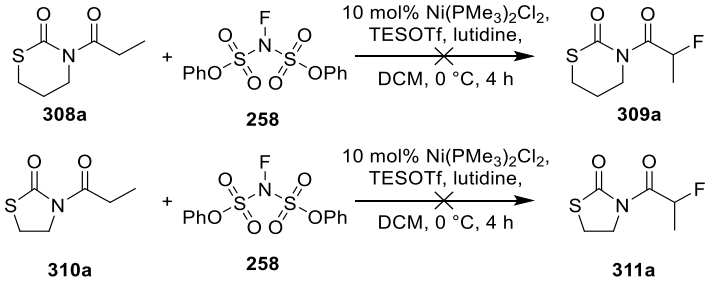
Fluorination

We also examined the fluorination reaction using the reagent **258** used by Sodeoka in her asymmetric fluorination reactions.[13,19] We attempted the reaction first with **283a** and $Ni(PMe_3)_2Cl_2$, but the desired product was never observed (Scheme 121). As predicted by Sodeoka, attempts with an exocyclic sulphur atom in the scaffold led to the nucleophilic fluorination of this sulphur position.[19] Indeed, the product formed was identified as the sulphur fluorinated product **307** which arises from the initial attack of the sulphur forming the intermediate **I** which then collapses as shown in Scheme 121.



Scheme 121: Attempt at Racemic Fluorination Reaction.

To neutralize this reactivity we synthesised the corresponding thiazinanethione and thiazolidinone scaffolds and upon acylation with propionyl chloride we obtained the two starting materials **308a** and **310a**, which contain an exocyclic oxygen atom in place of the sulphur (Scheme 122). This would remove the nucleophilic character of the scaffold and avoid the side reaction. Both substrates, when submitted to the reaction conditions did not produce any reaction and the expected adducts **309a** or **311a** were not observed and the starting materials were recovered. As observed in previous processes (see Scheme 106, Page 132) the reason was due to the exocyclic oxygen lending less activation to the α-position and the acidity not lowering enough for the enolate to easily be formed. This may be the reason Sodeoka took advantage of the stabilising aromatic acylated derivatives in her fluorination reactions, since the presence of the aromatic group should improve the acidity and facilitate the enolate formation.

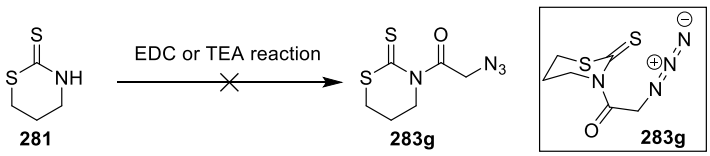


Scheme 122: Attempts of Enantioselective Fluorination with Thiazinanethione and Thiazolidinone Based Scaffolds.

With the potential solution being the limitation of the methodology to α-aryl substrates we decided it was not the best fit for our reaction profile and left the fluorination reaction for another potential project.

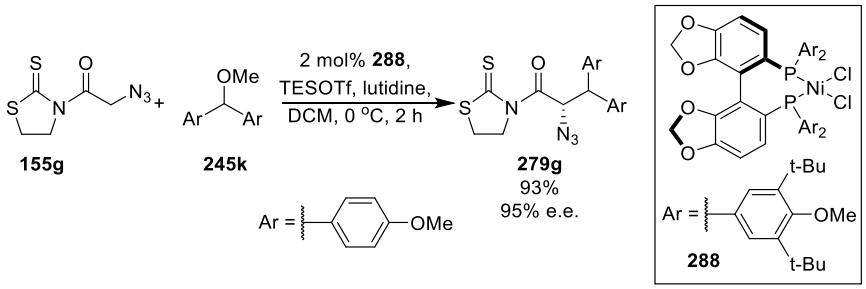
Azide Chain

One of the acyl chains we were not able to use in our initial methodology was the azidoacetyl group we had employed in various methodologies based on chiral auxiliaries.[6,8–10] Surprisingly, the synthesis of the starting material proved impossible. Using either the EDC coupling methodology with azidoacetic acid or triethylamine with the azidoacetyl chloride, we were unable to isolate the product **283g** (Scheme 123). At lower temperatures we saw the yellow colour indicative of the formation of the acylated dithiocarbamate structures and confirmed by TLC analysis, but upon either the warming or quenching of the reaction a black solution was quickly obtained and degradation of this adduct was observed. We speculate the reason for this degradation lays in the adduct's geometry which can place the nucleophilic sulphur close to the azide and then facilitate the attack of sulphur to the azide and cause degradation. It has been known for a long time that thionyl compounds can react with free azides and our acylated scaffold may inadvertently create the perfect geometry for an intramolecular version of this reaction.[31]



Scheme 123: Attempt at Forming the Azide Starting Material. Insert: Geometric Representation of Product.

Our experience on chiral *N*-azidoacetyl thiazolidinethione suggested that the five-membered scaffold might be a solution to solve such a drawback.[5,6,20] We believed that the less nucleophilic nature of the five-membered ring scaffold coupled with it being less flexible than the six-membered analogue should not produce degradation of the formed adduct. Pleasingly, we acquired the acylated thiazolidinethione product **155g** in good yields without hints of degradation. With the stable starting material in hand we were able to conduct the alkylation reaction to obtain the adduct **279g** with an exceptional yield and excellent selectivity Scheme 124).



Scheme 124: Reaction of Azide Thiazolidinethione Starting Material in the Alkylation Reaction.

The five-membered scaffold allowed us to use the previously unavailable azide functional group in the reaction and therefore presents an alternative if the more efficient six-membered scaffold becomes incompatible. With our methodology fully developed we turned our attention to a natural product as a synthetic target utilising our new alkylation reaction as the foundation for the synthesis.

Enantioselective Synthesis of Peperomin D

Peperomin D is a small natural product from the Peperomin family that was extracted from the *Peperomia* genus of plants.[32–35] It was first extracted in 1996 by Monache for the species *Peperomia Glabella* used in Venezuelan folk medicine as a treatment for asthma.[33] There are four other named compounds Peperomin A, B, C and E and many other related compounds that have been extracted from different species within the genus (Figure 31).[32,34,35] Whilst the biological activity of Peperomin D has not been studied, likely due to the lack of an efficient synthesis of the natural product, its family members have shown to have a wide range of biologically important effects including anti-cancer and anti-HIV activity.[32,34–41] For this reason an efficient synthesis of Peperomin D, which would allow the examination of its biological properties, is an important goal.

The five named Peperomin compounds are structurally related five membered lactones with a methyl or methylene substituent in the α-position and varying diaryl moieties at the β-position (Figure 31). The natural configuration of the A–D compounds had an *anti*-relationship between the methyl group and the diaryl substituents.

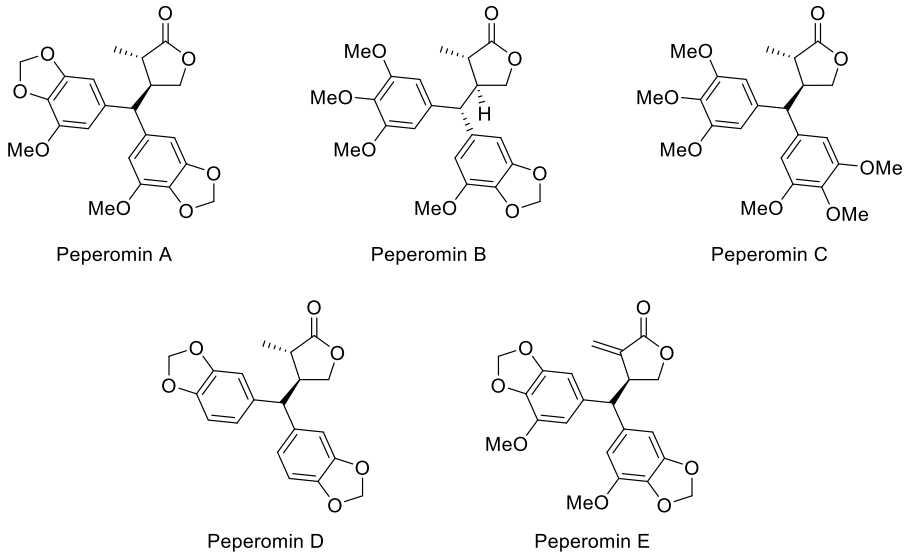


Figure 31: Natural Products from the Peperomin Family.

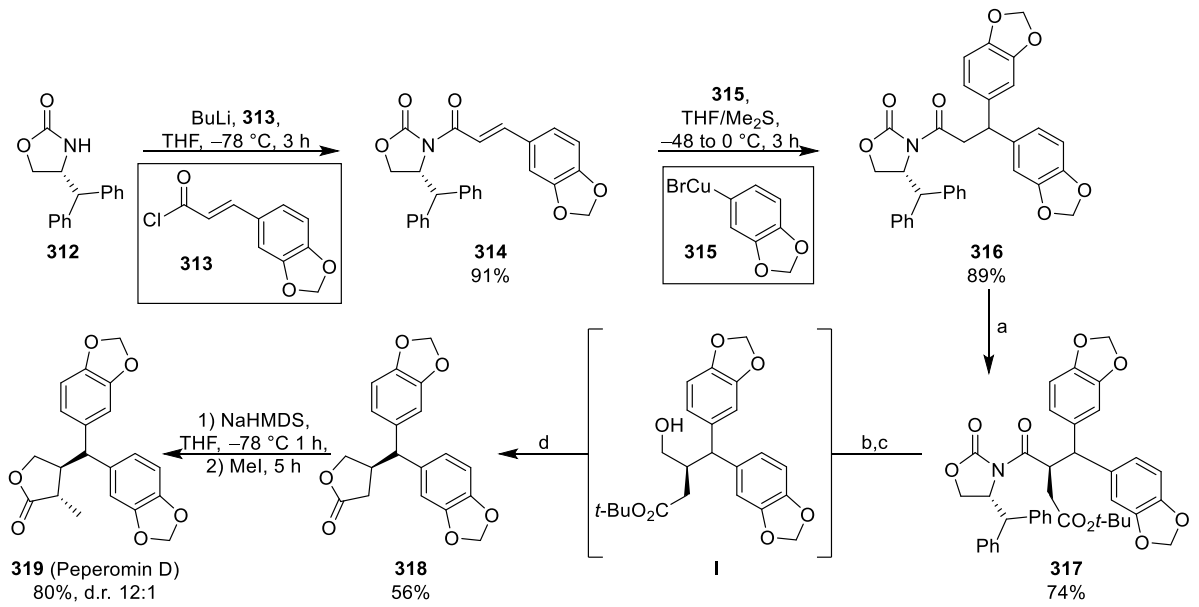
Due the structural similarity between the family we believed a methodology that revolved around the enantioselective introduction of a diaryl group such as the one we were developing would allow for the synthesis of various derivatives by simply changing the electrophile.

Previous Syntheses of Peperomin D and Related Analogues

Whilst there has only been one synthesis of Peperomin D to date,[42] various syntheses of the other members of the family have been reported.[42–48] Due to their structural similarity, all these syntheses are relevant to our investigation of Peperomin D even if they are racemic and therefore do not allow for a truly enantioselective synthesis of the natural products.[43,45,48]

Sibi's Synthesis of Peperomin A, C and D

Sibi published the (to date) only synthesis of the natural compound Peperomin D in a general methodology that also enabled the synthesis of the A and C natural analogues as well as two synthetic derivatives.[42] His synthesis of Peperomin D started from an Evans-like chiral auxiliary developed in his group (**312**, Scheme 125). This was acylated with a α,β-unsaturated acid chloride **313** to give the imide **314**. This introduced one of the required aryl groups in the molecule; the other was introduced in a subsequent conjugate addition. Indeed, addition of the aryl copper reagent **315** to the double bond gave the diaryl compound **316** in an excellent yield. The next reaction introduced the C3 stereocentre through alkylation of the sodium enolate of **316** with the *tert*-butyl α-iodo acetate to give **317** in a high yield with complete stereocontrol. A three-step process was then employed to move to **318**: first, the removal of the chiral auxiliary using lithium peroxide and reduction of the resulting carboxylic acid gave the alcoholic intermediate **I**; second, this was then submitted to acid-promoted lactonisation to give **318** in a moderate yield; and finally substrate-controlled methylation was achieved using the sodium enolate of **255** and methyl iodide to give **319** in a high yield and diastereoselectivity (d.r. 12:1). The stereocontrol of the reaction comes from the chiral centre introduced previously; the large diaryl group sterically hinders one π-face of the enolate and therefore promotes the approach of the electrophile from the other and provides the *anti*-diastereoisomer.



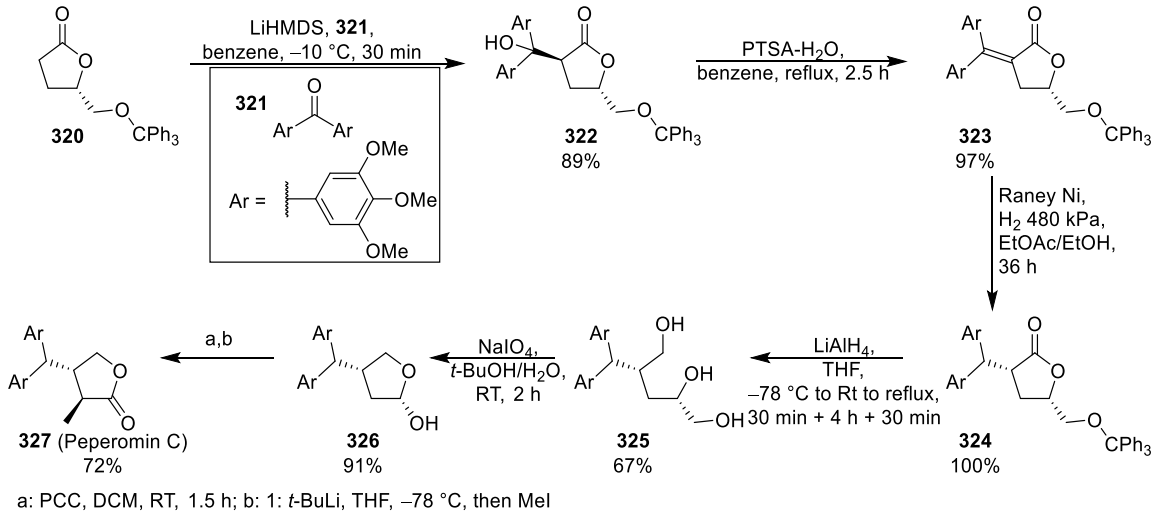
a: 1) NaHMDS, THF, -78 °C, 1 h, 2) ICH_2CO_2t-Bu, 6 h; b: LiOH, H_2O_2, THF/H_2O, 0 °C to RT, 5 h + 14 h; c: BH_3, THF, -10 °C to RT, 6 h + 14 h; d: PTSA, benzene, reflux, 2 h;

Scheme 125: Sibi's Synthesis of Peperomin D.

The overall yield of Peperomin D was 27% over seven steps. This synthetic sequence was also utilised for the synthesis of Peperomin A and C with overall yields of 34% and 35% respectively. Two other non-natural analogues were also synthesised.

Zee's Synthesis of Peperomin C

Zee was the first to report a synthesis of the Peperomin family in general; he first published a route to racemic Peperomin A, B and C,[43] followed by a stereoselective version using a chiral pool approach.[44] The synthesis started from the chiral, triphenylmethyl protected, (S)-γ-hydroxymethyl-γ-butyrolactone derivative **320** (Scheme 126). This was enolised to form the lithium enolate which was then reacted with the symmetric trimethoxy substituted benzophenone derivative **321** to give the alcohol **322** in an excellent yield. The stereocontrol comes from the bulky triphenylmethyl ether blocking one face of the lactone and forcing the approach of the electrophile to the *Re* π-face; however, both the stereochemistry being wrong and the need to remove the hydroxy group renders the selectivity superfluous. To remedy these two problems the alcohol was first removed under acidic conditions to give **323**. The resulting double bond was then hydrogenated using Raney nickel to give the lactone **324** in a quantitative yield. Again, the stereocontrol in the reaction is owed to the bulky triphenylmethyl ether which forces the Raney nickel to approach the double bond from the opposite side of the lactone, correcting the configuration of the diaryl group. The next step was a double-fold process: the removal of the triphenylmethyl group and the reductive opening of the lactone with lithium aluminium hydride to give the triol **325** in a good yield. Reaction with sodium periodate then gave the hemiacetal **326** in an exceptional yield, reforming the five-membered ring structure. Finally, two further reactions where employed to complete the synthesis of **327**: an oxidation with PCC gave the lactone structure, which was methylated via the lithium enolate using methyl iodide in a substrate controlled methylation, similar to that later used by Sibi.[42] These two reactions gave **327** in an high yield and completed the synthesis of Peperomin C.



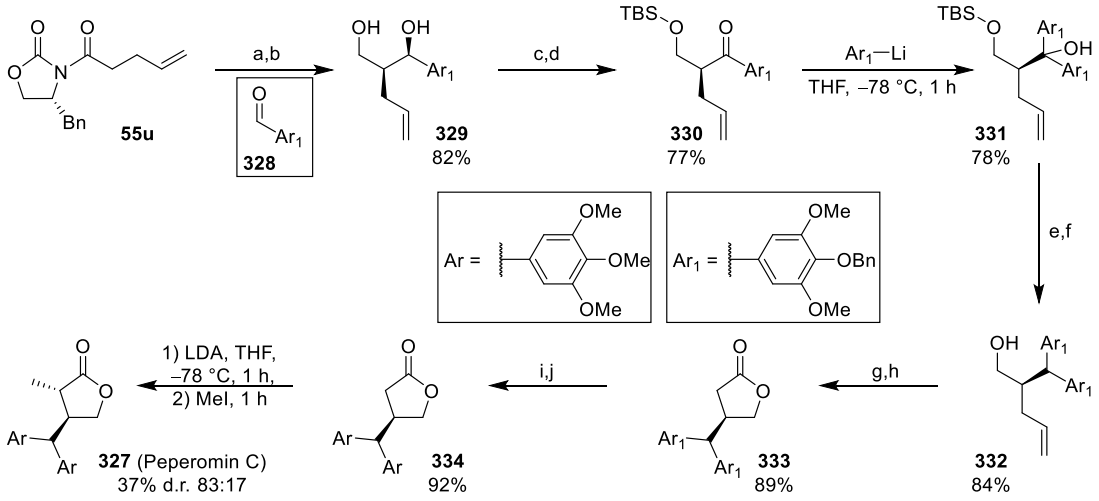
Scheme 126: Zee's Stereoselective Synthesis of Peperomin C.

The overall yield of Peperomin C was 38% over seven steps and represented the first total synthesis of both Peperomin C and also the first of the whole family of Peperomins.

Soorukram's Synthesis of Peperomin C

Some years later Soorukram published another synthetic route to Peperomin C based on the use of an Evans chiral auxiliary to control the C3 configuration.[47]

From the acylated auxiliary **55u** a boron mediated aldol reaction was conducted with aldehyde **328** and the chiral auxiliary removed to give the alcohol **329** in an excellent yield (Scheme 127). Selective silyl protection of the terminal alcohol followed by benzylic oxidation with MnO_2 gave ketone **330** in a high yield. This ketone was then reacted with the aryl lithium reagent in a carbonyl addition reaction to produce the tertiary alcohol **331** in a high yield hence furnishing the diaryl moiety needed. The alcohol was then removed by deoxygenation with triethylsilane and boron trifluoride and the silyl protecting group removed to reveal alcohol **332** in an excellent yield. The double bond was then submitted to oxidative cleavage using osmium tetraoxide and sodium periodate to give the aldehyde, which spontaneously cyclised to form the lactol product; this lactol was then directly oxidised to the lactone **333** using PCC in an excellent yield over the two steps. This represented the core structure of Peperomin C; however, the aryl groups were not those required as they contained a *p*-benzyloxy group instead of a *p*-methoxy. To rectify this, hydrogenolysis of the benzyl group followed by methylation of the phenol group was performed to provide the correct aryl group and lactone **334**. Finally, the completion of Peperomin C was achieved via the alkylation of the lactone using the lithium enolate and methyl iodide, similarly to Zee's approach,[44] giving **327** in a low yield and high selectivity.



a: **266**, Bu_2BOTf, DIPEA, DCM, –78 °C, 6 h; b: $LiBH_4$, THF, 0 °C, 1 h; c: TBSCl, DMAP, TEA, DCM, RT, 3 h; d: MnO_2, pentane, RT, 12 h, e: Et_3SiH, $BF_3.OEt_2$, DCM, –20 °C, 5 min f: TBAF, THF, 0 °C to RT, O/N; g: 1) OsO_4, NMO, DCM/*t*-BuOH/H_2O, RT, 9 h, 2) $NaIO_4$, RT, 30 min; h: PCC, DCM, RT, 4 h; i: $PdCl_2$, H_2, MeOH, RT, 2 h; j: Me_2SO_4, K_2CO_3, acetone, reflux, 1 h,

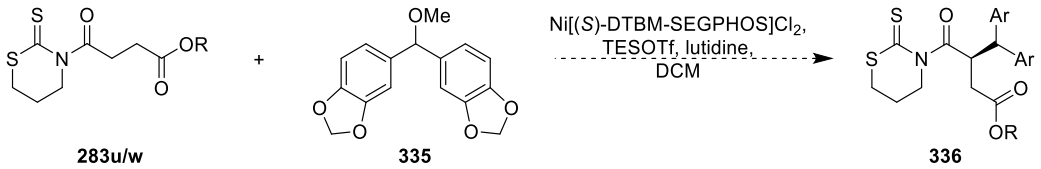
Scheme 127: Soorukram's Synthesis of Peperomin C.

The synthesis took a total of twelve steps with a total yield of 13%. The synthesis of the methylene derivative and the methyl epimer was also achieved via manipulation of the late-stage intermediate lactone **334**. Sookrukram also suggests the possibility of using the methodology to synthesise other natural and non-natural analogues using the same methodology by changing the aryl groups used in the aldol and carbonyl addition steps.

Whilst the previous syntheses of other analogues and the sole synthesis of Peperomin D are useful, a methodology that relied on asymmetric catalysis would be a considerable advance especially if it could shorten the route, improve the yield or both.

Design of Our Synthetic Approach

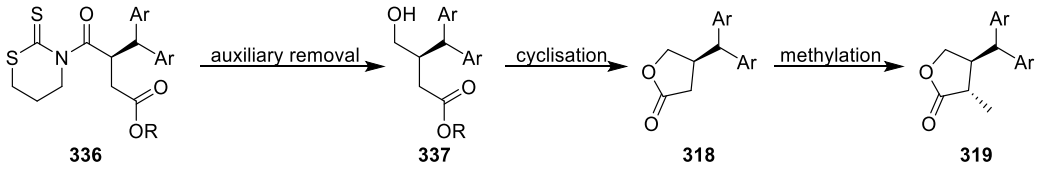
We envisaged that our newly developed enantioselective alkylation could offer the solution to the efficient and highly selective synthesis of Peperomin D and could also be applied to the less challenging family members. As our methodology had been proved to introduce diaryl groups with both exceptional enantioselectivity and generally excellent yields the synthesis of Peperomin D was a perfect way to demonstrate its synthetic utility. Using the diarylmethyl ether **335** and an ester terminal starting material **283u/w** we counted on the formation of the product **336** which would be a good platform for the completion of the synthesis (Scheme 128).



Scheme 128: Proposed Alkylation Reaction for the Synthesis of Peperomin D.

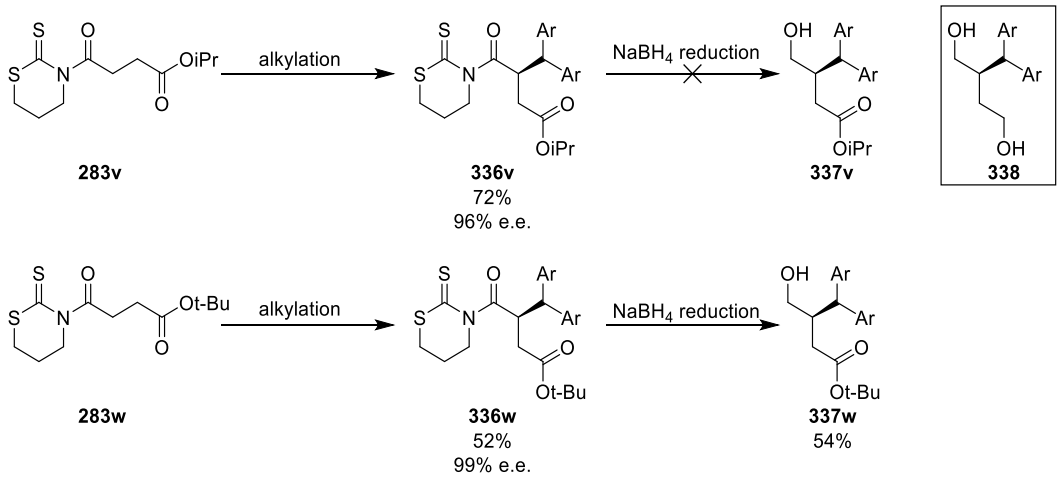
The rest of the synthetic sequence would then consist of the removal of the scaffold, cyclisation to form the lactone and then final methylation to give the desired product (Scheme 129). Sibi's synthetic route also hinted that an acid-promoted cyclisation could furnish the lactone from an ester γ-hydroxy ester.[42] Finally the substrate-controlled methylation had been proved to be successful, by Sibi, Zee and Soorukram to complete the synthesis of the Peperomin analogues.[42,44,47] Therefore, we were

confident our methodology could be easily applied in a maximum of four steps, which would represent a significant shortening over previous syntheses.



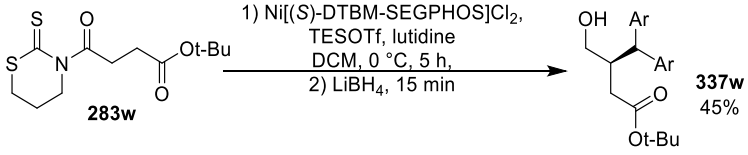
Scheme 129: Proposed Completion of the Synthesis of Peperomin D.

The first important question to resolve was the correct ester group to use in the starting material. Two key points were investigated. The first is the compatibility of the ester in the alkylation reaction in terms of selectivity and yield. The second regarded the stability under reductive conditions used to remove the scaffold and lability under acidic conditions to be able to promote the lactone formation. Whilst both methyl and isopropyl esters performed well in the alkylation reaction, upon reductive removal of the scaffold using the isopropyl ester the product spontaneously cyclised to the lactone. Unfortunately, isolating the lactone was not viable due to it reacting further in the reaction conditions giving products related to the opened lactone such as **338** (Top, Scheme 130). The *tert*-butyl ester performed slightly worse in the alkylation reaction in terms of yield but was stable to the reduction conditions and the hydroxy ester was able to be isolated (Bottom, Scheme 130).



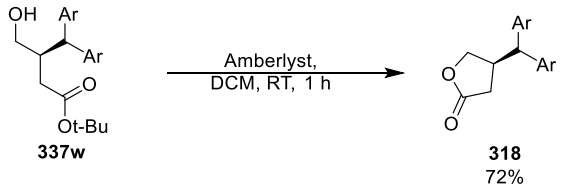
Scheme 130: Initial Results in Alkylation and Scaffold Removal with Isopropyl and tert-Butyl Ester Starting Materials. Insert: One Product Found from the Further Reduction of the Lactone Formed.

The initial yields were moderate and needed optimization: one option we envisaged was the addition of a reducing agent as a quench for the alkylation to provide the alcohol **337w** in a one-pot manner. We attempted this by running the alkylation reaction and then used a solution of lithium borohydride to quench the reaction, forming the alcohol in the reaction mixture. The initial results were promising, the yield for the alcohol increased to 45%, up from 28% in the two-step process (Scheme 131). We moved to lithium borohydride due to the facile availability of an organic solution, something lacking when using sodium borohydride. However, there was still room for further optimisation and the final results are seen in the following paper.



Scheme 131: One-Pot Alkylation and Reduction Reaction.

The next reaction step was the acid promoted cyclisation of the lactone. We trialled a few different acids before deciding on the polymeric resin Amberlyst®. This promoted the cyclisation in less than one hour with a high yield (Scheme 132). Furthermore, due to the heterogenous nature of the acid, only a simple filtration was needed in the work up.



337w **318** 72%

Scheme 132: Initial Result for the Amberlyst® Promoted Cyclisation Reaction.

Again, further optimisation of the reaction conditions was needed to improve the yield to the lactone (32% with alkylation-quench and cyclisation) for the synthesis to be efficient enough to be viable. Additional optimisation and the removal of purification steps (as demonstrated in our route to Peloruside A) were planned to improve the yield. The results of this can be seen in the following paper in our final route to Peperomin D.

The final step was the methylation of the lactone in the α-position. We carried this out in the same way as Sibi, who published a yield of 80% and a diastereoselectivity of 12:1, which represents the best methodology so far for the methylation of Peperomin lactone structures.[42] This then would complete our synthesis of Peperomin D. The final route with the fully optimised results can be found in the following paper.

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Letter

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Direct and Asymmetric Nickel(II)-Catalyzed Construction of Carbon−Carbon Bonds from *N*-Acyl Thiazinanethiones

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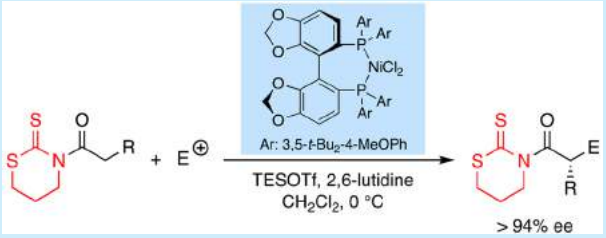
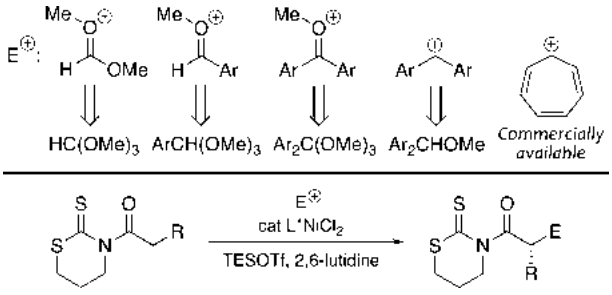
Supporting Information

ABSTRACT: A wide array of new *N*-acyl thiazinanethiones are employed in a number of direct and enantioselective carbon−carbon-bond-forming reactions catalyzed by nickel(II) complexes. The electrophilic species are mostly prepared in situ from ortho esters, methyl ethers, acetals, and ketals, which makes the overall process highly efficient and experimentally straightforward. Theoretical calculations indicate that the reactions proceed through an open transition state in a S_N1-like mechanism. The utility of this novel procedure has been demonstrated by the asymmetric preparation of synthetically useful intermediates and the total synthesis of peperomin D.



The stereocontrolled construction of carbon−carbon bonds from metal enolates holds a prominent position among carbon-backbone-forming methods in asymmetric synthesis.[1] Unfortunately, most of the reported methods hinge on the stoichiometric generation of the enolate and subsequent reaction with the chosen electrophile, so they do not meet the current demands for economy in synthesis.[2] Organocatalysis does meet such challenges,[3] but the source of nucleophiles is often restricted to aldehydes and a few privileged compounds.[4] Hence, there is a lack of direct, catalytic, and asymmetric transformations based on metal enolates from nonactivated carboxylic derivatives. In this context, pioneering studies underlined the benefits of working with easily removable scaffolds attached to the carboxylic moiety.[5−7] This led Kobayashi to use amides in highly enantioselective aldol and Michael additions,[8] and similarly, Evans described aldol reactions and orthoester alkylations from *N*-acyl thiazolidinethiones,[9] Kumagai and Shibasaki also reported a number of reactions based on 7-azaindoline amides.[10,11] Inspired by such precedents and taking advantage of our own experience in S_N1-like stereoselective transformations[12] and the *isolobal principle*,[13] we envisaged that treatment of *N*-acyl thioimides with easy to handle chiral nickel(II) complexes might catalytically produce the corresponding metal enolates. These would then be capable of taking part in asymmetric carbon−carbon-bond-forming reactions with cationic intermediates. According to such ideas, we herein report that the direct TESOTf-mediated addition of *N*-acyl thiazinanethiones to a wide array of electrophiles catalyzed by chiral nickel(II) complexes and the ensuing removal of the thiazinanethione scaffold provides enantiomerically pure compounds in high yields and in a straightforward manner (Scheme 1).

Scheme 1. Direct, Asymmetric, and Catalytic C−C-Bond-Forming Reactions



We were aware from the very beginning that such a challenging process called for (a) the catalytic formation of an enolate possessing the necessary chiral environment in parallel to (b) the generation of the required electrophile for (c) the installation of up to two new stereocenters while (d) minimizing undesired reactions. Therefore, we carried out a careful examination of all the species involved in such a process.

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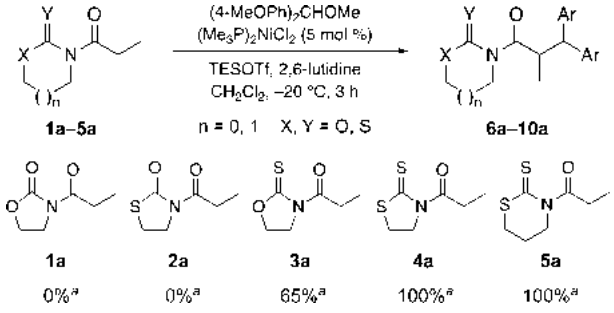
Exploratory studies on the addition of *N*-propanoyl derivatives **1a**−**5a** to 4,4′-dimethoxybenzhydryl methyl ether in the presence of commercially available $(Me_3P)_2NiCl_2$ demonstrated the crucial role of the exocyclic C═S bond (Scheme 2). Indeed, oxazolidinone **1a** and thiazolidinone **2a**

Scheme 2. Assessment of the Scaffold



did not react at all, whereas thiazolidinethione **4a** and thiazinanethione **5a** were converted into the alkylated products quantitatively.

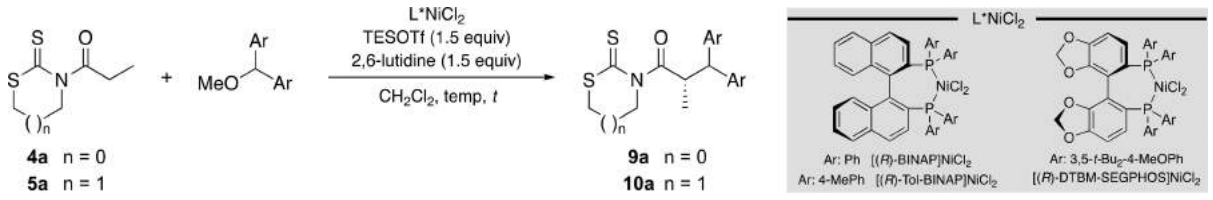
Therefore, we focused our attention on the alkylation of **4a** and **5a** promoted by a few chiral complexes (L*$NiCl_2$ in Table 1), easily prepared by simple heating of mixtures of $NiCl_2$ and the corresponding diphosphines in CH_3CN.[9b] Initial screening of the reaction conditions revealed that both substrates were appropriate platforms to carry out such alkylations. Thereby, treatment of thiazolidinethione **4a** with 4,4′-dimethoxybenzhydryl methyl ether, TESOTf, and 2,6-lutidine in the presence of 5 mol % L*$NiCl_2$ at −20 °C for 15 h produced the quantitative and enantioselective (ee up to 96%) conversion into the alkylated adduct **9a** (entries 1−3 in Table 1). Even better, parallel reactions from thiazinanethione **5a** afforded adduct **10a** as a single enantiomer (entries 4−6 in Table 1). Importantly, the temperature could be raised to 0 °C without any detrimental effect, which enabled us to dramatically reduce the reaction time and to scale down the catalyst loading (compare entries 6−9 in Table 1). Eventually, the alkylation of **5a** with a mere 1 mol % of [(*R*)-DTBM-SEGPHOS]$NiCl_2$ took place at 0 °C in just 10 min and gave **10a** with a 98% ee and a 96% yield after chromatographic purification (entry 8 in Table 1).

The optimized conditions were then applied to a broad array of *N*-acyl thiazinanethiones **5** (Table 2). The reaction proved to be sensitive to the bulk of the acyl group, so the catalyst loading had to be increased to 10 mol % for the sterically hindered (R: *i*-Pr) thiazinanethione **5d** (compare entries 1−4 in Table 2). Otherwise, it tolerated the presence of common functional groups as alkenes, alkynes, and carboxylic esters as well as C*α*-benzyl or phenyl ethers, in most cases with an outstanding enantiocontrol (ee up to 98%) and yields from 78 to 96% (entries 5−9 in Table 2). Unfortunately, the synthesis of the azidoacetyl thiazinanethione counterpart proved troublesome, but a parallel alkylation reaction was carried out successfully with the *N*-azidoacetyl thiazolidinethione **4j** (entry 10 in Table 2). Significantly, the results for **10i** and **9j** make this alkylation a new approach to the asymmetric synthesis of *α*-hydroxy and *α*-amino acids respectively (entries 9 and 10 in Table 2).

The thiazinanethione scaffold of the products **10** was easily removed to release alkylated products (Scheme 3).[14−16] Indeed, reduction of **10a** with $NaBH_4$ led to alcohol **11a** with a yield of 87%, whereas treatment of **10a** with methanol afforded ester **12a** with a 96% yield. In turn, (*S*)-*α*-methylbenzylamine and morpholine reacted smoothly with **10a** to produce amides **13a** and **14a**, respectively, in yields up to 96%. At this point, absolute configuration of adducts **10** was firmly established by chemical correlation of **11a**−**12a** and X-ray analysis of amide **13a**.[17] Interestingly, thiazinanethione may also act as a coupling reagent and permitted us to obtain diastereomerically pure *N*-acyl amino acid **15f** by simple addition of methyl (*S*) leucinate to adduct **10f** with an 89% yield.

Once the feasibility of the catalytic and asymmetric alkylation of **5** with 4,4′-dimethoxybenzhydryl methyl ether was established, we examined the synthetic potential of such a transformation through the use of other electrophiles represented in Scheme 1. The reactions with trimethyl orthoformate, a dimethyl ketal, and a tropylium salt, which involve the installation of a single stereocenter, proceeded smoothly and led to enantiomerically pure adducts **16a**−**18a**

Table 1. Initial Trials on the Direct and Asymmetric Reactions Catalyzed by Chiral Nickel(II) Complexes



entry	substrate	L*$NiCl_2$	mol %	temp (°C)	*t* (h)	ee (%)[a]	conversion (%)[b]	yield (%)[c]
1	**4a**	[(*R*)-BINAP]$NiCl_2$	5	−20	15	94	>97	
2	**4a**	[(*R*)-TolBINAP]$NiCl_2$	5	−20	15	95	>97	
3	**4a**	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	5	−20	15	96	>97	
4	**5a**	[(*R*)-BINAP]$NiCl_2$	5	−20	15	96	>97	
5	**5a**	[(*R*)-TolBINAP]$NiCl_2$	5	−20	15	98	>97	
6	**5a**	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	5	−20	15	98	>97	
7	**5a**	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	2	−20	1	98	>97	
8	**5a**	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	1	0	0.2	98	>97	96
9	**5a**	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	1	20	0.2	92	>97	

[a]Established by chiral HPLC. [b]Established by ^{1}H NMR. [c]Isolated yield after column chromatography.

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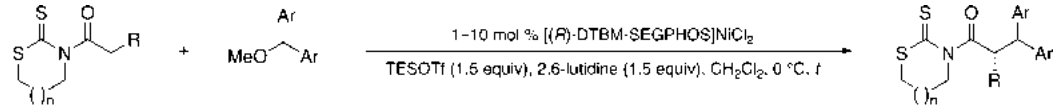
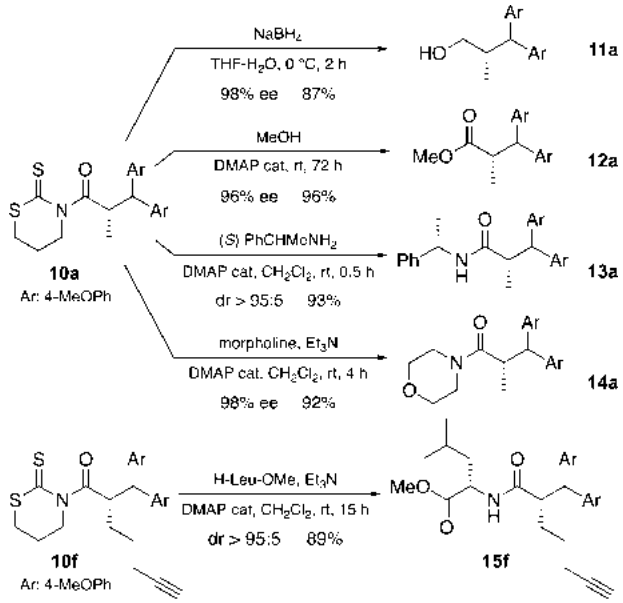
Table 2. Direct and Enantioselective Alkylation with $(4\text{-MeOPh})_2$CHOMe Catalyzed by a Chiral Nickel(II) Complex



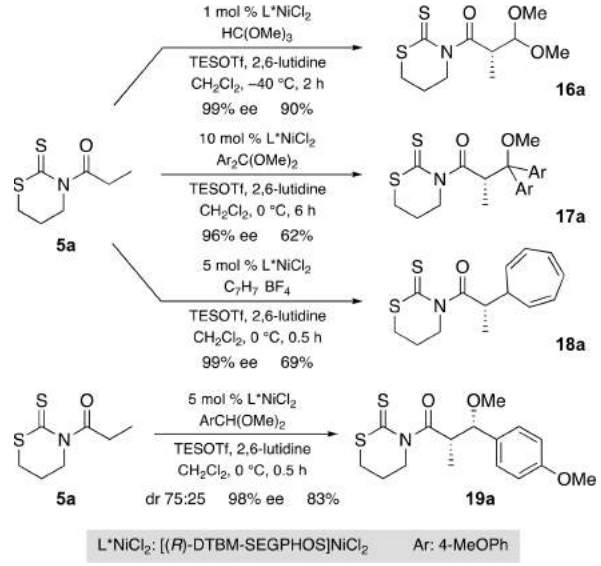
entry	substrate	R	mol % L*$NiCl_2$	t (h)	adduct	ee (%)	yield (%)[b]
1	**5a**	Me	1	0.2	**10a**	98	96
2	**5b**	Et	2	2	**10b**	95	88
3	**5c**	Bn	2	2	**10c**	96	81
4	**5d**	*i*-Pr	10	2	**10d**	98	78
5	**5e**	$(CH_2)_2CH{=}CH_2$	2	2	**10e**	98	78
6	**5f**	$(CH_2)_3CCH$	2	2	**10f**	98	96
7	**5g**	$(CH_2)_2CO_2Me$	2	2	**10g**	95	78
8	**5h**	OPh	10	2.5	**10h**	95	85
9	**5i**	OBn	2	4	**10i**	95	93
10	**4j**	N_3	2	2	**9j**	95	93

[a]Established by chiral HPLC. [b]Isolated yield after column chromatography.

Scheme 3. Removal of the Thiazinanethione Scaffold



Scheme 4. Reactions with Other Electrophiles



(ee ≥97%) after slight adjustments of the former experimental conditions (Scheme 4). More concretely, the reaction with trimethyl orthoformate was carried out at −40 °C to suppress the competitive alkylation of the exocyclic C═S bond, whereas the addition to the dimethyl ketal lasted for 6 h, probably because of the steric bulk of the oxo carbenium intermediate. Besides these results, it is important to highlight that the related reaction with 4-MeOPhCH$(OMe)_2$, which involves the simultaneous construction of two new stereocenters, was also satisfactory and afforded the *syn* adduct **19a** (dr 75:25, 98% ee for the *syn* diastereomer) and with a high overall yield (Scheme 4).

An S_N1-like mechanism based on the approach of cationic reagents to the *Re* face of a putative chiral nickel enolate accounts for all these results. [(*R*)-DTBM-SEGPHOS]$NiCl_2$ is a robust and bench stable nickel(II) complex with a distorted square planar geometry which can be seen in the crystal structure obtained;[17] it does not catalyze the alkylation reaction but it is easily activated in situ with TESOTf to produce the true catalyst containing two triflate ligands.[18] Coordination of this species to the thioimide moiety enhances the acidity of **5** and facilitates the deprotonation of the Cα position. At the same time, the TESOTf reacts with the benzhydryl methyl ether and produces the corresponding carbocation, which in turn adds to the nickel(II) enolate.[19] Once the carbon−carbon bond is formed, the alkylated adduct **10a** is released and the nickel(II) complex may start a new catalytic cycle (Scheme 5).

Eventually, we considered the synthesis of peperomin D (**20** in Scheme 6), a secolignan metabolite isolated from *Peperomia glabielle*.[20] Featuring a five-membered lactone with a benzhydryl appendage at the β position, we envisaged that it might be synthesized through alkylation of thiazinanethione **5k** with the appropriate benzhydryl methyl ether in the presence of [(*S*)-DTBM-SEGPHOS]$NiCl_2$.[21] Indeed, quenching the reaction mixture with $LiBH_4$ gave chemoselectivily the hydroxy ester **21**, which was then treated with Amberlyst resin to obtain the desired lactone **22** with an excellent stereocontrol (95% ee) and a 51% yield. Remarkably, just a single chromatographic purification was required. The installation of the α-stereocenter was next accomplished by substrate-controlled alkylation of **22**

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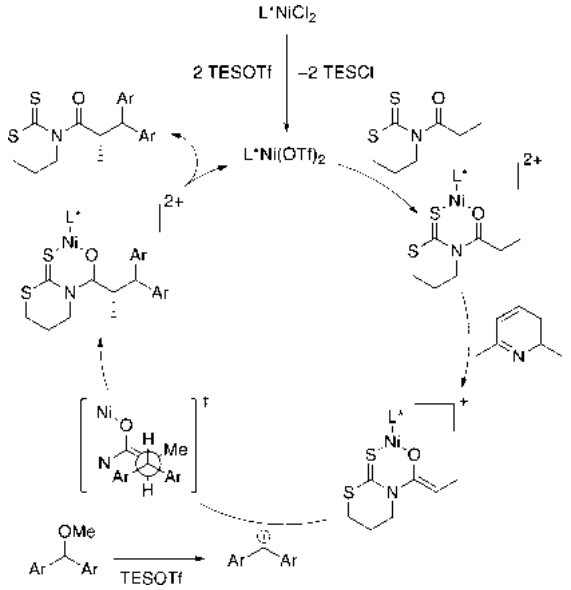
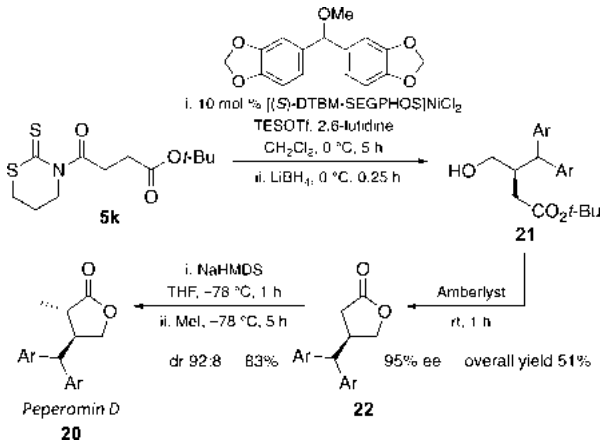
Scheme 5. Mechanistic Model



Scheme 6. Synthesis of Peperomin D



with MeI, which allowed us the isolation of enantiomerically pure peperomin D **20** with an overall yield of 42% over three steps.

In summary, we have demonstrated the utility of *N*-acyl thiazinanethiones in a number of direct, chemo- and enantioselective carbon−carbon-bond-forming reactions usually promoted by 1−5 mol % of [DTBM-SEGPHOS]$NiCl_2$. The thiazinanethione scaffold can be smoothly released from the resulting adducts to provide a broad array of enantiomerically pure intermediates. Theoretical studies suggest that these transformations proceed through an open transition state in an S_N1-like mechanism, in which the configuration of the α-stereocenter is absolutely controlled by the chiral biphosphine. The efficiency of such an alkylation has been proved in the total synthesis of peperomin D, a five-membered lactone containing two stereocenters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03757.

Experimental procedures and characterization data (PDF)

NMR spectra (PDF)

Accession Codes

CCDC 1857787−1857788 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of recently deceased Professor Josep Castells.

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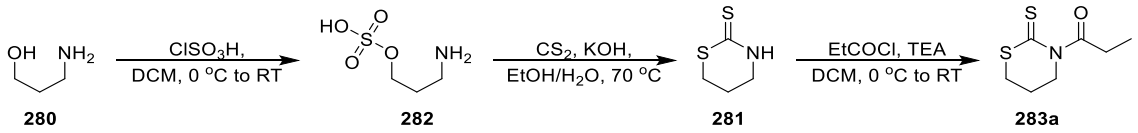
Scale-up of the Methodology

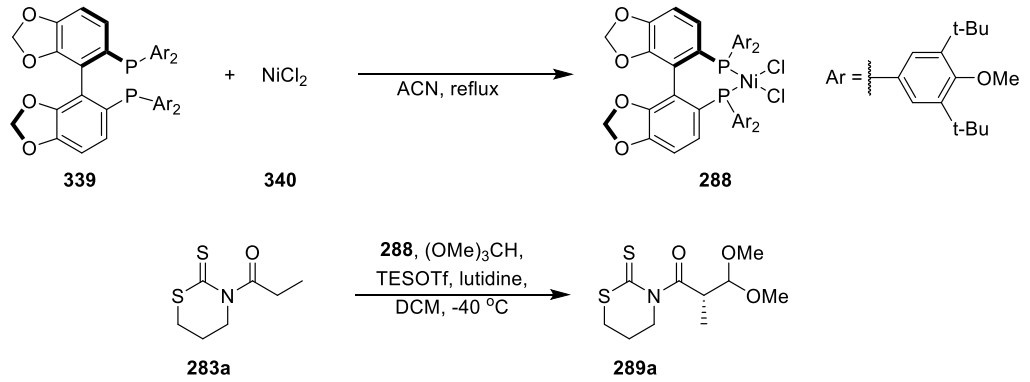
In the first steps towards the commercialisation of the new methodology for the alkylation of thiazinanethione, we assessed the scale up both of the synthesis of the starting materials and the enantioselective reaction. We then submitted the results to the *Organic Syntheses* journal which has long been a mark of quality for synthetic transformations and a common first step in the marketing of synthetic methodologies.

The first process deals with the synthesis of the scaffold **281** from the amino alcohol **280** and its subsequent acylation to give the product **283a** (Scheme 133). The synthesis of the scaffold was best achieved when passing through the hydrogen sulphate **282** before attempting cyclisation. The development of these reactions is discussed on Page 136. For the scale-up the *N*-propionyl acyl chain was chosen as it was the simplest and more generalised acyl chain.



Scheme 133: Synthesis of Starting Material.

The second process involved the formation of the pre-catalyst **288** and its use with the starting material **283a** in an enantioselective alkylation with trimethyl orthoformate to give the product **289a** (Scheme 134). The nickel(II) complex **288** was formed from the free diphosphine ligand DTBM-SEGPHOS **339** and nickel (II) chloride **340**. The alkylation reaction was then performed in the presence of triethylsilyl triflate to activate both the catalyst and electrophile and lutidine as the organic base. This reaction was discussed fully on Page 138.



Scheme 134: Preparation of Pre-Catalyst and Enantioselective Orthoformate Reaction.

Our aim was to scale the reactions to a multigram scale, adapting the conditions if the larger scale caused any unforeseen complications. The final methodology can be seen in the following papers.

Organic Syntheses

Synthesis and Acylation of 1,3-Thiazinane-2-thione

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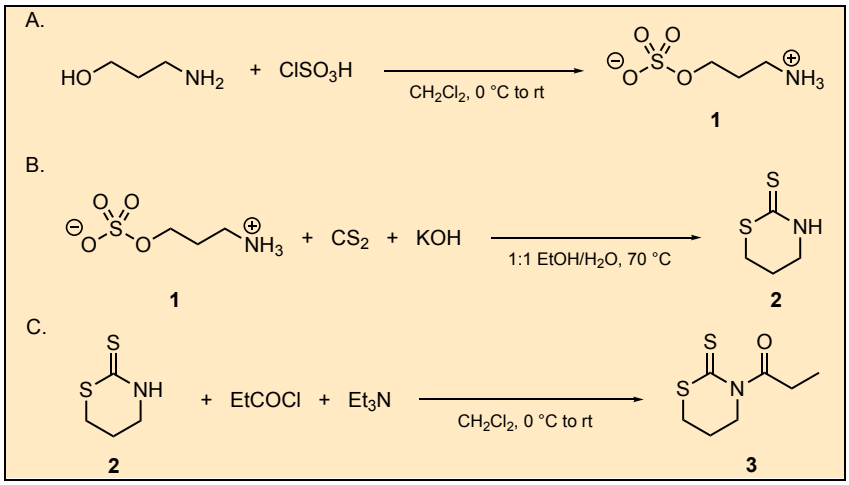


Procedure (Note 1)

A. *3-Ammoniopropylsulfate (**1**).* An oven dried single-necked 100 mL round-bottomed flask (14/23 joint), equipped with a 2.5-cm Teflon-coated magnetic stirbar, is charged with 3-amino-1-propanol (11.5 mL, 150 mmol, 1 equiv) (Note 2) and anhydrous dichloromethane (35 mL) (Note 3). A 50 mL pressure relieving addition funnel (14/23 joint) equipped with a $CaCl_2$ tube is attached to the round-bottomed flask and is then charged with chlorosulfonic acid (10.5 mL, 158 mmol, 1.05 equiv) (Note 4) using a 20 mL glass luer-lock syringe. The flask is immersed in an ice/water bath and the

solution is stirred for 5 min. The chlorosulfonic acid is added dropwise over 30 min, allowing the fumes to escape. A white precipitate is formed during the addition. Once the addition is complete, the reaction is stirred at 0 °C for 20 min and left to warm slowly to room temperature over 30 min (Note 5). Once at room temperature, the reaction mixture is stirred for 1 h. The resulting mixture is filtered through a 70 mm diameter Number 3 Glass filter funnel with a Buchner setup. A bent spatula and methanol (25 mL) (Note 6) are used to remove remaining product from the flask walls. The mixture in the filter funnel is triturated with methanol (40 mL, then 2 × 20 mL) (Note 6), using a spatula to break up the lumps each time. The resulting white solid is broken up into a coarse powder and transferred to a 100 mL round-bottomed flask (29/32 joint), where it is placed on a rotary evaporator (40 °C, 12 mmHg pressure) for 1 h. The resulting white solid is ground to a fine white powder using a 10 cm diameter glass mortar and pestle, retransferred to a 100 mL round bottom flask and dried on a high vacuum line (room temperature, 0.1 mmHg pressure) for 2 h giving the title compound **1** (20.79 g, 134 mmol, 89% yield) (Note 7) as a fine white powder.

Figure 1. Addition set-up (left), trituration (middle) and final product (right)

B. *1,3-Thiazinane-2-thione* (**2**). An oven dried single-necked 250 mL round-bottomed flask (29/32 joint), equipped with a 4-cm Teflon-coated magnetic stirbar, is charged with 3-ammoniopropylsulfate (18.70 g, 121 mmol, 1 equiv) and absolute ethanol (15 mL) (Note 8) at room temperature. The resulting solution is stirred at room temperature for a couple of minutes

and neat carbon disulfide (9.6 mL, 160 mmol, 1.3 equiv) (Note 9) is added quickly using a 10 mL syringe.

Separately, KOH beads (14.84 g, 265 mmol, 2.2 equiv) (Note 10) are weighed in a 250 mL conical flask equipped with a 4-cm Teflon-coated magnetic stir bar, and then dissolved in 1:1 ethanol/water (100 mL) solution. The mixture is stirred at room temperature and the resulting solution is transferred with a funnel to a 250 mL pressure relieved addition funnel (29/32 joint) attached to the round-bottomed flask. The neck of the addition funnel is sealed with a rubber septum and the system is purged with a nitrogen flow for 5 min. The KOH solution is added dropwise to the carbon disulfide solution in the round-bottomed flask over 30 min at room temperature to give a yellow solution. The addition funnel is replaced by a reflux condenser sealed with a rubber septum, and a N_2-filled balloon is attached to the reflux condenser through the septum. The reaction mixture is heated to reflux in an aluminum heating block (70 °C) for 1 h under a N_2 atmosphere and allowed to cool to room temperature slowly to give a fluffy white precipitate, which is further cooled to 0 °C with an ice/water bath for 15 min.

The mixture is filtered using a 70 mm diameter Number 3 glass filter funnel with a Buchner setup. The flask is rinsed with cold deionized water (3 × 15 mL) with the washings being added to the filter funnel. The solid in the filter funnel is dried *in vacuo* for 15 min, after which the receiving flask is changed for a fresh one. The solid is washed with dichloromethane (3 × 35 mL) (Note 11), each time breaking up the solid with a spatula and mixing thoroughly before applying the vacuum. The combined organic extracts are dried over $MgSO_4$ (40 g) (Note 12) and concentrated under reduced pressure to give pure crystalline powder of 1,3-thiazinane-2-thione **2** (5.23 g, 33% yield) (Note 13). The remaining solid (Note 14) from the filter funnel is transferred to a 250 mL round-bottomed flask (29/32 joint) equipped with a 4-cm Teflon-coated magnetic stir bar. This round-bottomed flask is charged with dichloromethane (150 mL) (Note 11), a reflux condenser sealed with a rubber septum is attached to the flask, the system is purged with a nitrogen flow for a couple of minutes, and a N_2-filled balloon is attached to the reflux condenser through the septum. The resulting mixture is stirred and heated to reflux for 1 h and then filtered through a Number 3 glass filter funnel with a Buchner setup whilst warm. The solid is washed with dichloromethane (2 × 50 mL) (Note 11), each time breaking up the solid with a spatula and mixing thoroughly before applying the vacuum as before. The combined filtrates are dried over $MgSO_4$ (35 g) (Note 12) and

concentrated to give pure thiazinanethione **2** (4.78 g, 30% yield). The combined thiazinanethione **2** weighs 10.01 g (62% overall yield) (Note 15).

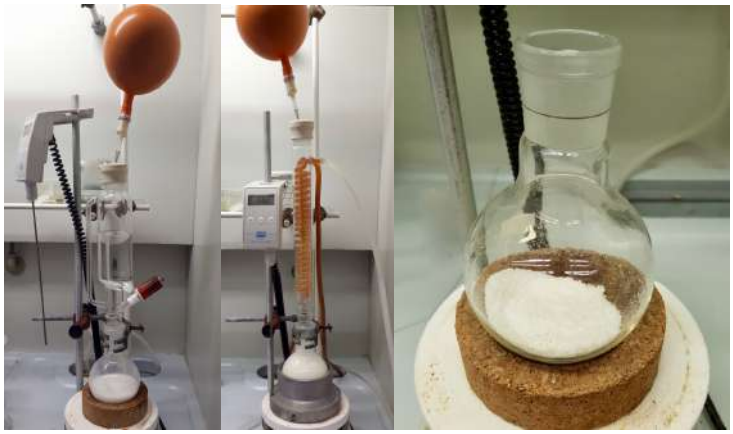


Figure 2. Reaction set-up (left), reflux set-up (middle) and final product (right)

C. *N-Propanoyl-1,3-thiazinane-2-thione* (***3***)**.** An oven dried single-necked 250 mL round-bottomed flask (29/32 joint), equipped with a 4-cm Teflon-coated magnetic stirbar, is charged with 1,3-thiazinane-2-thione (10.64 g, 80 mmol, 1 equiv). The flask is sealed with a rubber septum and the system is flushed with N_2. Finally, a N_2-balloon is left attached to the system. The flask is charged with anhydrous dichloromethane (80 mL) (Note 3) and immersed in an ice/water bath. The resulting solution is stirred for 2 min and freshly distilled triethylamine (14.50 mL, 104 mmol, 1.3 equiv) (Note 16) is added dropwise. The solution is stirred for 2 min and propionyl chloride (8.40 mL, 96 mmol, 1.2 equiv) (Note 17) is carefully added over 20 min producing a yellow solution. The ice/water bath is removed and the reaction mixture is stirred at room temperature for 2 h. The resulting dark yellow/orange mixture is cooled with an ice/water bath and quenched with a saturated solution of NH_4Cl (25 mL) (Note 18) and left to stir for 5 min.

The mixture is transferred to a 500 mL separating funnel. The flask is rinsed with dichloromethane (4 × 40 mL) (Note 11) and water (3 × 40 mL), which are added to the separating funnel. The mixture is shaken vigorously and the layers separated. The aqueous layer is extracted with dichloromethane (40 mL) (Note 11). The combined organic extracts are

washed with 2 M NaOH (120 mL) (Note 19), dried over $MgSO_4$ (25 g), and filtered, with the flask and solid being washed with dichloromethane (3 × 40 mL) (Note 11). The solution is concentrated under reduced pressure and the resulting residue is submitted to flash column chromatography on silica gel (60 Å) using a 6 cm diameter column with a length of 25 cm of silica (*ca* 400 g) (Note 20). This is first compacted with 90:10 hexanes/ethyl acetate (1 L) (Notes 21 and 22) and the surface levelled. The residue is dissolved in ethyl acetate (4 mL) (Note 22), diluted in hexanes (8 mL) (Note 21), and added onto the compacted column. After absorption, the flask is washed with 90:10 hexanes/ethyl acetate (3 × 8 mL, or until the flask is no longer yellow) (Notes 21 and 22), each time waiting until the liquid is adsorbed. The walls of the column are then washed with 90:10 hexanes/ethyl acetate (3 × 8 mL) (Notes 21 and 22) and once absorbed thick sand is added to protect the silica. The column is eluted with 90:10 hexanes/ethyl acetate (*ca* 4.5 L) (Notes 21 and 22) until all of the yellow color has left the column and the eluent runs clear (see Figure 3). Product is collected in *circa* 150 30 mL–test tubes. The tubes pure by TLC (80:20 hexanes/ethyl acetate) (see Figure 4) are sequentially added to a 1 L round bottom flask and concentrated. Once all pure tubes are concentrated, the resulting thick yellow oil is diluted with dichloromethane (50 mL) (Note 11) and transferred to a 100 mL round-bottomed flask, concentrated under reduced pressure and kept under high vacuum (0.1 mmHg) at room temperature for 4 h to afford pure acylated product **3** (12.85 g, 85% yield) (Note 23).

Figure 3. Column chromatography (left and middle) and final product (right)

Figure 4. Image of a TLC plate (UV) of a pure sample

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with chlorosulfonic acid, carbon disulfide, triethylamine, propionyl chloride, sodium hydroxide, potassium hydroxide, Celite®, silica gel, dichloromethane, methanol, hexane, and ethyl acetate.
2. 3-Amino-1-propanol (99%) was purchased from Acros Organics and used as received.

3. Dichloromethane (99%) was purchased from Acros Organics and was freshly distilled from CaH_2.
4. Chlorosulfonic acid (99%) was purchased from Acros Organics and used as received.
5. If the reaction becomes too vigorous it can be kept cooled.
6. Methanol (99%) was purchased from Acros Organics and used as received.
7. 3-Ammoniopropylsulfate (**1**) has the following physical and spectroscopic properties: mp 196–198 °C; IR (ATR): 3123, 3066, 2974, 1622, 1527, 1192, 1166, 1030, 979, 916, 818, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.77–1.84 (m, 2H), 2.83–2.88 (m, 2H), 3.82 (t, J = 6.1 Hz, 2H), 7.68 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 27.3 (CH_2), 36.9 (CH_2), 63.4 (CH_2); HRMS (+ESI) m/z calcd for $C_3H_{10}NO_4S$ $[M + H]^+$ 156.0325, found 156.0329.
8. Absolute ethanol (99%) was purchased from Acros Organics and used as received.
9. Carbon disulfide was purchased from Sigma Aldrich (ACS reagent, 99.9%) and used as received.
10. KOH (98%) beads was purchased from Panreac and used as received.
11. Dichloromethane (99%) was purchased from Acros Organics and used as received.
12. Anhydrous $MgSO_4$ was purchased from Panreac and used as received.
13. 1,3-Thiazinane-2-thione (**2**) has the following physical and spectroscopic properties: mp 130–133 °C [lit.[2] mp 132–133 °C]; IR (ATR): 3164, 3088, 2946, 1565, 1461, 1309, 1226, 1154, 1049, 910, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.15–2.21 (m, 2H), 2.99–3.02 (m, 2H), 3.46–3.49 (m, 2H), 8.92 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 20.5 (CH_2), 30.0 (CH_2), 44.3 (CH_2), 194.6 (C); HRMS (+ESI) m/z calcd for $C_4H_8NS_2$ $[M + H]^+$ 134.0093, found 134.0093.
14. The remaining solid is a thick paste containing impurities formed in the reaction.
15. The quantities of both crops can vary but the overall yield is consistent.
16. Triethylamine (99%) was purchased from Fluorochem and was freshly distilled over CaH_2.
17. Propionyl chloride (99%) was purchased from Acros Organics and used as received.
18. Ammonium chloride was purchased from Panreac and used as received.
19. NaOH (98%) beads was purchased from Panreac and used as received.

20. Silica gel was purchased from Sigma Aldrich.
21. Hexane (99%) was purchased from VWR International and used as received.
22. Ethyl acetate was purchased from Panreac and used as received.
23. *N*-Propanoyl-1,3-thiazinane-2-thione (**3**) has the following physical and spectroscopic properties: yellow–orange oil; R_f 0.30 (80:20 hexanes/EtOAc); IR (ATR): 2974, 2933, 2873, 1698, 1470, 1347, 1302, 1280, 1125, 1020, 967, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, J = 7.3 Hz, 3H), 2.22–2.30 (m, 2H), 3.05 (t, J = 6.7 Hz, 2H), 3.08 (q, J = 7.3 Hz, 2H), 3.94–3.89 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 10.0 (CH_3), 22.8 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 46.4 (CH_2), 178.9 (C), 202.8 (C); HRMS (+ESI) m/z calcd for $C_7H_{12}NOS_2$ $[M + H]^+$ 190.0355, found 190.0353**.**

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

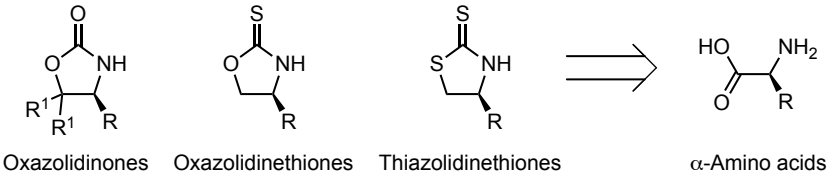
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of

individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

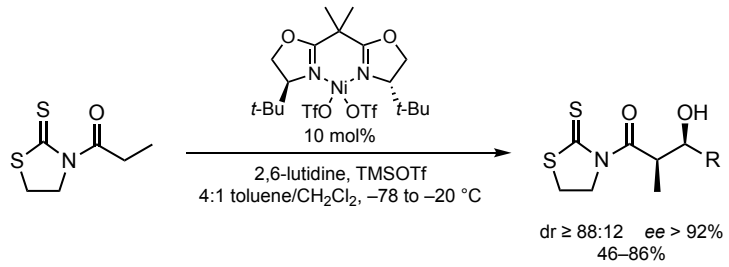
Discussion

Chiral heterocycles are widespread platforms from which a variety of stereoselective transformations can be carried out.[3] Indeed, chiral oxazolidinones (Scheme 1) introduced by Evans in the 80s still hold a prominent position among the most efficient chiral auxiliaries[4–6] and are currently employed for the synthesis of natural products.[7] Furthermore, structurally similar oxazolidinethiones and thiazolidinethiones (Scheme 1) have also played a crucial role in stereoselective synthesis.[8–11] Irrespective of the high stereocontrol provided by such auxiliaries, their prevalence is also due to their straightforward synthesis from proteinogenic α-amino acids (Scheme 1).[5,6,8,12]



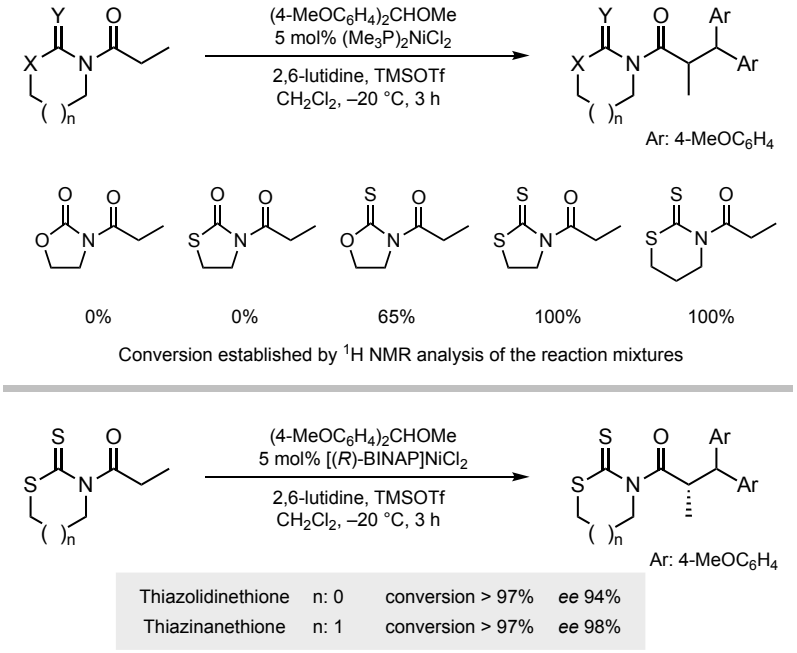
Scheme 1. Heterocycles used as chiral auxiliaries

Importantly, the quest for new catalytic and asymmetric transformations adhered to the atom economy principle[13] have also aroused the interest in the achiral counterparts of such heterocycles. Indeed, Evans reported the crucial role played by achiral *N*-propanoyl-1,3-thiazolidine-2-thione in enantioselective aldol reactions catalyzed by a chiral nickel(II) complex (Scheme 2).[14]



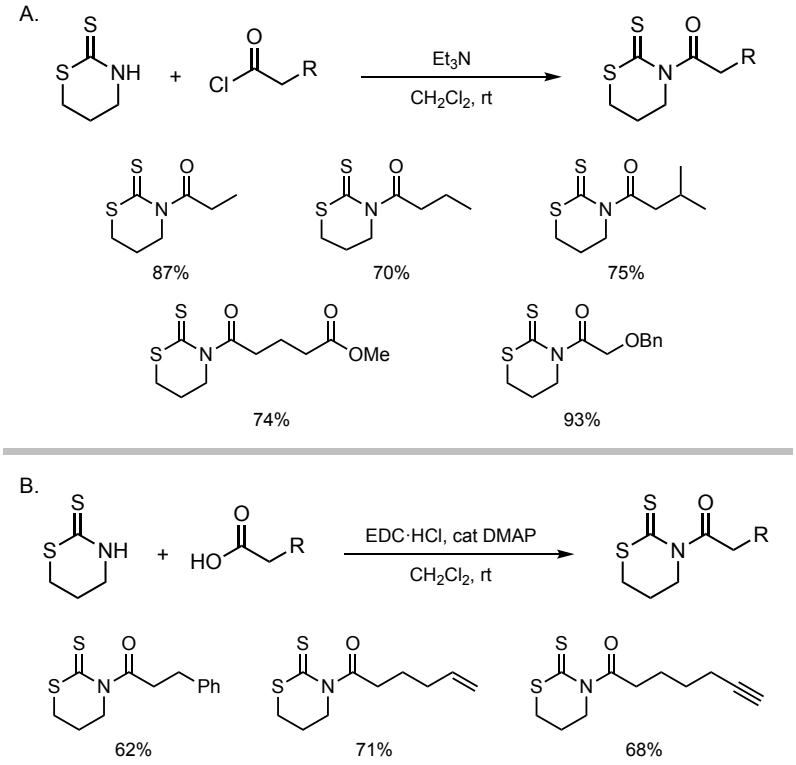
Scheme 2. Achiral *N*-propanoyl-1,3-thiazolidine-2-thione in enantioselective aldol reaction

Five membered achiral scaffolds may thus mimic the performance of their chiral counterparts shown in Scheme 1. Surprisingly, there is a lack of similar reactions based in the corresponding six membered heterocycles.[2] In this context, we have recently reported that *N*-propanoyl-1,3-thiazinane-2-thione undergoes highly efficient alkylation reactions with benzhydryl methyl ethers, slightly more enantioselective than the parallel thiazolidinethione scaffold (Scheme 3).[15] Therefore, a six-membered thiazinane heterocycle may be a valuable platform for asymmetric synthesis.



Scheme 3. Alkylation of *N*-propanoyl heterocycles with (4-MeOC$_6$H$_4$)$_2$CHOMe

Acylation of 1,3-thiazinane-2-thione with acyl chlorides at 10–15 mmol provides the corresponding *N*-acyl thiazianethiones with yields up to 93% (Scheme 4. Part A). Alternatively, such acylations can be carried out by coupling of 1,3-thiazinane-2-thione and carboxylic acids with EDC at 5–10 mmol scale (Scheme 4. Part B).



Scheme 4. Acylation of 1,3-thiazinane-2-thione

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

3-Amino-1-propanol: 1-Propanol, 3-amino-; (156-87-6)
Chlorosulfonic acid: Chlorosulfuric acid; (7790-94-5)
3-Ammoniopropylsulfate: 1-Propanol, 3-amino-, 1-(hydrogen sulfate); (1071-29-0)
Carbon disulfide: Carbon disulfide; (75-15-0)
1,3-Thiazinane-2-thione: 2*H*-1,3-Thiazine-2-thione, tetrahydro-; (5554-48-3)
Triethylamine: Ethanamine, *N*,*N*-diethyl-; (121-44-8)
Propionyl chloride: Propanoyl chloride; (79-03-8)
N-Propanoyl-1.3-thiazinane-2-thione: 1-Propanone, 1-(dihydro-2-thioxo-2*H*-1,3-thiazin-3(4*H*)-yl)-; (2138126-72-2)

Stuart C. D. Kennington, born in 1992 in Cambridgeshire, England, received his MChem degree from the University of Warwick in 2015. He is currently carrying out his PhD Thesis under the supervision of Prof. Fèlix Urpí and Pedro Romea at the University of Barcelona with a FI scholarship from the Generalitat de Catalunya. His research focuses on new catalyzed asymmetric synthesis methodologies and their application to the total synthesis of natural products.

Oriol Galeote, born in Barcelona in 1997, received his Degree in Chemsitry from the University of Barcelona in 2019. He collaborated as an undergraduate internship in the direct and asymmetric construction of carbon–carbon bonds from *N*-acyl-1,3-thiazinane-2-thiones catalyzed by nickel(II) complexes under the supervision of Prof. Fèlix Urpí and Pedro Romea. He is currently enrolled in the Master in Organic Chemistry of the University of Barcelona.

Miguel Mellado-Hidalgo, born in Barcelona in 1996, received his Degree in Chemistry from the University of Barcelona in 2018. Then, he enrolled in the Master in Organic Chemistry in the same university, joining the group of Prof. Fèlix Urpí and Pedro Romea to study new direct and enantioselective aldol reactions from *N*-acyl-1,3-thiazinane-2-thiones catalyzed by nickel(II) chiral complexes. Currently, he is carrying out his PhD Thesis under their supervision, focusing his research on new catalytic and asymmetric methods and their application to the synthesis of natural products.

Pedro Romea completed his B.Sc. in Chemistry at the University of Barcelona and followed PhD studies from 1987 to 1991 under the supervision of Professor Jaume Vilarrasa at the same University of Barcelona. Then, he joined the group of Professor Ian Paterson at the University of Cambridge (UK), where he participated in the total synthesis of oleandolide. Back to the University of Barcelona, he became Associate Professor in 1993. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.

Felix Urpí received his B.Sc. in Chemistry at the University of Barcelona and completed PhD studies under the guidance of Professor Jaume Vilarrasa at the University of Barcelona in 1988. He then worked as a NATO postdoctoral research associate in titanium enolate chemistry with Professor David A. Evans, at Harvard University in Cambridge, MA. He moved back to the University of Barcelona and he became Associate Professor in 1991, where he holds a chair of Full Professor in Organic Chemistry since 2017. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.

Organic Syntheses

Synthesis of [(*R*)-DTBM-SEGPHOS]$NiCl_2$ and Orthoformate Reaction

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Department of Inorganic and Organic Chemistry, Section of Organic Chemistry, and Institute of Biomedicine (IBUB), University of Barcelona, Carrer Martí i Franqués 1-11, 08028 Barcelona, Catalonia, Spain

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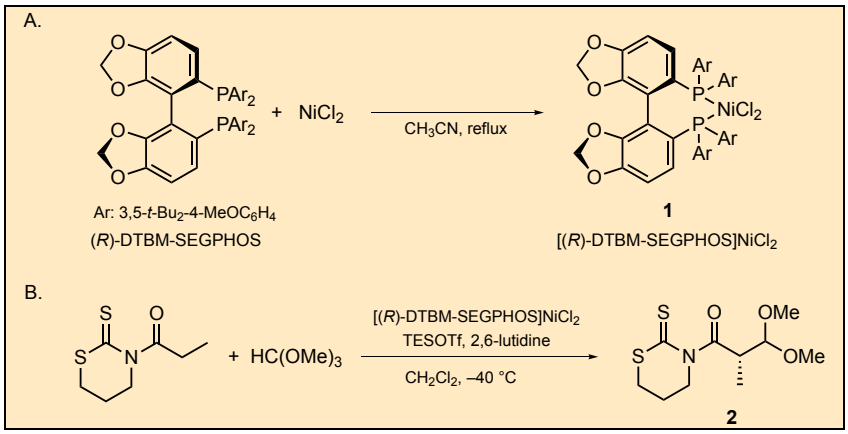


Procedure (Note 1)

A. *[(R)-DTBM-SEGPHOS]$NiCl_2$ (**1**).* An oven dried single-necked 25 mL round-bottomed flask (14/23 joint), equipped with a 1.5-cm Teflon-coated magnetic stirbar, is charged with (*R*)-DTBM-SEGPHOS (1.00 g, 0.85 mmol, 1 equiv) (Note 2) and $NiCl_2$ (110 mg, 0.85 mmol, 1 equiv) (Note 3), and acetonitrile (15 mL) (Note 4). A reflux condenser (14/23 joint) with a rubber septum is attached to the round-bottomed flask and the system is purged for 5 min with N_2, after which a N_2-filled balloon is used to seal the system. The mixture is then heated at reflux in an oil bath for 16 h.

A Number 3 Glass filter funnel connected with a vacuum adaptor to a single-necked 500 mL round-bottomed flask (29/32 joint) is charged with Celite® (25 g) (Note 5). The Celite® is wetted with acetonitrile (70 mL) (Note 4) and allowed to settle. Whilst the reaction mixture is still warm, the contents are poured over the Celite®. Once absorbed, the Celite® is carefully washed (Note 6) with acetonitrile (300 mL) (Note 4) until the color completely passes to the round-bottomed flask. The filtrate is concentrated on a rotary evaporator (30 °C, 12 mmHg pressure). The resulting solid is dissolved in dichloromethane (20 mL) (Note 7) and transferred to a vial (20 mL). The solution is concentrated on a rotary evaporator (30 °C, 12 mmHg pressure) and the resulting solid broken up with a spatula and dried on a high vacuum line (room temperature, 0.1 mmHg pressure) for 4 h giving the title compound **1** (1.10 g, 0.84 mmol, 99% yield) (Note 8) as a fine dark green-black powder.

Figure 1. Reaction set-up (left), final color (middle), and Celite® filtration (right)

B. *N-[(S)-(3,3-Dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione* (**2**). An oven dried single-necked 50 mL round-bottomed flask (14/23 joint), equipped with a 2-cm Teflon-coated magnetic stirbar, is charged with *N*-propanoyl-1,3-thiazinane-2-thione (1.89 g, 10 mmol, 1 equiv) (Note 9) and **1** (196 mg, 0.15 mmol, 1.5 mol%). The round-bottomed flask is sealed with a rubber septum and purged with N_2 for 5 min, after which a N_2-filled balloon is attached to the system. Freshly distilled dichloromethane (20 mL) (Note 7) is added to the mixture, followed by trimethyl orthoformate (1.3 mL, 12

mmol, 1.2 equiv) (Note 10). The resultant mixture is stirred and cooled to –40 °C with an acetonitrile/liquid N_2 bath. Then, triethylsilyl triflate (3.2 mL, 14 mmol, 1.4 equiv) (Note 11) is added and the mixture is stirred for 5 min. Finally, freshly distilled 2,6-lutidine (1.75 mL, 15 mmol, 1.5 equiv) (Note 12) is added and the resultant mixture is stirred for 2 h at –40 °C.

Figure 2. Reaction set-up (left) and final appearance (right)

The reaction is quenched with saturated NH_4Cl aqueous solution (10 mL) and the mixture is transferred to a 250 mL separating funnel. The round-bottomed flask is washed with dichloromethane (2 × 25 mL) (Note 13), which is then transferred to the separating funnel. Deionized water (2 × 25 mL) was used to wash the round-bottomed flask and added to the separating funnel. After shaking vigorously, the lower organic layer is collected and the remaining aqueous layer is further extracted with dichloromethane (50 mL) (Note 13). The combined organic extracts are dried over $MgSO_4$ (30 g) (Note 14) and filtered into a 250 mL round-bottomed flask (29/32 joint); the remaining $MgSO_4$ (Note 14) is further washed with dichloromethane (50 mL) (Note 13) and filtered. The combined filtrates are concentrated on a rotary evaporator (25 °C, 12 mmHg pressure) to produce a yellow–brown oil.

The residue is then submitted to flash column chromatography using a 4.5 cm diameter column with a length of 25 cm of silica gel (60 Å) (Note 15). This is first compacted with 95:5 dichloromethane/triethylamine (500 mL) (Notes 13 and 16), washed once with dichloromethane (500 mL) (Note 13),

and the surface levelled. The residue is dissolved in dichloromethane (10 mL) (Note 13) and transferred onto the compacted column with a pipette. The round-bottomed flask is washed with further dichloromethane (2 × 5 mL) (Note 13) and the washings added to the column. Once adsorbed, thick sand is added to protect the silica. The column is eluted with dichloromethane (*ca* 500 mL) (Note 13) until all of the yellow color has left the column and the eluent runs clear. All pure tubes are collected in a 500 mL round-bottomed flask and concentrated on a rotary evaporator (35 °C, 12 mmHg pressure). Neat dichloromethane (2 × 25 mL) (Note 13) is added and the resultant solution transferred to a vial (20 mL) where it is concentrated on a rotary evaporator (35 °C, 12 mmHg pressure). The resultant solid is kept under high vacuum (0.1 mmHg) at room temperature for 4 h to afford pure product **2** (2.29 g, 87% yield) as a yellow solid (Note 17).

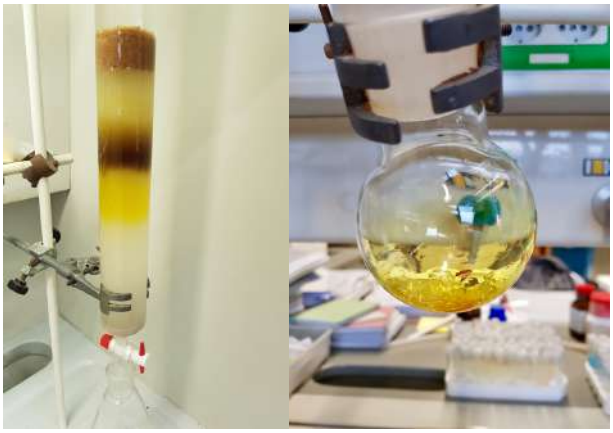


Figure 3. Column chromatography (left) and final product (right)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the

hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with trimethyl orthoformate, triethylsilyl triflate, 2,6-lutidine, triethylamine, Celite®, silica gel, acetonitrile, and dichloromethane.

2. (*R*)-DTBM-SEGPHOS (> 99%) was purchased from TCI Europe and used as received.
3. $NiCl_2$ (99%) was purchased from Sigma-Aldrich and used as received.
4. Acetonitrile (99%) was purchased from VWR International and used as received.
5. Celite@ was purchased from Fluorochem and used as received.
6. It is important to wash the Celite® surface carefully to minimally stir up the solid.
7. Dichloromethane (99%) was purchased from Acros Organics and was freshly distilled from CaH_2.
8. [(*R*)-DTBM-SEGPHOS]$NiCl_2$ (**1**) has the following physical and spectroscopic properties: mp 255–257 °C; IR (ATR): 2955, 1439, 1407, 1391, 1223, 11135, 1112, 1049, 1002, 844, 805 cm^{-1}; HRMS (+ESI) *m*/*z* calcd for $C_{74}H_{100}ClNiO_8P$ $[M - Cl]^+$ 1271.5930, found 1271.5919.
9. *N*-Propanoyl-1,3-thiazinane-2-thione has been reported in the preceding paper.
10. Methyl orthoformate (99%) was purchased from Sigma-Aldrich and used as received.
11. Triethylsilyl triflate (> 98%) was purchased from Fluorochem and used as received. Importantly, triethylsilyl triflate must be new and fresh. It is imperative that it resembles a clear liquid.
12. 2,6-Lutidine (98%) was purchased from Sigma-Aldrich and freshly distilled over CaH_2.
13. Dichloromethane (99%) was purchased from Acros Organics and used as received.

14. Anhydrous $MgSO_4$ was purchased from Panreac and used as received.
15. Silica gel was purchased from Sigma-Aldrich and used as received.
16. Triethylamine (> 99%) was purchased from Sigma-Aldrich and used as received.
17. *N*-[(*S*)-(3,3-Dimethoxy-2-methylpropanoyl)]-1,3-thiazinane-2-thione (**2**) has the following physical and spectroscopic properties: R_f 0.40 (CH_2Cl_2); chiral HPLC (Phenomenex Lux® Amylose-2 column, 10% *i*-PrOH in hexane, flow 1 mL min^{-1}] R_t 11.4 min [R_t minor 18.9 min], 99% *ee*; mp 56–57 °C; $[\alpha]_D^{20}$ +352 (*c* 1.00, $CHCl_3$); IR (ATR): 2936, 2823, 1704, 1460, 1374, 1344, 1289, 1127, 1096, 1047, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (d, *J* = 6.7 Hz, 3H), 2.15–2.35 (m, 2H), 2.97–3.14 (m, 2H), 3.30 (s, 3H), 3.33 (s, 3H), 3.48 (ddd, *J* = 13.3, 9.3, 4.2 Hz, 1H), 3.95 (dq, *J* = 8.1, 6.7 Hz, 1H), 4.13 (dt, *J* = 13.3, 5.0 Hz, 1H), 4.41 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.8 (CH_3), 22.5 (CH_2), 31.8 (CH_2), 45.8 (CH), 47.6 (CH_2), 52.0 (CH_3), 55.2 (CH_3), 107.4 (CH), 181.4 (C), 201.1 (C); HRMS (+ESI) *m*/*z* calcd for $C_9H_{14}NO_2S_2$ $[M - OMe]^+$ 232.0460, found 232.0462.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment

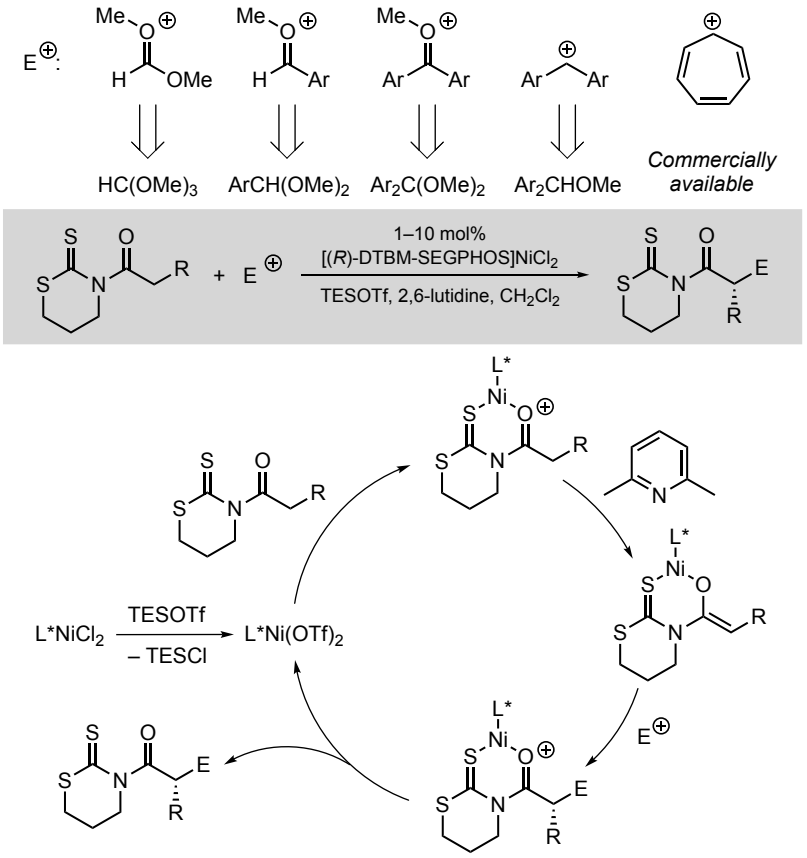
and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

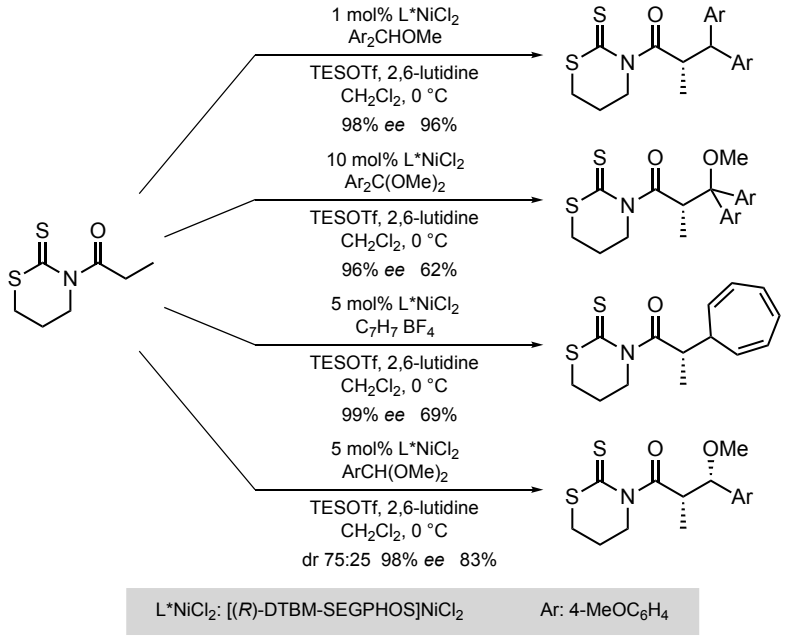
The enantioselective and catalytic construction of carbon–carbon bonds from enolates has attracted much attention in recent years.[2] Indeed, Evans,[3] Shibasaki,[4] and Trost[5] have described insightful approaches taking advantage of privileged scaffolds and chiral nickel(II), copper(II), or zinc complexes. Regardless the outcome of such transformations, availability and easily handled catalysts are important issues to make them useful to be applied to the asymmetric synthesis of natural products.

In this context, we have recently reported the reaction of *N*-acyl-1,3-thiazinane-2-thione with a range of electrophiles in the presence of 1–10 mol% of [(*R*)-DTBM-SEGPHOS]$NiCl_2$.[6,7] Evidence suggests that such a complex is activated *in situ* with TESOTf to produce the true catalytic species, [(*R*)-DTBM-SEGPHOS]$Ni(OTf)_2$, whose coordination with the *N*-acyl thiazinanethione makes possible the Cα deprotonation with 2,6-lutidine (Scheme 1). In turn, TESOTf is also necessary to generate *in situ* the electrophilic reacting species from methyl orthoformate, acetals, ketals, or benzhydryl methyl ethers. Then, the resultant chiral nickel(II) enolate approaches the electrophilic intermediate through an open transition state to produce the corresponding adduct containing a new carbon–carbon bond and up to two new stereogenic centers (Scheme 1).



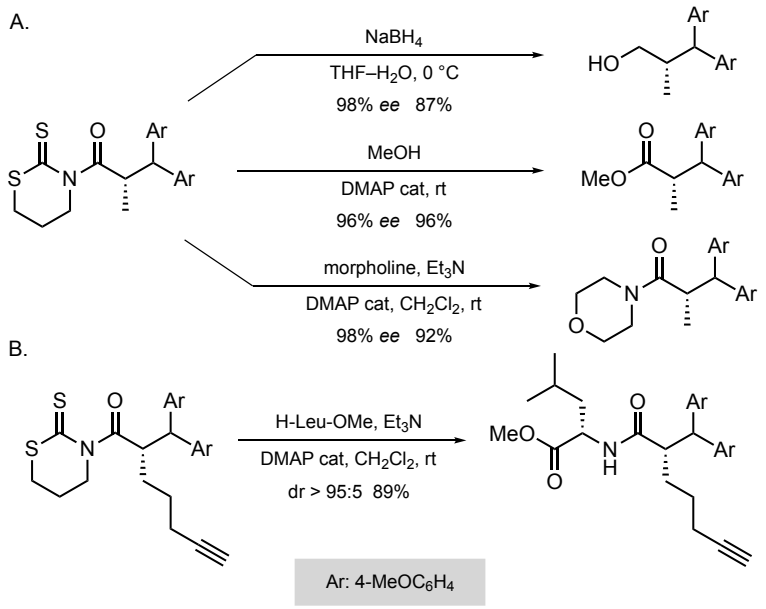
Scheme 1. Enantioselective carbon–carbon bond forming reactions from *N*-acyl-1,3-thiazinane-2-thiones and [(*R*)-DTBM-SEGPHOS]$NiCl_2$

Such a process turns out to be successful and may provide alkylated and aldol-like products in high yields and excellent stereocontrol. Indeed, aside from the 3,3-dimethoxy derivative described before, it is possible to obtain the adducts represented in Scheme 2 as a single enantiomer (ee ≥ 96%) in good to high yields.



Scheme 2. Enantioselective carbon–carbon bond forming reactions from *N*-propanoyl-1,3-thiazinane-2-thione catalyzed by [(*R*)-DTBM-SEGPHOS]$NiCl_2$

Finally, the thiazinanethione scaffold can be easily removed under mild experimental conditions to afford enantiomerically pure alcohols, esters, or amides as shown in Part A of Scheme 3. Interestingly, the thiazinanethione may also act as a coupling reagent and permits the synthesis of a diastereomerically pure *N*-acyl amino acid by simple addition of methyl (*S*) leucinate to the corresponding adduct with an 89%yield (Part B Scheme 3).[8]



Scheme 3. Removal of the thiazinanethione scaffold

References

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6. Kennington, S. C. D.; Taylor, A. J.; Romea, P.; Urpí, F.; Aullón, G.; Font-Bardia, M.; Ferré, L.; Rodrigalvarez, J. *Org. Lett.* **2019**, *21*, 305–309.
7. The preparation of [(*R*)-DTBM-SEGPHOS]$NiCl_2$ has been adapted from that reported for [(*R*)-Tol-BINAP]$NiCl_2$. See reference 3b.
8. For a related example proving the synthetic potential of such an approach for the synthesis of peptides, see: Fernández-Valparís, J.; Romea, P.; Urpí, F. *Eur. J. Org. Chem.* **2019**, 2745–2752.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

[(*R*)-DTBM-SEGPHOS]: Phosphine, 1,1'-(4*R*)-[4,4'-bi-1,3-benzodioxole]-5,5'-diylbis[1,1-bis[3,5-bis(1,1-dimethylethyl)-4-methoxyphenyl]-; (566940-03-2)

N-Propanoyl-1,3-thiazinane-2-thione: 1-Propanone, 1-(dihydro-2-thioxo-2H-1,3-thiazin-3(4H)-yl)-; (2138126-72-2)

Trimethyl orthoformate: Methane, trimethoxy-; (149-73-5)

Triethylsilyl triflate: Methanesulfonic acid, 1,1,1-trifluoro-, triethylsilyl ester; (79271-56-0)

2,6-Lutidine: Pyridine, 2,6-dimethyl-; (108-48-5)

N-[(*S*)-3,3-Dimethoxy-2-methylpropanoyl]-1,3-thiazinane-2-thione: 1-Propanone, 1-(dihydro-2-thioxo-2H-1,3-thiazin-3(4H)-yl)-3,3-dimethoxy-2-methyl-, (2*S*)-; (2270858-10-9)

Stuart C. D. Kennington, born in 1992 in Cambridgeshire, England, received his MChem degree from the University of Warwick in 2015. He is currently carrying out his PhD Thesis under the supervision of Prof. Fèlix Urpí and Pedro Romea at the University of Barcelona with a FI scholarship from the Generalitat de Catalunya. His research focuses on new catalyzed asymmetric synthesis methodologies and their application to the total synthesis of natural products.

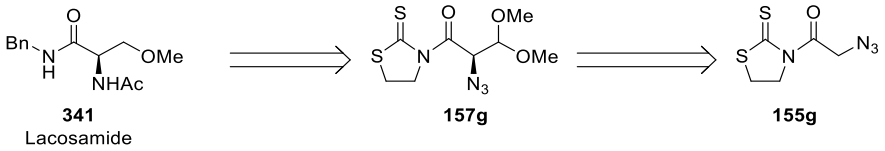
Pedro Romea completed his B.Sc. in Chemistry at the University of Barcelona and followed PhD studies from 1987 to 1991 under the supervision of Professor Jaume Vilarrasa at the same University of Barcelona. Then, he joined the group of Professor Ian Paterson at the University of Cambridge (UK), where he participated in the total synthesis of oleandolide. Back to the University of Barcelona, he became Associate Professor in 1993. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.

Felix Urpí received his B.Sc. in Chemistry at the University of Barcelona and completed PhD studies under the guidance of Professor Jaume Vilarrasa at the University of Barcelona in 1988. He then worked as a NATO postdoctoral research associate in titanium enolate chemistry with Professor David A. Evans, at Harvard University in Cambridge, MA. He moved back to the University of Barcelona and he became Associate Professor in 1991, where he holds a chair of Full Professor in Organic Chemistry since 2017. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.

The Synthesis of Lacosamide and Derivatives

Following our success at developing a new enantioselective alkylation methodology and its subsequent application to the synthesis of the natural product Peperomin D, we aimed to expand its utility by focusing on not only the synthesis of another biologically active molecule but a extensive investigation into the manipulation of one of the initial alkylation adducts. This would allow us to develop a methodology for the rapid synthesis of the original product and various derivatives to show the wide range of use our synthons have.

We chose the synthetic drug Lacosamide (**341**) due to its structural similarity to the products of our enantioselective orthoformate reaction (Scheme 135). In fact, using the adduct **157g** easily available from the *N*-azidoacetyl thiazolidinethione **155g** as discussed previously would permit to synthesize lacosamide as well as a library of synthetic derivatives in a new and efficient manner. This intermediate would arise from the azide starting material using the five-membered scaffold (discussed on Page 143) in the orthoformate reaction (discussed on Page 138).



Scheme 135: Lacosamide and Our Retrosynthetic Analysis.

Lacosamide

Lacosamide was first synthesised Kohn in the context of a study into the anticonvulsant properties of *N*-benzyl-2-acetamidopropionamides and emerged as the lead candidate.[49–53] Thus, it has been the focus of various biological studies for its use as an anticonvulsant medicine both *in-vitro, in-vivo* testing and clinical trials.[54–60] Studies into its mode of action have also been conducted and was shown to moderate voltage gated sodium channels; in comparison to other related drugs it was shown to inhibit slowly the mechanism and at a different active site representing a new mode of action.[57] This lends stabilisation to hyperexcitable neuronal membranes. It was also shown to have some analgesic properties for neuropathic disorders;[59,61] specifically it has been investigated for the use at treatment for diabetic neuropathy and fibromyalgia.[62–65] The method of administration was also studied and its combination use with existing drugs also examined.[55,56,58] While investigation is still ongoing as of yet the active site and binding mode of Lacosamide has not yet been defined.

Lacosamide is approved both by the FDA and the EMA as a drug for seizures since 2008 and is administered both solely or in combination with other drugs. Actually it is sold under the market name of Vimpat® as either tablets, oral solutions or through injections.[66,67]

Previous Syntheses of Lacosamide

Due to the biological properties and its small and simplistic structure many syntheses have been described since the original published by Kohn.[49,50,68–78] Furthermore many patents have been filed for the synthesis of Lacosamide.[79–84] Whilst most approaches utilise the chiral pool,[49,50,70,72,73,75,78] a few catalytic processes and a chemoenzymatic resolution have also been reported.[68,69,74,76,77]

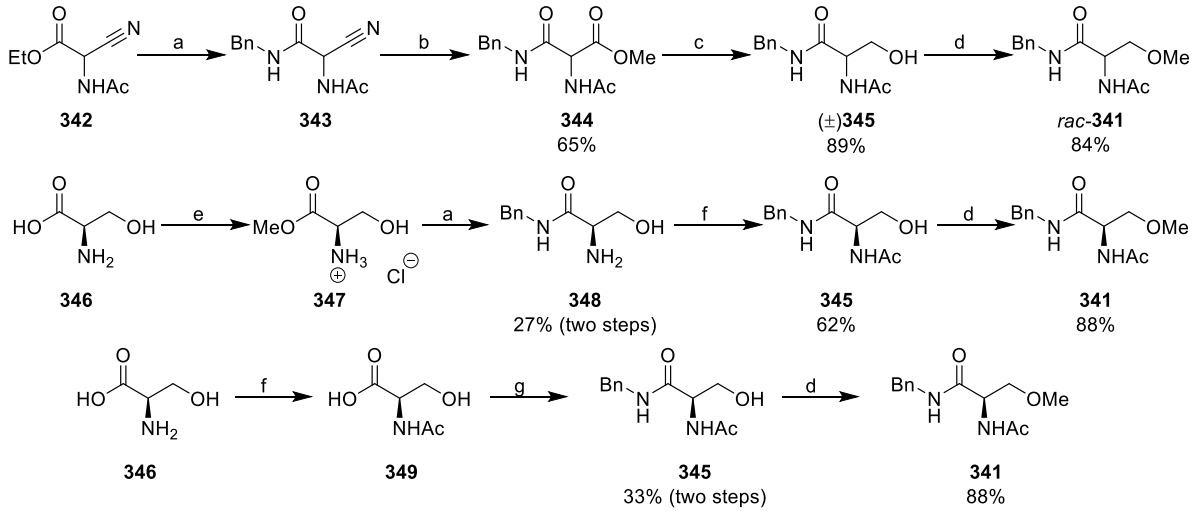
Kohn's original approach consisted of an initial racemic synthesis and various derivatives to create lead target molecules. Later, this was then adapted to the asymmetric synthesis of these lead targets, including Lacosamide. The final improved route is described in Scheme 136.[49]

The racemic synthesis was based on the cyanoester **342**, which was first transformed into the benzylamide by reflux in benzylamine and methanol (Top, Scheme 136). The nitrile group was then

converted into the methyl ester **344** through acidic catalysed reaction with methanol in good yields. Reduction with lithium borohydride and lithium chloride led to the alcohol (±)**345** in an excellent yield which was then methylated to give racemic Lacosamide in an excellent yield. The overall yield was 49% from **343** (the yield for the reaction of **342** to **343** was not given).

The first asymmetric synthesis was a chiral pool approach starting from D-serine (**346**) which was transformed into the methyl ester **347** and directly to the benzylamide **348** to give a low yield over two steps (Centre, Scheme 136). The free amine was then protected as an acetyl amide to give **345** in a good yield. Finally, the alcohol was methylated as with the racemic route to give Lacosamide in an excellent yield. The overall yield was 15% for this route.

An improved methodology also started from D-serine, but the route differed somewhat from the initial design. The first step was acylation of the amine group to give the hydroxy-acid **349**; this was immediately transformed to the benzylamide **345** through the formation of the chloroformate activated species which was then displaced by the benzylamine to give **345** but in a low yield. The low yield is possibly due to polymerisation through the alcohol forming ester groups with the chloroformate. Although the yield is low, it is considerably higher than the 17% from the previous route to reach the intermediate **345**. The synthesis was then completed as previously described with an overall yield of 29%.

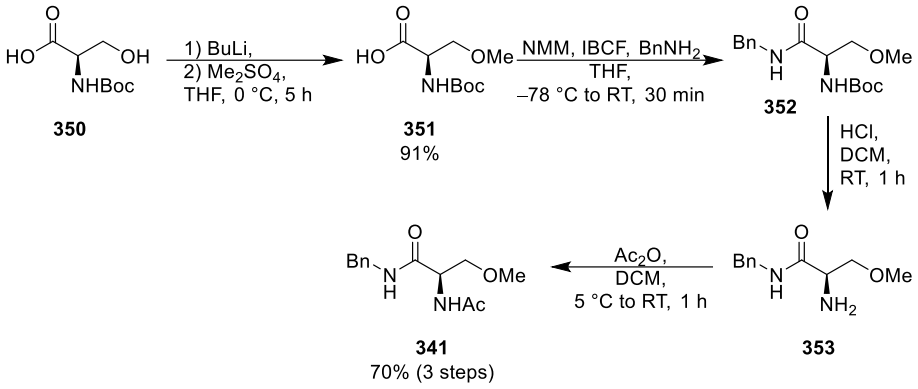


a: $BnHN_2$, MeOH, reflux, 18 h; b: PTSA, MeOH, reflux, 12 h; c: LiCl, $NaBH_4$, EtOH, THF, RT, 5 h; d: MeI, AgO_2, ACN, RT, 4 d; e: MeOH, HCl, reflux, 18 h; f: AcO_2, DCM, RT, 1 h; g: NMM, IBCF, $BnNH_2$, THF, –78 °C to RT, 30 min.

Scheme 136: Kohn's Original Synthesis of Lacosamide. Top: Racemic Synthesis; Centre: Initial Asymmetric Synthesis; Bottom: Improved Asymmetric Synthesis.

Riedner next described a total synthesis of Lacosamide in two patents published in 2004 and 2006.[79,83] The route was again a chiral pool approach from a derivative of D-serine. Similar approaches were also described by others.[70,73,80]

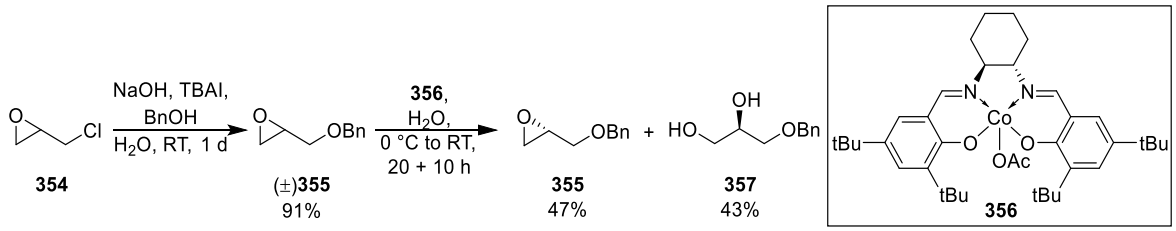
The synthesis started from the Boc-protected D-serine derivative **350** which was deprotonated with butyl lithium and methylated with dimethyl sulphate to give the ether **351** in an exceptional yield (Scheme 137). This was then transformed to the benzylamide using Kohn's method to give amide **352**. The amide was reacted without further purification to remove the Boc-group to give amine **353** which was finally protected with an acetyl group to form Lacosamide in a high yield of 70% over three steps. The overall yield for the synthesis was 64%.



Scheme 137: Synthesis of Lacosamide by Riedner.

Various other chiral pool approaches have been described for the synthesis of Lacosamide, the majority starting from a derivative of the amino acid serine.[70,72,73,78] These approaches have not been represented due to the similarity to other syntheses and our focus on enantioselective catalysis.

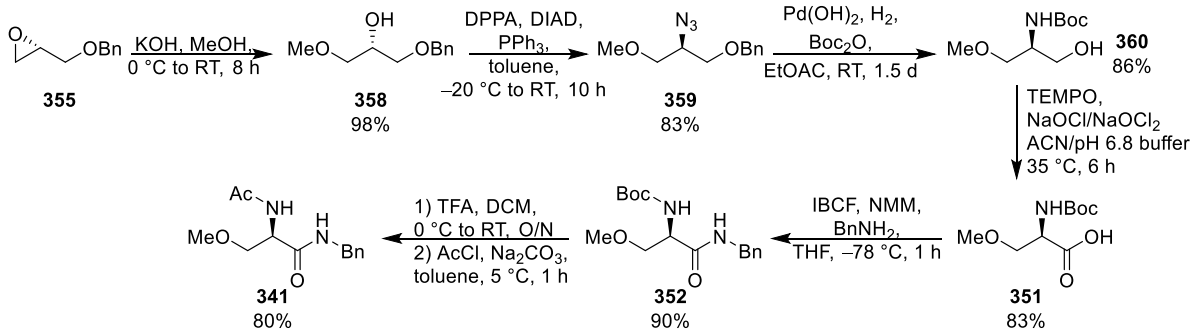
The first synthesis based on an asymmetric transformation was published in 2011 by Muthukrishnan and was based on a hydrolytic kinetic resolution.[69] The formation of a racemic protected hydroxy epoxide followed by stereospecific hydrolysis of one enantiomer provided an enantioenriched epoxide for use in the synthesis (Scheme 138). Indeed, the chloro-epoxide **354** was transformed to the benzyl protected hydroxy epoxide (±)**355** in an exceptional yield by displacement of the chloride by benzyl alcohol. This racemic epoxide was then treated with the Jacobsen cobalt-salen catalyst **356**, which left the desired enantiomer of the epoxide **355** untouched in a yield of 47% (50% max). This type of stereospecific discriminatory resolution inherently carries a disadvantage of limiting the yield to 50% due to the racemate being equally both enantiomers; however, the high enantiopurity and ease of the process offsets this slightly, especially as it is used in the preparation of a starting material with inexpensive reagents.



Scheme 138: Kinetic Resolution in the Preparation of Lacosamide.

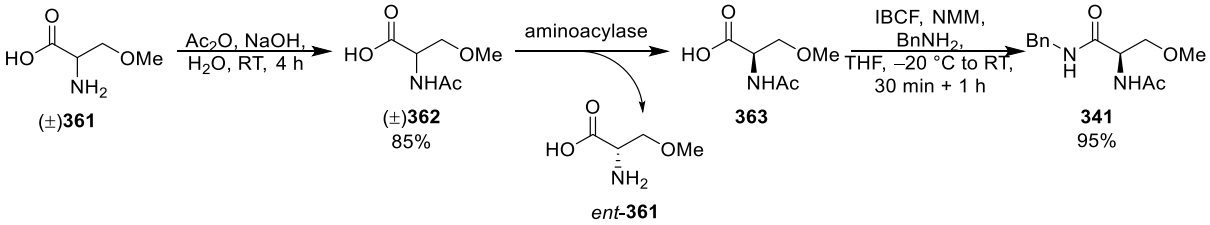
With the enantiopure epoxide **355** prepared the synthesis continued. First the epoxide was opened with methanol in basic conditions to give the secondary alcohol **358** in an almost quantitative yield (Scheme 139). The alcohol was replaced by an azide group in a Mitsunobu reaction with inversion of the configuration to give the azido compound **359** in an excellent yield. Three transformations were conducted in the next step: the reduction of the azide to the amine, the resulting protection with a Boc-group, and the deprotection of the benzyl alcohol; this was achieved using hydrogenation with palladium hydroxide in the presence of Boc-anhydride to give the boc-protected amino alcohol **360** in an excellent yield. The alcohol was then oxidised to the carboxylic acid using sodium chlorite catalysed by TEMPO and bleach giving **351** in an excellent yield. The benzylamide was formed from the carboxylic acid, in much the same way as previously described by Riedner and Kohn,[49,79,83] using isobutyl chloroformate, *N*-methylmorpholine and benzylamine to give the amide **352** in an excellent yield. Finally, Lacosamide was formed via the protecting group exchange of Boc to the acetyl group on

the nitrogen to give **341** in a high yield. The overall yield for the synthesis of Lacosamide was 17% over eight steps.



Scheme 139: Completion of Synthesis of Lacosamide by Muthukrishnan.

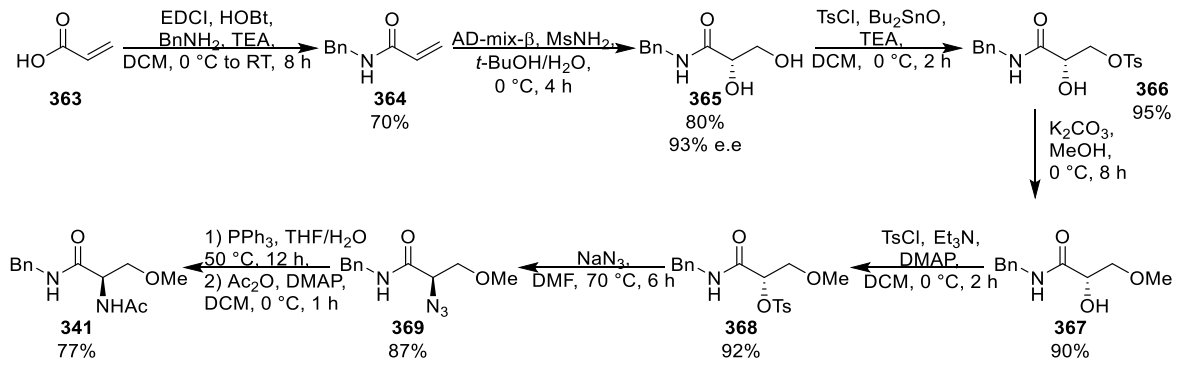
A related approach using stereo-differentiation of a racemic mixture has been also carried out with a chemoenzymatic resolution.[74] This route starts from the commercially available racemic *O*-methyl-DL-serine (±)**361** which is first acylated to give the protected amine (±)**362** in an excellent yield (Scheme 140). The chemoenzymatic step then proceeded and utilised an aminoacylase enzyme to perform the resolution. The enzyme selectively reacted with the undesired enantiomer to remove the acetyl group and gave *ent*-**361**, leaving untouched the desired enantiomer **363**. Again, the limitation of using a racemate means the maximum yield becomes 50% for the reaction. The now enantiopure carboxylic acid **363** was transformed to Lacosamide via the chloroformate mixed anhydride methodology.



Scheme 140: Chemoenzymatic Route to Lacosamide.

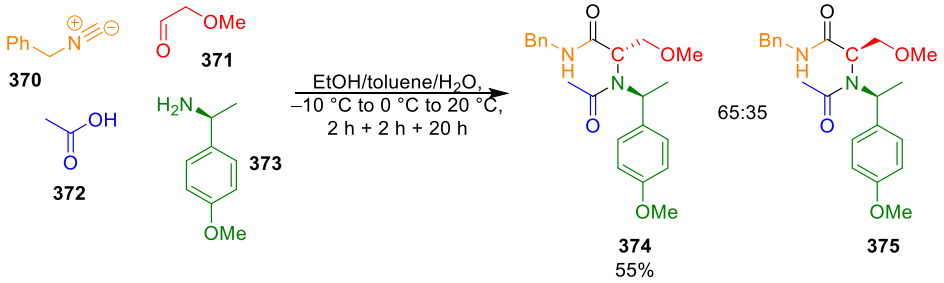
In turn, a patent used chiral column chromatography in a large scale to separate a racemic mixture. Furthermore, the opposing enantiomer could be recovered and re-racemised and fed into the resolution process to increase the yield.[81] Another patent described diasteromeric chiral salts for a chemical resolution.[85]

The first enantioselective synthesis not based on a chemical resolution step was published in 2013 by Narsaiah and was based on a Sharpless asymmetric dihydroxylation reaction.[68] The synthesis commenced from acrylic acid **363**, which was transformed into **364** through an amide coupling with benzylamine using HOBt and EDC iodide with a good yield (Scheme 141). Next an asymmetric dihydroxylation using AD-mix-β furnished the chiral diol **365** in a high yield and excellent enantioselectivity. The terminal alcohol was then selectively activated using tosyl chloride to give the tosylate **366** in an exceptional yield. This was then transformed to the methyl ether **367** through the one-pot formation of the epoxide and opening with methanol that provided **367** in an excellent yield. The secondary alcohol was activated to the tosylate **368** in an exceptional yield. The C2 stereocentre with the correct configuration was next installed through an S_N2 reaction with sodium azide to give the azido deivative **369** in an excellent yield. Finally, a two-step process involving the Staudinger reduction of the azido group and the subsequent acylation completed the synthesis of Lacosamide **341** in a high yield. The overall yield was 29.5% over eight steps.



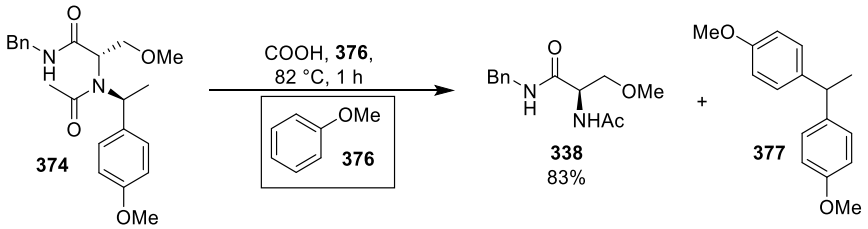
Scheme 141: Narsaiah's Synthesis of Lacosamide Utilizing a Sharpless Asymmetric Dihydroxylation.

One of the more unique syntheses of Lacosamide came from Wehlan. [77] This compeletely different approach featured a four component Ugi reaction in a very concise route to the final product. This four-component reaction formed the entire backbone in just one step with a high yield but modest stereocontrol (Scheme 142). The scheme has been colour coded to highlight where the starting materials end up in the final molecule. the reaction between the isocyanide **370** (orange), the aldehyde **371** (red), acetic acid **372** (blue), and finally the amine **373** (green), which both controls the stereochemistry and furnishes the amine, led directly to an advanced intermediate towards Lacosamide. The stereoselectivity of the reaction is somewhat poor but this is countered by the yield of 55% for the major isomer **374**, which is just one step away from the final product.



Scheme 142: Wehlan's Ugi Reaction in the Synthesis of Lacosamide.

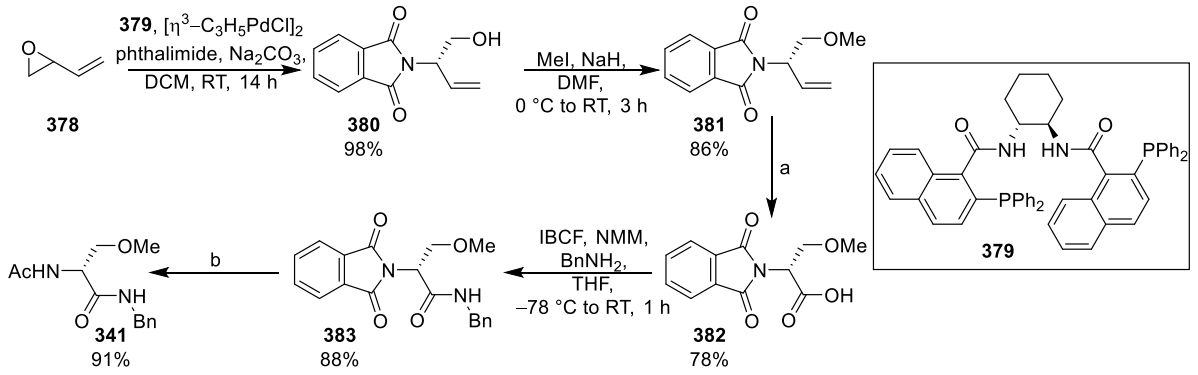
The synthesis was then completed by the removal of the chiral alkyl group on the nitrogen. This was achieved by the heating of **374** in formic acid and anisole (**376**) giving an excellent yield of Lacosamide. The side product formed in the reaction was the di-anisole ethane **377** and its mono *meta* derivative. This completed the synthesis of Lacosamide in just two steps with an overall yield of 46% using an efficient four-component reaction to shorten the synthetic sequence.



Scheme 143: Completion of Lacosamide Synthesis by Wehlan.

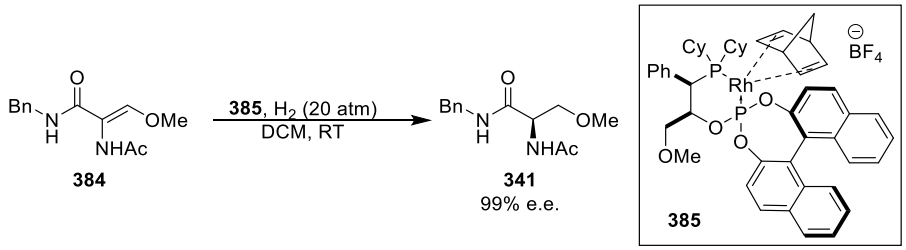
Pandey described a route based on the asymmetric catalysed opening of an epoxide through dynamic kinetic resolution.[76] The asymmetric reaction, described by Trost, hinges on the formation of a η^3-allyl-palladium complex between the substrate and catalyst, which can equilibrate through a σ-compound to favour one enantiomer.[86] The Trost reaction between starting material **378** and

phthalimide gave the alcohol **380** in an almost quantitative yield; the reaction was catalysed by palladium and the chiral ligand **379** (Scheme 144). The free alcohol was then methylated with methyl iodide to give methyl ether **381** in an excellent yield. The terminal alkene was then submitted to an oxidative cleavage to give the carboxylic acid **382** in a high yield. The benzylamide was formed as previously seen via the mixed anhydride and the displacement with benzylamine to give **383** in an excellent yield. Finally, a protecting group exchange sequence completed the synthesis of Lacosamide **341** in an exceptional yield. The total yield was 53% over five steps.



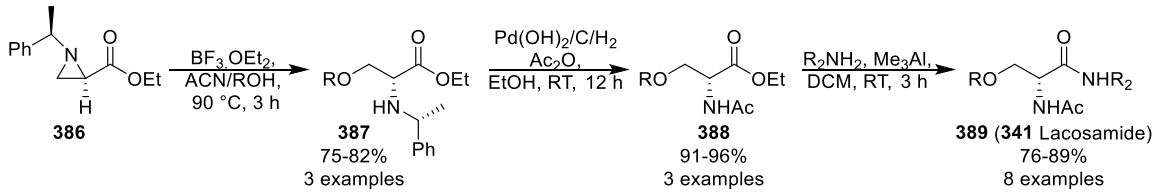
Scheme 144: Synthesis of Lacosamide by Pandey.

While not a total synthesis, the formation of Lacosamide from a late-stage intermediate by Vidal-Ferran is worth noting.[87] He used an asymmetric hydrogenation catalysed by a chiral rhodium-BINOL based complex to control the C2 configuration (Scheme 145). The enantiocontrol was exceptional, but the isolated yield was not reported. Although described as a test of concept for the methodology it provides an interesting alternative as the synthesis of the starting material can be racemic and provides a late-stage introduction of the chirality which avoids any potential problems of racemisation.



Scheme 145: Vidal-Ferran's Hydrogenation to Form Lacosamide.

One other synthesis using a chiral pool approach was published in 2017 by Ha starting from a commercially available chiral aziridine complex and is worth mentioning due to its adaptability of the process to easily synthesise derivatives.[75] Enantiomerically pure aziridine **386** was opened with alcohols to give amides **387** in high to excellent yields, for the synthesis of Lacosamide the alcohol used was methanol (Scheme 146). Removal of the chiral benzyl group via hydrogenation and acylation of the resulting amine to yield **388** proceeded smoothly. Finally, substitution of the ester group with various amines, completed the synthesis of Lacosamide **341** and a handful of derivatives **389** in yields ranging from good to excellent. The synthesis was also scaled up to a multigram scale with an overall yield of 72% over the three steps. This represents the highest yield so far for Lacosamide but starting from an advanced intermediate compared to other routes.



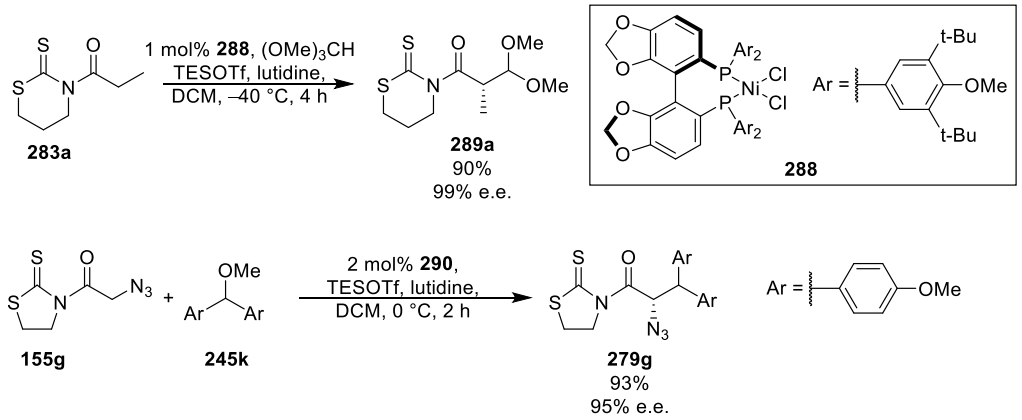
Scheme 146: Ha's Synthesis of Lacosamide and Derivatives.

Design for Our Synthetic Strategy for the Synthesis of Lacosamide and Derivatives.

Our paper discussed earlier in this chapter dealt with the enantioselective alkylation of *N*-acyl achiral scaffolds with various electrophiles.[88] Two of these reactions specifically led us to believe we could easily fabricate the desired intermediate for the synthesis of Lacosamide.

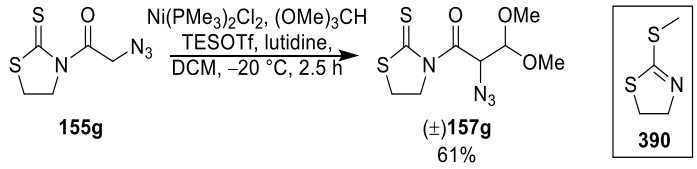
The first was the reaction of *N*-propionyl thiazinanethione **283a** with trimethyl orthoformate in the presence of **288**, triethylsilyl triflate and lutidine to give the adduct **289a** in an excellent yield and exceptional enantioselectivity (Top, Scheme 147). This would allow us to introduce a dimethyl acetal moiety which would be reduced to the methyl ether needed in Lacosamide.

The second reaction involved the alkylation of *N*-azidoacetyl thiazolidinethione **155g** with diarylmethyl ethers in an exceptional yield and excellent enantioselectivity (Bottom, Scheme 147). This reaction proves that the azide chain is compatible with our alkylation conditions and should be able to provide the amino group required for the Lacosamide product.



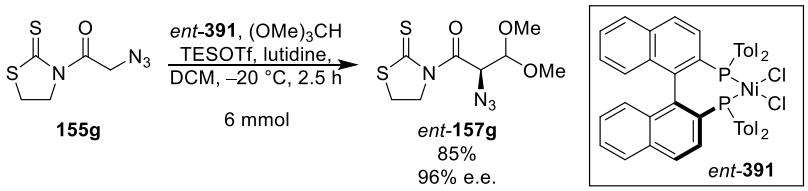
Scheme 147: Precedent from Our Previous Paper for the Synthesis of Lacosamide Intermediate. Top: Orthoformate Reaction; Bottom: Alkylation of N-Azidoacetyl Thiazolidinethione with Diarylmethyl Ether.

With strong hints that our alkylation reaction could work we had to test the combination of the azide chain with the trimethyl orthoformate alkylation reaction to confirm the feasibility. We examined the reaction using the achiral nickel(II) catalyst to make sure the reaction proceeded correctly before using chiral catalysts or performing any optimisation. We were glad to see the formation of (±)**157g** in a good yield, demonstrating the reaction was viable (Scheme 148). We also saw little formation of the corresponding side product **390** at –20 °C, confirming that the nucleophilic character of the exocyclic sulphur in the five-membered scaffold was less pronounced than in the six-membered counterpart.



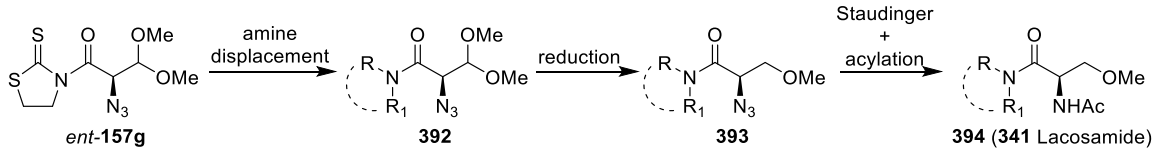
Scheme 148: Test of Orthoformate Alkylation on Azide Starting Material with Racemic Catalyst.

With the proof of concept for the reaction completed we then moved to optimise the reaction, examining different five-membered scaffolds, chiral catalysts, and reaction conditions to achieve the best yield and enantioselectivity. This was done by Saul F. Teloxa in his PhD Thesis. In summary, the best conditions involved the use of the original **155g** and the Tol-BINAPNiCl$_2$ complex *ent*-**391**, TESOTf, and lutidine at –20 °C (Scheme 149).



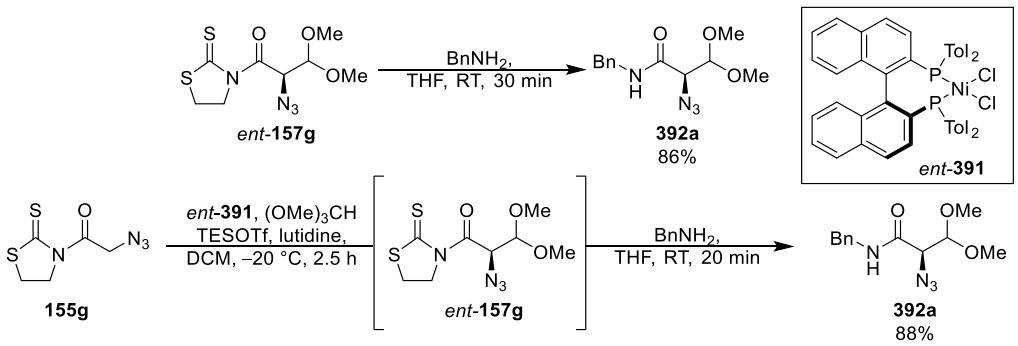
Scheme 149: Final Reaction Conditions for Trimethyl Orthoformate Alkylation for the Synthesis of Lacosamide.

With the key intermediate *ent*-**157g** successfully developed then synthesis moved forward to outline the synthetic strategy summarized in Scheme 150. The first step from the intermediate *ent*-**157g** was the displacement of the scaffold by various amines to give the amide **392**. The acetal group was then be reduced to give the methyl ether compound **393** and finally a Staudinger reaction followed by an acylation of the resultant amine gave the desired Lacosamide **341** and a large array of derivatives **394**. All the details are summarised in the following paper. This was done by Saul F. Teloxa in his PhD Thesis.



Scheme 150: Synthetic Scheme for the Synthesis of Lacosamide Derivatives from the Key Intermediate ent-***157g***.

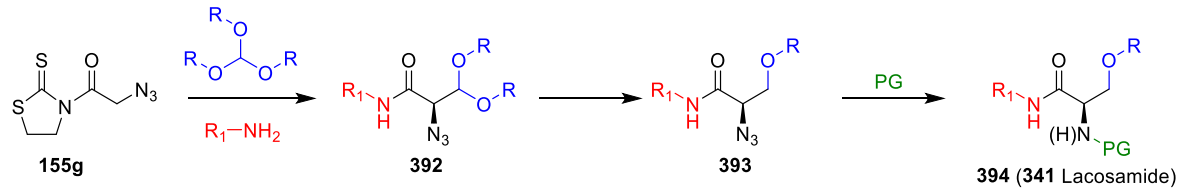
In initial tests removing the scaffold using benzylamine with the adduct *ent*-**157g** showed the reaction proceeded correctly and we were able to achieve the benzylamide **392a** in an excellent yield (Top, Scheme 151). Due to our previous experience using the reaction quench to perform secondary reactions we believed it could be possible to perform the enantioselective alkylation and form the amide through a quench with the amine reagent. Our synthesis of Peperomin D took advantage of this concept to perform a reduction reaction in the quench (see Page 148).[88] Therefore, we performed the alkylation reaction and quenched with benzylamine and obtained the benzylamide **392a** in an excellent yield in a one-pot reaction sequence (Bottom, Scheme 151). There was no loss of stereoselectivity over the two-step process and the yield was considerably better (88% compared to 73% for the two-step process).



Scheme 151: Displacement of Scaffold with Benzylamine. Top: Reaction with Intermediate ent-***157g***; *Bottom: One-Pot Alkylation with Amine Quench.*

The rest of the methodology and the synthesis of derivatives was completed by Saul F Teloxa in his PhD thesis currently underway and Marc Camats during his Masters project. The results can be found in the following paper.

Remarkably, a library of Lacosamide derivatives was synthesized by them with the same methodology. In fact, the derivatisation is not limited just to the type of amide in the final structure (Red, Scheme 152). Without any changes in the experimental procedure both the ether chain and the nitrogen protecting group can equally be tuned. By changing the orthoester used in the initial alkylation reaction various ether structures can be introduced into the final structure (Blue, Scheme 152). Also, the nature of the protecting group can be changed by altering the final protection step (Green, Scheme 152), in this way a large library of derivatives can be synthesised in a very short time frame in an efficient and selective manner.



Scheme 152: Highly Adaptable Synthesis of Lacosamide Derivatives, Colour Coded for Each Point of Derivatisation.

Full Paper
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Organic Chemistry |Hot Paper|

Direct, Enantioselective, and Nickel(II) Catalyzed Reactions of *N*-Azidoacetyl Thioimides with Trimethyl Orthoformate: A New Combined Methodology for the Rapid Synthesis of Lacosamide and Derivatives

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Dedicated to Professor Sergio Castillón

Abstract: A direct and highly enantioselective reaction of *N*-azidoacetyl-1,3-thiazolidine-2-thione with trimethyl orthoformate catalyzed by Tol-BINAPNiCl$_2$ in the presence of TESOTf and 2,6-lutidine is reported. The heterocyclic scaffold can be easily removed by addition of a wide array of amines to give the corresponding enantiomerically pure 2-azido-3,3-dimethoxypropanamides in high yields. Appropriate manipulation of the *N*-benzyl amide derivative provides an efficient access to the antiepileptic agent lacosamide through a new enantioselective C–C bond-forming process. DFT computational studies uncover clues for the understanding of the remarkable stereocontrol of the addition of a nickel(II) enolate to a putative oxocarbenium intermediate from trimethyl orthoformate.

Introduction

Despite the tremendous advancements in the asymmetric and catalytic construction of carbon–carbon bonds achieved during the last years, there is still a need for versatile methods that will enable the synthesis of a broad range of molecular architectures.[1–3] In this context, Evans[4] and Shibasaki[5] have convincingly established that both thiazolidinethione and azaindoline are suitable scaffolds to carry out direct and highly enantioselective aldol reactions catalyzed by chiral nickel(II) and copper(I) complexes, respectively. Inspired by such studies, we have recently reported that simple *N*-propanoyl-1,3-thiazinane-2-thione is a valuable platform from which to carry out direct and enantioselective carbon–carbon bond forming reactions with a plethora of cationic reagents using 1–5 mol% of robust and easy to handle [(*R*)-DTBM-SEGPHOS]NiCl$_2$.[6] Particularly, the direct addition to trimethyl orthoformate activated by TESOTf produces a single enantiomer of the corresponding adduct in 90% yield (Scheme 1 A). Furthermore, former evidence on similar reactions based on chiral *N*-acyl 1,3-thiazolidine-2-thiones catalyzed by (Me$_3$P)$_2$NiCl$_2$ indicated that the *N*-azidoacetyl counterpart was particularly suitable to provide highly stereocontrolled transformations (Scheme 1 B),[7] which resulted in being especially appealing due to the well-known instability of metal enolates from those substrates.[8–10] In view of such results, we envisaged that the azido group might be used as a masked amino group to synthesize enantiomerically pure α-amino acids or derivatives in a straightforward manner.[11] Thus, aiming to expand the scope of such processes, we launched a project to develop direct, enantioselective, and nickel(II) catalytic reactions of *N*-azidoacetyl thioimides with carbenium and oxocarbenium intermediates.

We hereby describe our first results on the enantioselective addition of *N*-azidoacetyl thioimides to trimethyl orthoformate and the application of this method to the synthesis of lacosamide[12,13] and several related compounds as a proof of concept (Scheme 1 C).

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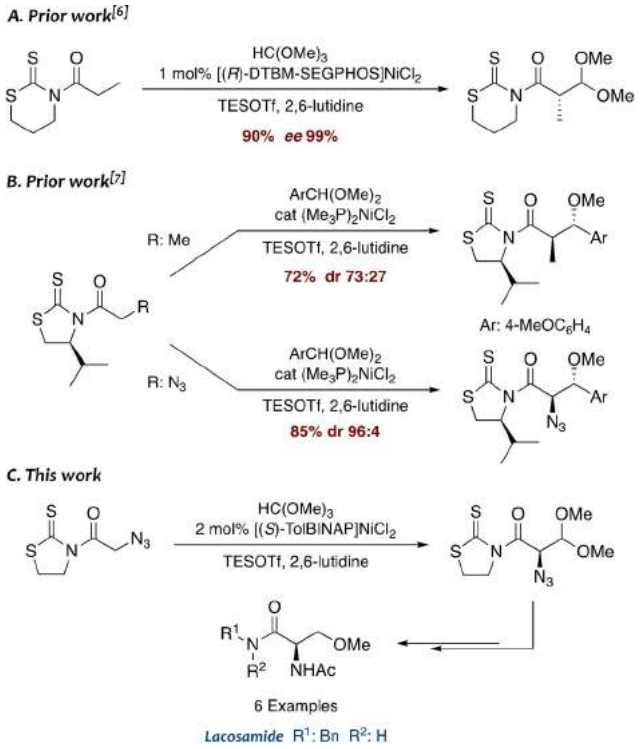


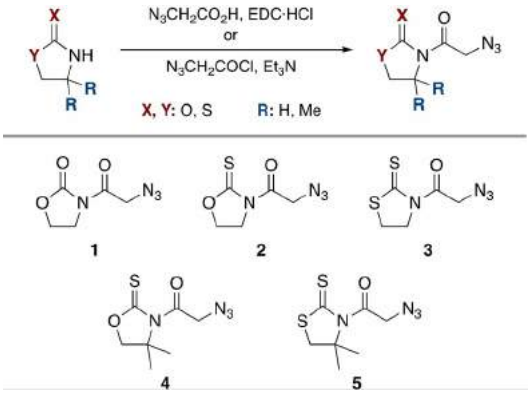
Scheme 1. Direct and stereoselective reactions from *N*-acyl thioimides catalyzed by nickel(II) complexes.

Results and Discussion

Direct and Ni^{II}-catalyzed addition of *N*-azidoacetyl thioimides to trimethyl orthoformate

Our experience from the carbon–carbon bond-forming reactions of *N*-propanoyl thioimides indicated that the 6-membered thiazinanethione was slightly more selective and active than the 5-membered thiazolidinethione counterpart.[6] Unfortunately, we were unable to synthesize the corresponding *N*-azidoacetyl-1,3-thiazinane-2-thione. The use of both azidoacetic acid and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as a coupling agent or azidoacetyl chloride and triethylamine at 0 °C under conditions previously described led to a complex mixture and no presence of the desired product. Conducting the reaction at −20 °C showed signs of product formation (the solution turned yellow as expected along with a new TLC spot) but when either warmed or quenched the solution turned black and the product could not be detected in the crude mixture. These results suggest that whilst the *N*-azidoacetyl thiazinanethione might be initially formed at −20 °C it is unstable at room temperature and therefore not viable.

For this reason, we decided to evaluate various 5-membered scaffolds. Five different heterocycles were chosen to assess the influence of the heteroatoms as well as geminal dimethyl groups in the direct addition to trimethyl orthoformate. Importantly, all candidates were acylated smoothly and the ensuing *N*-azidoacetyl derivatives **1**–**5** shown in Scheme 2 were completely stable and could be satisfactorily isolated in a pure form.

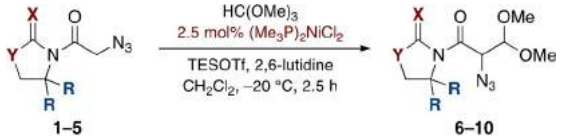


Scheme 2. Synthesis of *N*-azidoacetyl scaffolds.

Then, we evaluated the reactivity of **1**–**5** with trimethyl orthoformate and commercially available $(Me_3P)_2NiCl_2$. Taking advantage of our former experience, TESOTf was chosen to both activate the nickel(II) complex via ligand exchange and to create the required oxocarbenium electrophile from the trimethyl orthoformate.[14] Then, the addition of *N*-azidoacetyl derivatives **1**–**5** to trimethyl orthoformate in the presence of 2,6-lutidine and TESOTf was initially tested with 2.5 mol% of achiral $(Me_3P)_2NiCl_2$ for a relatively short reaction time of 2.5 h to better grasp the differences between the scaffolds. The results are summarized in Table 1.

As expected, oxazolidinone **1** gave low conversion in the nickel catalyzed reaction and the starting material was recovered unaltered (entry 1 in Table 1), which further confirmed the need for an exocyclic sulfur atom (X = S in Table 1). The endocyclic sulfur (Y = S in Table 1) also held a key importance as the isolated yield from thiazolidinethione **3** was considerably higher than that attained from oxazolidinethione **2** (compare entry 2 and 3 in Table 1). This concurred with previous results making the sulfur–sulfur combination (X, Y = S in Table 1) superior.[14] Eventually, it was thought that the introduction of geminal dimethyl groups at C4 in **4** and **5** might improve the stereochemical outcome of the addition, but the conversion observed for both compounds was too low to be deemed useful

Table 1. Direct and nickel(II) catalyzed addition of *N*-azidoacetyl derivatives to trimethyl orthoformate.



Entry	Starting material	X	Y	R	Product	Yield [%][a]
1	**1**	O	O	H	**6**	< 5
2	**2**	S	O	H	**7**	39
3	**3**	S	S	H	**8**	61
4	**4**	S	O	Me	**9**	< 10
5	**5**	S	S	Me	**10**	< 10

[a] Isolated yield.

(entry 4 and 5 in Table 1). Therefore, these results pointed to the *N*-azidoacetyl-1,3-thiazolidine-2-thione (**3**) as the most appropriate substrate to conduct the enantioselective trimethyl orthoformate reaction.

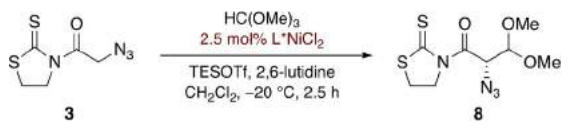
Direct, enantioselective, and Ni^{II}-catalyzed addition of *N*-azidoacetyl-1,3-thiazolidine-2-thione to trimethyl orthoformate

Having chosen the scaffold from which to carry out the desired addition, we next screened the chiral ligands necessary to achieve the highest enantioselectivity. The ligands tested were the traditional (4*S*,5*S*)-(+)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane (DIOP) as well as BINAP and SEGPHOS families. The required chiral complexes L*$NiCl_2$ were prepared via the simple reflux of the chiral diphosphine ligand and $NiCl_2$ in acetonitrile. These were compared to the achiral $(Me_3P)_2NiCl_2$ and both the enantioselectivity and efficiency were evaluated, which is summarized in Table 2.

Initially, DIOP gave almost no conversion and was therefore discarded (entry 2 in Table 2). The BINAP family performed much better in terms of activity and gave full conversion and good yields in all cases (entry 3–5 in Table 2). Importantly, the enantioselectivity was high, especially with Tol-BINAP, which gave an 80% yield (entry 4 in Table 2). Instead, the SEGPHOS family gave worse results with respect to conversion, yield, and selectivity (entry 6 and 7 in Table 2) and provided the desired adduct **8** in modest yields (52–61%) with a somewhat eroded stereocontrol (*ee* 88–94%). The conclusion of the ligand screening left Tol-BINAP as the most selective diphosphine and highest yielding and therefore [(*R*)-Tol-BINAP]$NiCl_2$ was selected as the complex of choice for this reaction.

We next analyzed the catalytic loading and temperature to complete the optimization of the reaction conditions. As shown in Table 3, the catalyst loading could be decreased to 2 mol% without adverse effects; further reduction showed incomplete conversion and a decrease in the yield of **8**. In turn, raising the temperature led to the formation of a side product resulting from the nucleophilic attack of the exocyclic sulfur atom of the thiazolidinethione heterocycle on the oxocarbenium species, which leads to an *S*-methyl alkylation product. Interestingly, we had previously observed a similar reaction when working with the *N*-propanoyl thiazinanethione scaffold (see Scheme 1),[6] the nucleophilic character of which was more pronounced and the reaction had to be conducted at −40 °C. Alongside this study, the (*S*)-C2 configuration of the resultant adduct **8** was initially established through chemical correlation.

Table 2. Influence of nickel(II) ligands on the addition of *N*-azidoacetyl thioimide **3** to trimethyl orthoformate.

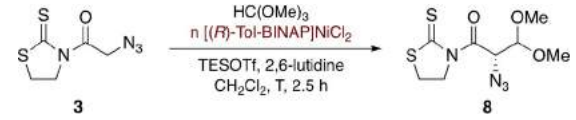


3 8

Entry	L*	Yield [%] [a]	*ee* [%] [b]
1	$(Me_3P)_2$	61	–
2	(+)-DIOP	<5	n.d.
3	(*R*)-BINAP	78[c]	94
4	(*R*)-Tol-BINAP	80[c]	96
5	(*R*)-Xyl-BINAP	72[c]	92
6	(*R*)-SEGPHOS	61[d]	88
7	(*R*)-DTBM-SEGPHOS	52[d]	94

[a] Isolated yield. [b] Established by chiral HPLC analysis. [c] Full conversion. [d] Incomplete conversion, ca. 85%. n.d. = not determined.

Table 3. Direct and enantioselective addition of thioimide **3** to trimethyl orthoformate catalyzed by [(*R*)-TolBINAP] $NiCl_2$.



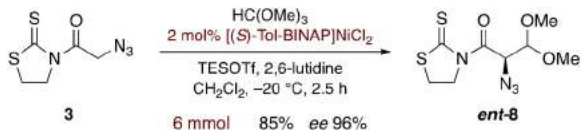
3 8

Entry	*n* [mol%]	*T* [°C]	Yield [%] [a]
1	3.0	−20	81
2	2.5	−20	80
3	2.0	−20	82
4	1.5	−20	69
5	2.0	0	59
6	2.5	20	53

[a] Isolated yield.

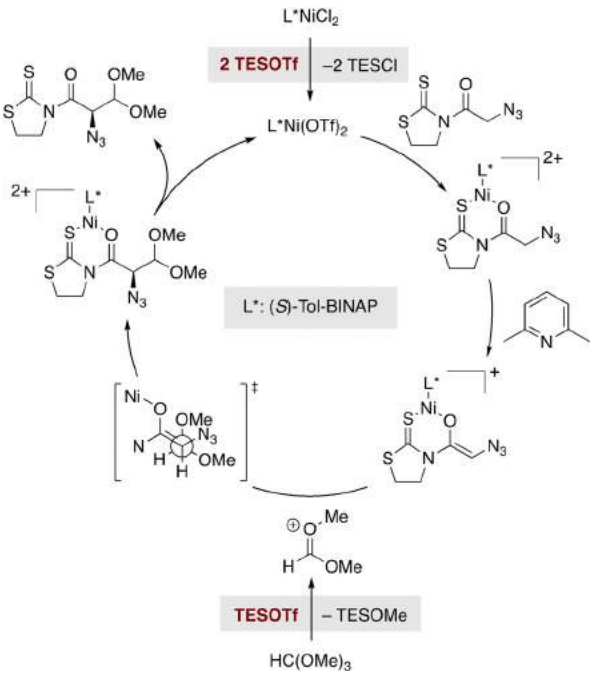
Once established the main framework of the reaction, we focused our attention to the synthesis of lacosamide (vide infra). Since exploratory studies indicated that the required configuration was the opposite to that provided by [(*R*)-Tol-BINAP]$NiCl_2$ we moved to use the (*S*) enantiomer. Then, we tackled the scale-up of the reaction and a comprehensive analysis of the experimental conditions. Importantly, the progressive increase of the reaction from 1, to 3, and up to 6 mmol of *N*-azidoacetyl thiazolidinethione **3** with trimethyl orthoformate in the presence of 2 mol% [(*S*)-Tol-BINAP]$NiCl_2$ showed that ***ent*-8** could be isolated with an 85% yield and 96% *ee* at 6 mmol scale by stirring the reaction mixture at −20 °C for 2.5 h (Scheme 3).[15]

Mechanistically, this reaction may be occurring via an S_N1-like pathway, in which TESOTf plays a key role.[16] Indeed, the silyl triflate activates the chiral nickel(II) complex, [(*S*)-Tol-BINAP]$NiCl_2$, to form the true catalytic species, [(*S*)-Tol-BINAP]-$Ni(OTf)_2$, shown in Scheme 4. Complexation with the thioimide in the presence of 2,6-lutidine triggers the formation of a nickel(II) *Z*-enolate, able to add to an oxocarbenium intermediate, $HC(OMe)_2^+$, generated in situ by the reaction of TESOTf with methyl orthoformate. The approach of such an electrophile to the *Re* face of the enolate leads to the formation of the carbon-carbon bond and the further release of the desired adduct allows for the regeneration of the active nickel(II) complex to start a new catalytic cycle.[17]



3

Scheme 3. Direct and enantioselective addition of *N*-azidoacetyl thioimide **3** to trimethyl orthoformate catalyzed by [(*S*)-Tol-BINAP]$NiCl_2$.



Scheme 4. Proposed mechanism for the reaction.

DFT calculations

Taking into account the mechanism described in Scheme 4, we carried out computational studies for an accurate understanding of the outstanding stereocontrol provided by the Tol-BINAP catalyst. Assuming that the reaction proceeds through the addition of a nickel(II) *Z*-enolate of [{(*R*)-Tol-BINAP}Ni(*N*-azidoacetyl-1,3-thiazolidine-2-thione]$^+$ (Figure 1) to an oxocarbenium intermediate from trimethyl orthoformate, a theoretical study was carried out. Importantly, NMR spectra of [(*R*)-Tol-BINAP]$NiCl_2$ were an undeniable proof for its diamagnetic character and molecular geometries for the *Z*-enolate have therefore been calculated in the singlet ground state. Several conformations have been optimized for *S*,*O*-chelate and thiazolidinethione rings with a nickel environment closer to square-planar coordination, resulting in a range of 8 kcal mol^{-1} for Gibbs free energies in solution. Taking the most stable one, it shows an important deviation for the planarity evaluated by continuous shape measures ($S_{SQ\text{-}4}=3.7$), and P-Ni-S and P-Ni-O angles are 159° and 160°, respectively, clearly influenced by the P-Ni-P bite angle of the diphosphine ligand (97°).

To understand the reaction between $HC(OMe)_2^+$ and [{(*R*)-Tol-BINAP}Ni(*N*-azidoacetyl-1,3-thiazolidine-2-thione)]$^+$, we have analyzed the corresponding energy profile. Since the electrophilic oxocarbenium can be approached by two π-faces of the nickel enolate (**I** and **II**), and it can also present three different relative orientations for the methoxy groups, six transi-

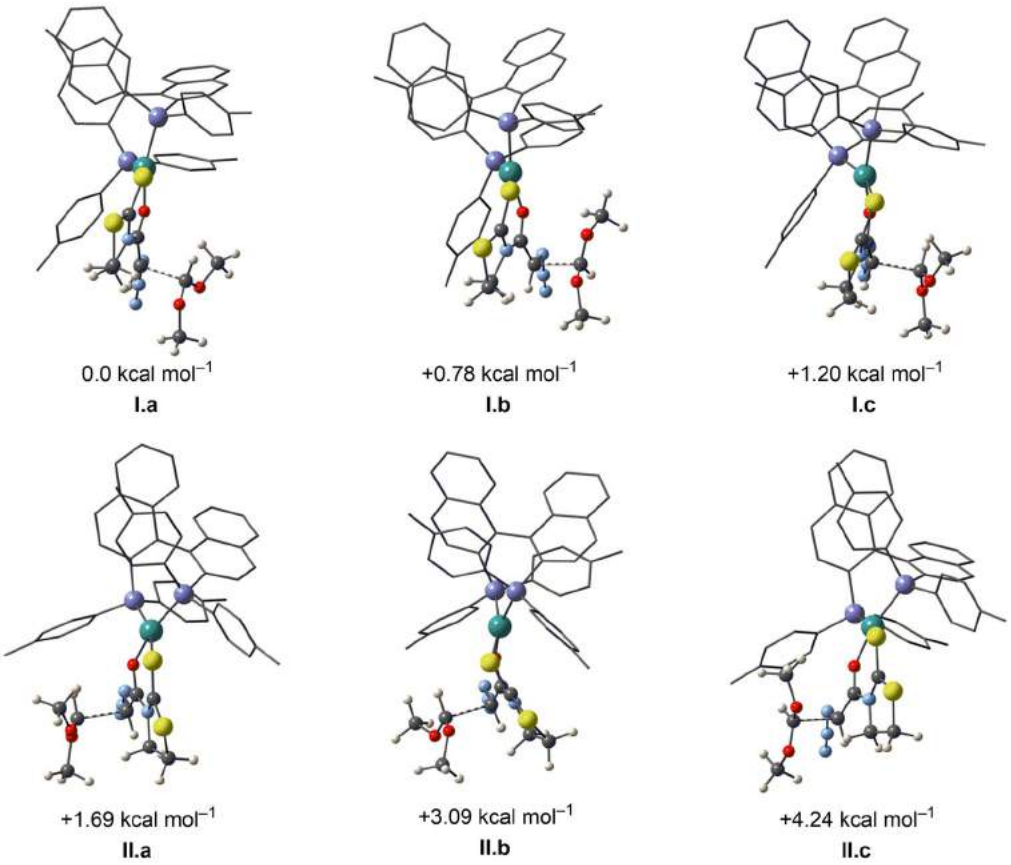


Figure 1. Addition of a *Z*-nickel(II) enolate to an oxocarbenium intermediate.

tion states were proposed and fully characterized. They are shown in Figure 1, together with the corresponding relative Gibbs free energies in dichloromethane solution. Several transition states present energies included within a range of less than 1 kcal mol^{-1}, and we could anticipate the reaction evolving by different pathways. In the three first transition states (**I.a**, **I.b**, and **I.c**), the electrophile is approached on the same side of the nickel(II) enolate from the *N*-azidoacetyl-1,3-thiazolidine-2-thione giving the same stereoisomer with different orientations for the methyl groups, but their small differences suggest that the three pathways all participate in the reaction (calculated values are about 74, 16, and 7%, respectively). However, the three transition states for the opposite side, and therefore the other enantiomer (**II.a**, **II.b**, and **II.c**), are higher in energy and their contributions clearly become smaller. According to the energetic distribution of the six transition states, estimation for the ratio of final products at −20 °C would be 97:3, in excellent agreement to experimental data (e.r. 98:2).

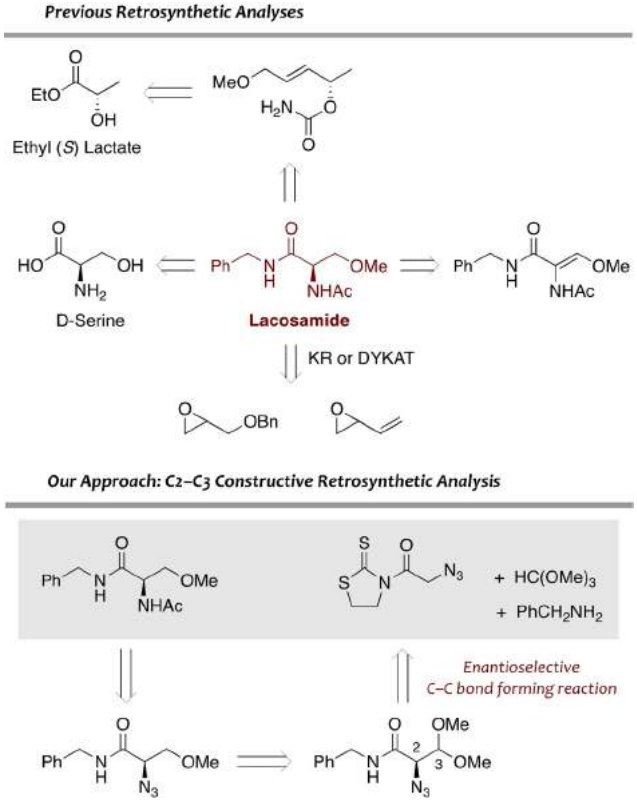
These results can be explained by the steric hindrance caused by the (*R*)-Tol-BINAP diphosphine. The optimized conformation of the nickel complex presents two π–π stacking interaction between *p*-tolyl and naphthyl aromatic rings (3.2–3.6 Å), whereas another *p*-tolyl substituent is aligned at ≈3.8 Å to the planar methine group of the nickel complex (see the Supporting Information). This situation is also reproduced for other conformations of the reactant blocking only one π-face for reaction pathway (< 3.5 kcal mol^{-1}). Consequently, those transition states in which the oxocarbenium is approaching from the external region become more stable than those from the internal one by geometric requirements (**I** and **II**, respectively). In the first cases, geometries for nickel remain closer to reactant, while the latter becomes the most planar environment. Thus, the excellent stereocontrol observed for such a reaction hinges on the position of one of the *p*-tolyl substituents blocking the *Re* π-face of the nickel(II) *Z*-enolate.

With a fully optimized procedure in hand and a complete understanding of the keys for the remarkable stereocontrol, the attention was then paid to the synthesis of lacosamide.

Lacosamide

Retrosynthetic analysis

The development of new enantioselective carbon–carbon bond forming reactions from *N*-azidoacetyl thioimides may offer a lucrative route towards biologically active α-amino acid derivatives. One of such compounds is the antiepileptic agent lacosamide (Scheme 5). First synthesized in 1996, lacosamide[12] and structurally related compounds show an important anticonvulsant activity[18] for which they have recently received much attention.[13] Despite such an interest, most of the synthetic approaches reported up to now rely on the appropriate treatment of D-serine or other starting materials from the chiral pool.[18,19] Alternatively, a few syntheses involve kinetic resolution steps[20] or are based on asymmetric reactions applied to substrates containing the required carbon backbone.[21] However, none of them hinge on the enantioselective construction of the C2-C3 bond. Hence, seeing the potential



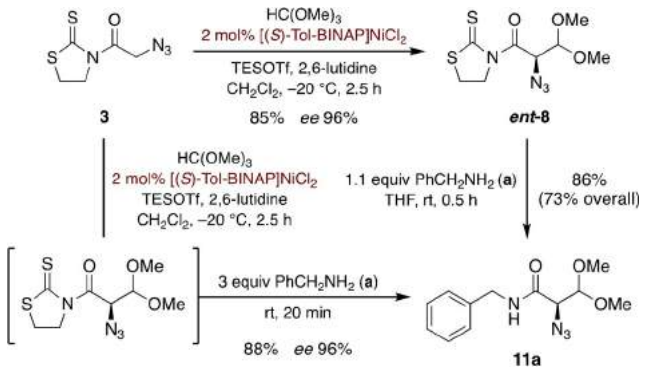
Scheme 5. Retrosynthetic analyses of lacosamide.

for an enantioselective synthesis with the utility of easily accessible derivatives without any methodological changes, we envisaged that the retrosynthetic analysis depicted in Scheme 5, based on our newly developed orthoformate reaction and the easy removal of the thiazolidinethione scaffold[22,23] might allow us to gain access to lacosamide and a wide array of structurally related compounds keeping the C3 methyl ether that is apparently essential to their antiepileptic activity.

Preliminary studies

With the asymmetric reaction fully optimized, we turned our attention to the removal of the 1,3-thiazolidine-2-thione moiety with an amine to form the amide group present in lacosamide and its derivatives. We started the assessment using benzylamine as a model, which would form the required *N*-benzyl amide for lacosamide, in two differing routes. One would involve the displacement of the scaffold from the purified product with benzylamine, while an advanced one-pot process would be based on the quenching of the carbon–carbon bond forming reaction with benzylamine to directly furnish the desired amide (Scheme 6).

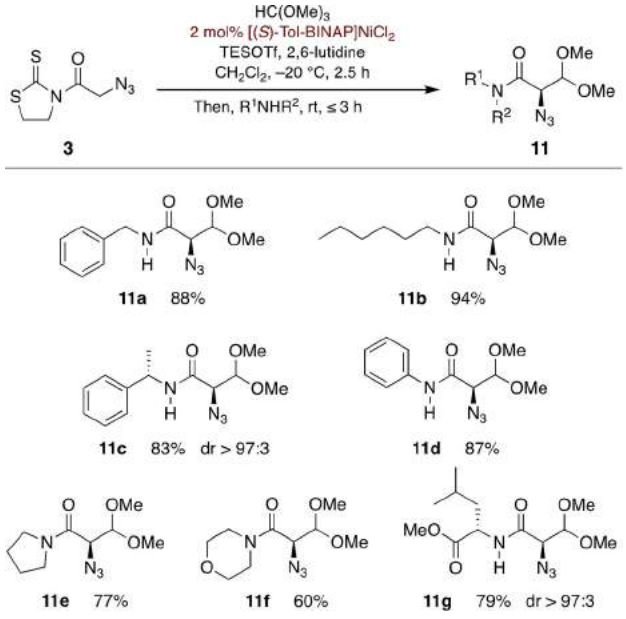
Both steps of the sequential approach proceeded smoothly (Scheme 6). Indeed, the desired *N*-benzylpropanamide **11 a** was isolated with a 73% overall yield using a stoichiometric amount of benzylamine (**a**). In turn, the one-step process needed an excess of amine and a careful monitoring by TLC to make sure that the starting *N*-azidoacetyl thiazolidinethione **3**



Scheme 6. First steps towards lacosamide.

had completely reacted before adding the amine. This is a key requirement. If full conversion is not achieved before the addition of the amine it can lead to the formation of the corresponding *N*-azidoacetyl amide, which is difficult to separate from the product. Taking into account such premises, the one-pot process allowed an increase in the yield over the sequential process and produced benzylamide **11 a** with an 88% overall yield and *ee* 96% at a 3 mmol scale (Scheme 6).

Six more amines (**b**–**g**) were then applied in this transformation and the results are summarized in Scheme 7. Different reaction times were required for each substrate; however, they only varied between 1 h and 3 h to reach full conversion. The methodology supported various primary amines, alkyl and aromatic variants both gave excellent results (**11 a**–**d**, **11 g**); furthermore, the use of chiral amines provided the corresponding amides as a single diastereomer (**11 c** and **11 g**). Secondary amines were also tolerated, with a slight decrease in the yield, and the pyrrolidine amide **11 e** as well as the morpholine amide **11 f** were both obtained with good yields. Furthermore, the displacement with a chiral amino ester derived from leucine afforded the diastereomerically pure peptidic product **11 g** with a remarkable 79% yield.



Scheme 7. Amide-like derivatives prepared by treatment of the reaction mixture with primary and secondary amines.

Importantly, X-ray analysis of crystals from amide **11 c** confirmed the configuration of the new Cα stereocenter (Figure 2).

The reduction of the dimethyl acetal to the corresponding methyl ether with $TiCl_4$ and Et_3SiH was the next step in the synthetic pathway towards lacosamide.[24,25] First, the reaction was examined using the benzylamide derivative **11 a** as a model. Low conversion was observed when using only 1.5 equivalents of both $TiCl_4$ and Et_3SiH (entry 1 in Table 4). Furthermore, it became clear that the reaction needed temperatures above 0 °C to function (compare entry 2–4 in Table 4). Therefore, the addition of 2.5 equivalents of $TiCl_4$ and Et_3SiH was tested via two routes. We found that the addition of an extra equivalent of both $TiCl_4$ and Et_3SiH after 4 h led to an increase in the conversion and yield (entry 5 in Table 4), while the initial use of 2.5 equivalents at the beginning of the reaction provided full conversion and a 57% yield (entry 6 in Table 4). Using these conditions, we were able to run this reaction on 9 mmol scale with a comparable yield (entry 7 in Table 4).

With the model compound optimized, we strove to expand the scope to the amides **11 b**–**g**. Unfortunately, the use of these reaction conditions on *N*-hexyl amide **11 b** led to incomplete conversion and the corresponding methyl ether **12 b** was

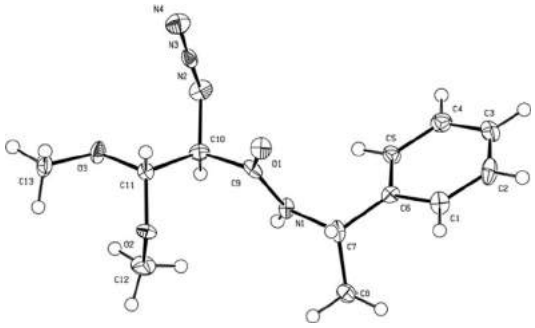
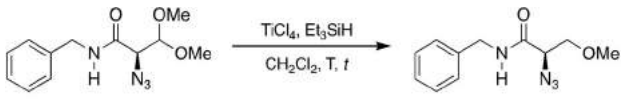


Figure 2. X-ray of amide **11 c**.

Table 4. Acetal reduction of *N*-benzyl amide **11 a**.



Entry	Equiv $TiCl_4$	Equiv Et_3SiH	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]
1	1.5	1.5	−20	6	<5	n.d.
2	2.0	2.0	−20	16	<5	n.d.
3	2.0	2.0	0	16	<5	n.d.
4	2.0	2.0	20	16	27	n.d.
5[c]	1.5+1	1.5+1	20	4+12	46	n.d.
6	2.5	2.5	20	16	57	96
7[d]	2.5	2.5	20	16	54	96

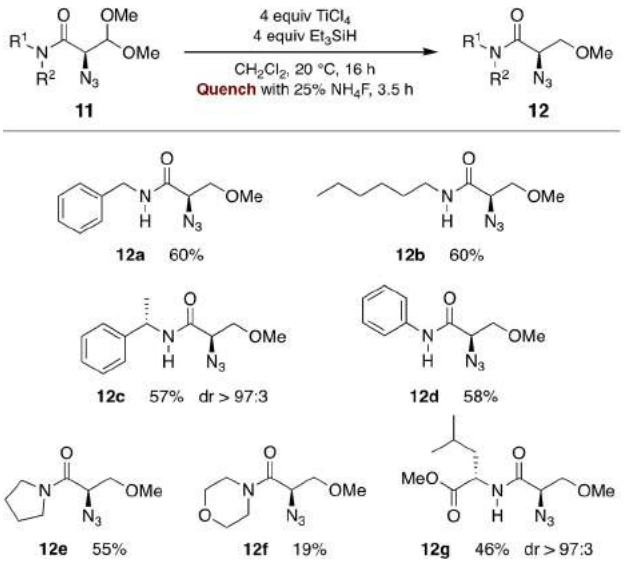
[a] Isolated yield. [b] Established by chiral HPLC analysis. [c] Initial loading of 1.5 equiv of $TiCl_4$ and Et_3SiH followed by 1 equiv of both reagents 4 h later. [d] Addition at 9 mmol scale. n.d. = not determined.

isolated in 42% yield. Thus, we conducted a finetuning of the optimization to achieve a more general protocol. The use of 4 equivalents of $TiCl_4$ and Et_3SiH led to full conversion, but with a yield lower than expected (entry 1 in Table 5). This made us suspect that some of the product was not being liberated in the workup, possibly due to the formation of titanium complexes, which led us to scrutinize the quench of the reaction mixture.[26] We found that the yield improved when the mixture was left stirring for 3.5 h after the quench (compare entry 1 and 2 in Table 5). Moreover, the use of NH_4F instead of NH_4Cl provided a 60% yield of product **12b** after 3.5 h (entry 4 in Table 5); no further improvement was observed at longer times (compare entry 4 and 5 in Table 5).

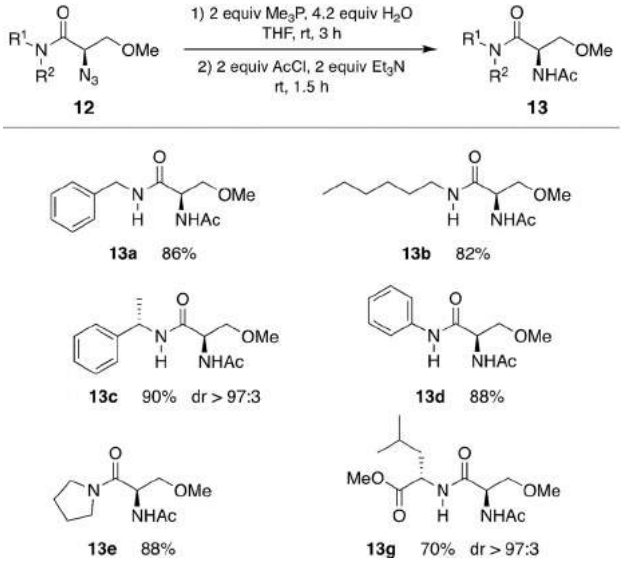
This advance combined with the use of four equivalents of $TiCl_4$ and Et_3SiH provided a general procedure for the reduction of the acetal that was applied to the remaining amides **11**. Unfortunately, the morpholine amide **11f** turned out to be unsuitable and gave a considerably lower yield of product **12f** that was inseparable from the starting material (Scheme 8). In turn, the peptide fragment **11g** provided the corresponding product **12g** with a slightly lower yield of 46%, which can be attributed to its higher complexity. Apart from these cases, the tolerance of the reaction to these conditions was high and the majority of the β-methoxy amides **12** were isolated with yields of around 60%, as shown in Scheme 8.

The final step in the synthesis of lacosamide and its derivatives involved the conversion of the azido group into an acetamide using a Staudinger reaction and subsequent in situ acylation (Scheme 9).[27] Such a transformation proved very reliable and lacosamide (**13a**) was isolated as planned with a yield of 86%. The application of such a one-pot reduction and protective sequence gave also excellent results when applied to other amides **12** and afforded the desired acetamido derivatives in 80–90% yields for all of the examples except **12g**. This decrease is unsurprising owing to the complexity of the molecule compared to the other examples and so a yield of 70% is very respectable. Again, the tolerance for the method was wide, with the primary, secondary, alkyl and aryl amides all giving excellent yields.

This completed the synthesis of lacosamide as summarized in Scheme 10. The final route consists of five reactions in a

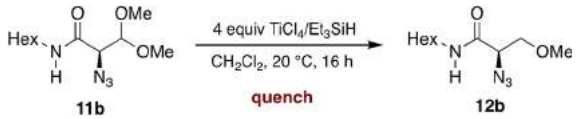


Scheme 8. Acetal reduction of amides **11**.



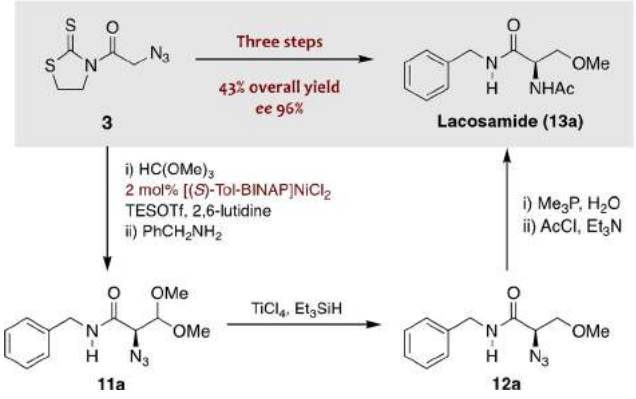
Scheme 9. Azide reduction and acylation of amides **12**.

Table 5. Work-up of the reaction.



Entry	Quenching reagent	t [h][a]	Yield of **12b** [%][b]
1	sat. NH_4Cl	0.15	42
2	sat. NH_4Cl	3.5	50
3	25% w/w NH_4F	0.5	47
4	25% w/w NH_4F	3.5	60
5	25% w/w NH_4F	7	57

[a] Stirring time after quench. [b] Isolated yield.



Scheme 10. Lacosamide synthesis.

three-step synthetic sequence with an overall yield of 43% and complete optical purity after recrystallization, making it a highly efficient process. Furthermore, due to the development of the adaptable methodology we were able to synthesize five other derivatives of lacosamide without any significant change in the reaction conditions. The number of derivatives able to be made by this method are considerably larger due to there being three points of divergence in the synthesis: the ortho ester addition, the amine displacement of the scaffold, and the protection of the Staudinger product. By changing either the ortho ester, amine, or acyl agent a new derivative can thus be synthesized with ease.

Conclusions

A direct, catalytic, and highly enantioselective addition of *N*-azidoacetyl-1,3-thiazolidine-2-thione to trimethyl orthoformate has been reported. Interestingly, the reaction proceeds through a nickel(II) enolate from Tol-BINAPNiCl_2 in which the α-azido group remains stable, which provides facile access to a variety of enantiomerically pure α-amino acid derivatives. Theoretical calculations have uncovered the origin of such an outstanding stereocontrol. Furthermore, the thiazolidinethione scaffold may be easily removed by a wide array of amines to give enantiomerically pure 2-azido-3,3-dimethoxyamides through a simple reaction in which the heterocycle acts as a coupling reagent. The synthetic potential of such an approach is demonstrated by converting the *N*-benzyl amide into the antiepileptic agent lacosamide based on a novel C2–C3 bond-forming reaction and the synthesis of several previously unsynthesized derivatives.

Experimental Section

General procedure for the Ni^{II} catalyzed reaction with trimethyl orthoformate and in situ scaffold removal

A solution of **3** (606 mg, 3.0 mmol) and [(*S*)-Tol-BINAP]NiCl_2 (48 mg, 0.06 mmol, 2 mol%) in CH_2Cl_2 (7.5 mL) under N_2 was cooled to −20 °C and trimethyl orthoformate (360 μL, 3.3 mmol), TESOTf (1.0 mL, 4.4 mmol), and 2,6-lutidine (520 μL, 4.5 mmol) were added dropwise after 1, 3, and 7 min, respectively. The reaction mixture was stirred at −20 °C and after 2.5 h, or complete conversion by TLC, warmed to 0 °C, and the corresponding amine (9.0 mmol, 3 equiv) was slowly added. The resultant mixture was stirred for 10 min at 0 °C and then at room temperature for 0.5–3 h. It was quenched with sat NH_4Cl (3 mL), diluted with H_2O (30 mL), and extracted with CH_2Cl_2 (3×30 mL), and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting brown oil was purified by column chromatography to afford pure amides **11a–g**.

X-ray crystallographic data

Deposition Number 1984006 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Computational methods

ONIOM calculations were carried out using the Gaussian 09 package.[28] High quantum layer is defined by nickel, phosphorous and the *N*-azidoacetyl-1,3-thiazolidine-2-thione together the electrophile in the reaction pathway, while low layer includes organic frameworks of diphosphane ligand (excluding phosphorous atoms) by treated by universal field force (UFF).[29] The hybrid density functional known as B3LYP was applied.[30] The all-electron basis sets having triple-ζ quality with an extra polarization function were used for all elements (TZVP).[31] The geometries were fully optimized without restrictions and transition states were confirmed by vibrational analysis. Solvent effects of dichloromethane were taken into account by PCM algorithm,[32] keeping the optimized geometry for the gas phase (single-point calculations).

Continuous shape measures were calculated with the SHAPE program,[33] that provides quantitative information of how much the environment is deviated from an ideal polyhedron.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · catalysis · C–C bond forming reactions · lacosamide · synthetic methods

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Conclusions

We have developed new enantioselective and direct carbon-carbon bond forming reactions from carbonyl compounds using a new class of achiral scaffold and a new chiral nickel(II) catalyst.[88] The new scaffold is a six-membered thiazinanethione, which performs better in terms of yield and selectivity than five-membered derivatives and differing combinations of heteroatoms. The novel catalyst is prepared *in-situ* from the corresponding nickel (II) chloride complexed with the bulky diphosphine ligand DTBM-SEGPHOS.[19]

The initial reaction we have developed is based on the alkylation of *N*-acyl thiazinanethiones with diarylmethyl ethers, which introduced selectively a diaryl group to the starting material through the formation of a carbenium ion in the reaction mixture. The optimising of the reaction conditions was performed with the simplest *N*-propionyl starting material and later applied to other acyl chains with wide success. The use of differing acyl chains required slightly longer reaction times and slight (in two cases large) increases in the catalyst loading but the enantioselectivity was consistently above 95% e.e. and the yield above 78% for all ten examples. Chain elongation, branching, differing degrees of unsaturation were all well tolerated with the exception of the isovaleryl chain containing the bulky α-isopropyl group required a larger catalyst loading to achieve both comparable yields and selectivity. Heteroatoms were also tolerated in the α-position with both oxygen and nitrogen derivatives being synthesised. The benzyl protected oxygen compound gave results similar to the other chains; however, the use a phenyl protected alcohol required a higher catalyst loading to attain a comparable yield, with the products of both oxygenated adducts giving α-hydroxy acid structures. Finally, the application to the azide chain to give an α-amino acid derivative was achieved; however, due to the degradation of the starting material the five-membered scaffold derivative was utilised to conduct the reaction.

The methodology was then applied to other electrophiles with great success. The orthoformate electrophile used by Evans was first examined.[3] With a change in the reaction temperature to supress a side product formed with the activated electrophile and the nucleophilic sulphur in the exocyclic position we achieved both a yield and selectivity comparable to that of Evans' analogue (90% with 99% e.e. vs 73% and 97% e.e from Evans). We next applied the reaction to a diarylmethyl ketal substrate; this furnished the corresponding adduct selectively, something which could have potential for further reactions due to its similarity to the original electrophile. Although the electrophile required more forcing conditions, the product was obtained with excellent selectivity and a good yield. The methodology was also applied to the tropylium salt we had previously used in our chiral auxiliary based approach (see Chapter 2).[9] With only a small increase in the catalyst loading we were able to achieve the enantiopure adduct with a good yield. Finally we examined the use of a dimethyl acetal substrate to create two new stereocentres.[8,10,11] We discovered the diastereoselectivity was highly dependent on the nature of the catalyst and with the DTBM-SEGPHOS catalyst we were able to achieve a 3:1 ratio towards the *syn*-product. While not as high as other methodologies based on chiral auxiliaries, we believe it was a good starting point for the investigation of asymmetric catalysis in the reaction with acetal-like electrophiles.

We applied the newly developed methodology to the synthesis of a small natural product: Peperomin D.[88] The starting material and electrophile were different to those used to test the scope of the reaction, the first being a terminal ester with a shorter chain and different ester groups in comparison to that previously used and the second a benzhydryl methyl ether, with a cyclic ether substituted aromatic ring structure. Once the initial alkylation adduct was obtained, the synthetic route consisted of a reductive removal of the scaffold, acid promoted cyclisation to form the lactone structure and substrate-controlled methylation to give Peperomin D. We were able to conduct the alkylation and

reduction in the same step through a quench with lithium borohydride; furthermore, the cyclisation step was eventually conducted on the crude mixture of the alkylation-reduction reaction. This allowed us to run four transformations in just three steps with only two column chromatography purifications. This innovative method allowed us to obtain Peperomin D in a 51% overall yield, considerably higher than the previously reported 27% by Sibi,[42] and higher than the best yield of 38% for any member of the Peperomin family.[44] Furthermore our methodology was open to the synthesis of other derivatives, both natural and synthetic, of the Peperomin family by simply changing the substitution of the diaryl compound; the methylation could also be swapped for a methylenation to obtain Peperomin E and similar derivatives.

We were able to scale up the two-step synthesis of the six-membered scaffold to a multigram scale (150 mmol starting amount) as well as the formation of the pre-catalyst. Finally, we have also scaled up the reaction with trimethyl orthoformate This is currently being checked in the laboratory by the journal *Organic Synthesis* for publication after passing the initial stages of publication in the journal.

With a broad methodology developed and an example of its synthetic use published we turned our sights on developing a highly derivable synthesis of another synthetic target, this time the epileptic drug Lacosamide.[96] The reaction we took advantage of was the addition of trimethyl orthoformate to the azidoacetyl starting material which gave an intermediate which could easily be transformed to the final product. After the initial stages were proven to work, Lacosamide and six derivatives have been synthesised by Saul Teloxa and Marc Camats, with the possibility of various more by varying the experimental procedure. The overall yield for Lacosamide was 43%, which while not the highest yield achieved so far stands out for the easy synthesis of various derivatives using the same methodology. For a retrosynthetic analysis, our approach is the only based on the stereocontrolled construction of the C2–C3 bond.

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Chapter 4: Direct and Enantioselective Aldol Reactions with Simultaneous Silyl Protection Catalysed by Chiral Nickel(II) Complexes.

Aldol Reactions

As discussed in the General Introduction, aldol reactions have long been studied as a comprehensive methodology for the asymmetric creation of β-hydroxy carbonyl structures.[1–10] In this context, it is easy to imagine that the main goal of stereoselective aldol reactions is to provide access to one of the four potential stereosiomers shown in Figure 32: a pair of enantiomers *syn* or *anti.*

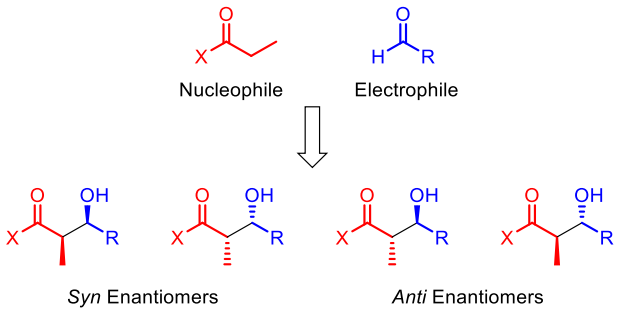
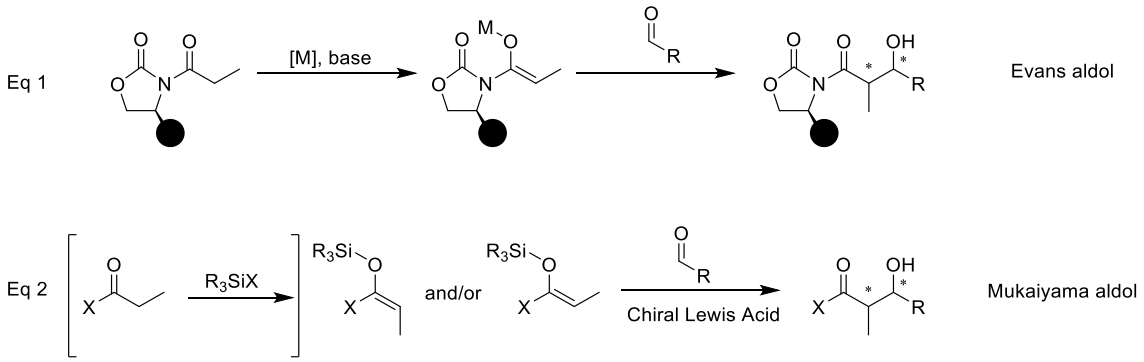


Figure 32: Four Possible Stereoisomers in the Aldol Reaction.

Initially the focus on the nucleophilic species for stereoselective aldol reactions was on either acylated chiral auxiliaries forming stoichiometric enolates championed by Evans (Eq 1 in Scheme 153), or silyl enol ether substrates first reorted by Mukaiyama (Eq 2 Scheme 153), in the presence of chiral Lewis acids to activate the aldehyde.[4–6,11,12] In the case of Evans, acylated chiral auxiliaries are transformed into the enolate by treatment with strong bases or Lewis acids in the presence of amines, which then reacts with the aldehyde. In turn, the Mukaiyama aldol reaction takes advantage of silyl enol ether compounds (pure or mixtures of *E/Z* isomers) which can be prepared *in-situ* or preformed and used directly; these species then react with the aldehyde, provided that it is properly activated by a chiral Lewis acid complex. More recently the attention has been focused on enantioselective aldol reactions with the stereocontrol deriving from a catalytic species; this can be in the form of an organocatalyst or a chiral metal-based Lewis acid.[13–17]

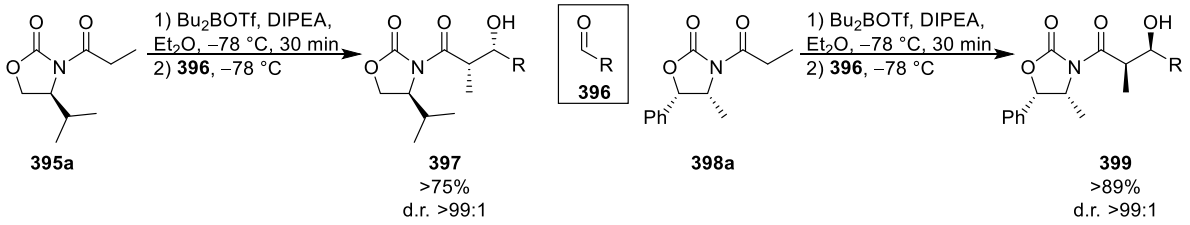


Scheme 153: Generic Representation of Evans and Mukaiyama Style Aldol Reactions.

With the creation of two new stereocentres, stereoselectivity is a key factor in the development of methodologies for aldol reactions. The selectivity towards the *syn* or *anti*-aldol products is determined mainly through the geometry of the enolate and the type of transition state involved in the bond-forming step. The preference of one enantiomer over others is achieved using a chiral source, either internal in the starting materials or external in the form of a catalyst or Lewis acid. A combination of controlling the enolate geometry, the transition state and a chiral source can be merged to obtain one of the four possible stereoisomers over the other three.

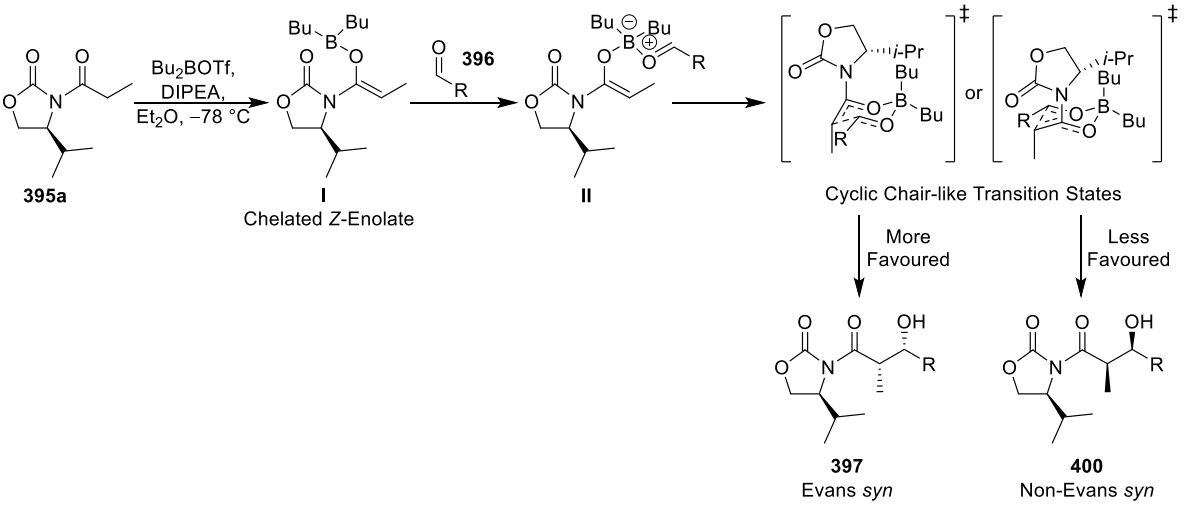
Evans Oxazolidinone Aldol Reactions

The use of Evans famous chiral oxazolidinone auxiliaries in the aldol reaction was arguably one of the largest advancements to date in the stereoselective aldol reaction. Depending on the auxiliary usedand taking advantage of the high ordered transition states provided by the resultant boron enolates, Evans was able to selectively form one *syn*-product over the other with a high selectivity.[18] The use of the acylated C4-isopropyl auxiliary **395a** led to the *syn*-product **397** in high to excellent yields with exceptional selectivity using three different aldehydes **396** (Left, Scheme 154). Using this methodology, the *syn*-isomers can selectively be formed by a simple change in the auxiliary used.



Scheme 154: Syn-*Selective Aldol Reactions from* N-*Acyl Oxazolidinone Auxiliaries.*

The mechanism for such a process is outlined below in Scheme 155. First the acylated auxiliary **395a** is treated with a boron triflate complex in the presence of an amine base, which promotes the formation of the chelated *Z*-enolate **I**. This is highly favoured over the corresponding *E*-enolate due to the large A(1,3) interactions, which are not present in the *Z*-enolate. Upon the addition of the aldehyde **396** an activated compound **II** is then formed; this contains a negative boron centre and a positive carbonyl bonded to it. This compound has two possible chair-like transition states available to it; the more favoured one leads to the Evans *syn*-aldol **397**, whereas the other that leads to the non-Evans *syn*-aldol **400** contains an unfavourable steric clash between the isopropyl group and the axial butyl group. Other transition states are theoretically possible to achieve the *anti*-isomers but are highly unfavoured and therefore normally inaccessible.

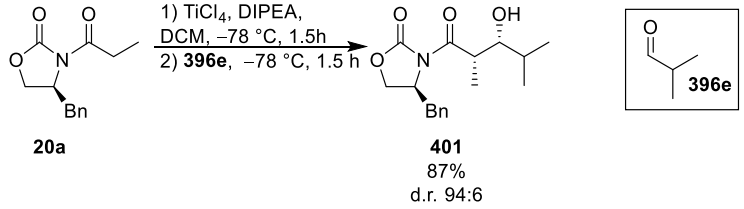


Scheme 155: Mechanism for the Evans Type Aldol Reaction.

One of the clear trends from the reactions described by Evans and others is the importance of the enolate geometry in selectivity in aldol reactions.[9,19–21] The exclusive formation of one geometry of enolate over the other is one of the first and most important steps in the selectivity of aldol reactions.[20–27] Here, the use of the cyclic chair-like transition state further homes in the selectivity with the restricted configuration leading to the favouring of one isomer over the other.[9,28] This, coupled

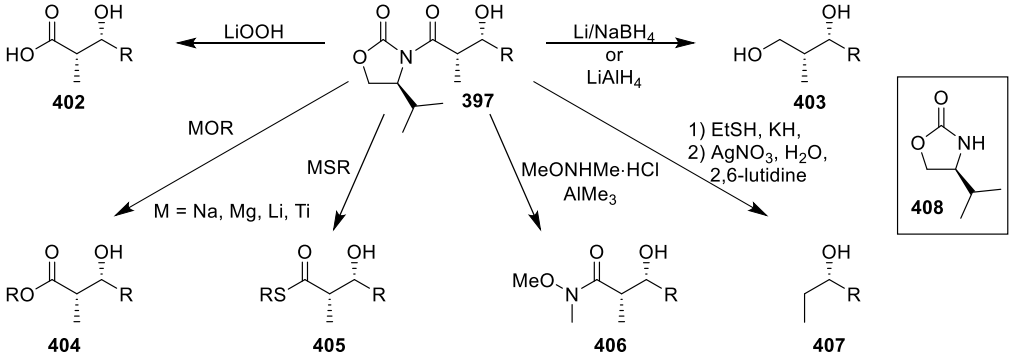
with the restricted geometry, leads to a clear selectivity based on the type of enolate used: *E*-enolates being selective to the *anti*-products and *Z*-enolates being selective towards the *syn*-products.[20]

In 1990 Evans reported a new methodology for the formation of metal enolates from *N*-acyl oxazolidinones using titanium chloride with amine bases to form the *Z*-enolate,[29] which was rapidly applied to stereoselective aldol chemistry of *N*-acyl oxazolidinones, other chiral ketones and also some achiral starting materials (Scheme 156).[30,31] The acylated chiral auxiliary **20a** led to the Evans *syn* product **401** in an excellent yield and selectivity, in line with the results from the boron enolates used previously.[18]



Scheme 156: Application of Titanium Chloride Enolates to the Stereoselective Aldol Reaction.

In addition to the outstanding stereocontrol provided by the Evans oxazolidinone chiral auxiliaries, one of their benefits is the ability to transform the resulting products into various synthons via the removal of the auxiliary under different conditions.[32] From the same starting material (**397** in this case) a variety of options are available. First, treatment with lithium hydroperoxide affords the carboxylic acid **402**. The alcohol **403** is then accessible by using reductive conditions with either a borohydride or aluminium hydride reagent. The ester **404** and thioester **405** are accessed by treatment with a metal alkoxide or thioalkoxide respectively. Transamination with methoxymethylamine hydrochloride provides the Weinreb amide **406** which can be further transformed to other functional groups. Finally, decarboxylation leads to the alkyl compound **407**. In all cases the auxiliary **408** is recovered and can be reused.



Scheme 157: Representative Removals of the Evans Oxazolidinone Auxiliary.

Unfortunately one drawback to these auxiliaries is the lack of direct access to certain functional groups, including aldehydes, β-ketoesters and simple amides. Also, the formation of the ester and thioester compounds require harsh reagents. Another undesired reaction can also take place in where the auxiliary rather than being removed opens through endocyclic cleavage.[33] These problems arise due to strength of the auxiliary's attachment to the molecule and thus alternatives were sought which should be easier to remove. Two alternatives were championed by Crimmins (oxazolidinethiones) and Nagao (thiazolidinethiones), which we able to conduct aldolic reactions and were easier to remove (Figure 33).[32,34–37]

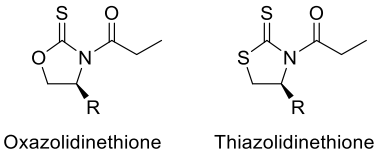
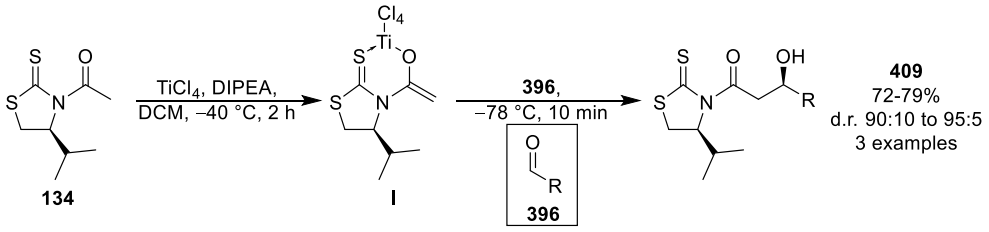


Figure 33: Oxazolidinethione and Thiazolidinethione Auxiliary Starting Materials.

Acetate Limitation

As explained in Chapter 1 acetate aldol reactions are a challenging prospect due to the large variety of transitions states possible. Unlike the mechanism shown above (Scheme 155) the geometry when using oxazolidine acetate auxiliaries can also be boat-like or twisted boat-like which decreases the energy barrier between the different products (see Chapter 1, Pages 69-70). Therefore, using oxazolidine auxiliaries is not an option and an alternative procedure is necessary.

In this context Urpí-Vilarrasa developed a highly stereoselective acetate aldol reaction using a chiral thiazolidinethione auxiliary.[38,39] Using the chiral *N*-acetyl thiazolidinethione **134** the titanium enolate **I** was first formed and then reacted with aldehydes to give the products **409** (Scheme 158).[38] As previously discussed in Chapter 1, the sulphur atoms in the starting material are essential for coordination in the transition state and forms a cage-like structure with the aldehyde which exerts the high stereocontrol. Other Lewis acids were also explored but gave worse results both with tin and boron.



Scheme 158: Urpí-Vilarrasa Acetate Aldol Reaction.

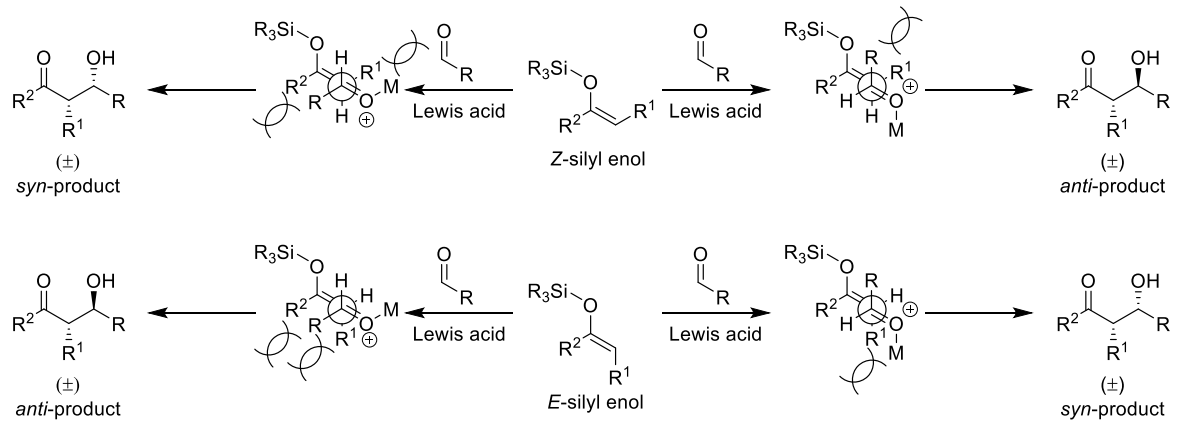
Whilst the use of chiral auxiliaries as a source of chirality in indirect aldol reactions is a highly researched field and extremely useful and applicable to total synthesis it has yet to provide a solution to achieve the *anti*-product.

Mukaiyama's Aldol Reactions

As mentioned previously, Mukaiyama aldol reactions involve the addition of silyl enol ethers or related species to activated aldehydes.[6] From the very beginning it became clear that chiral ligands on the metal activating the carbonyl bond might produce the corresponding aldol products in a highly stereocontrolled manner. Indeed, the use of sterically hindered ligands may, in principle, control the approach of the nucleophile to the carbonyl bond and thus determine the configuration of the β-stereocentre. Unfortunately, the configuration of the α-stereocentre hinges on subtle interactions shown in Scheme 159, which are usually responsible for low *syn*/*anti* diastereoselectivities.

At the beginning of the decade Noyori postulated an open transition state for the reaction mechanism which explained the diastereoselectivity of the Lewis acid mediated reaction of silyl enol species with acetal species.[40] This was then extended to the aldol reaction through the analogous reaction with aldehydes in place of acetals with later computational studies supporting the model (Scheme 159).[41–43]

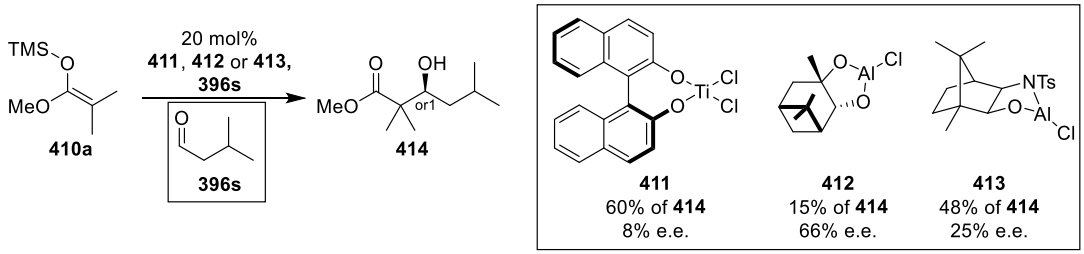
For each geometry of the silyl enol the aldehyde can approach in one of two ways which leads to two different transition states which produce either the *syn* or *anti*-aldol adduct (Scheme 159). The transition states contain different potential steric clashing interactions; depending on the nature of the different R-groups the importance of these interactions can change and favour one product over the other. For the *Z*-silyl enol starting material the transition state leading to the *syn*-product has two potential clashing interactions: one between the R^2 of the silyl enol and the R of the aldehyde, and another between the R^1 of the silyl enol and the Lewis acid of the aldehyde. The transition state leading to the *anti*-product contains one potential steric clashing interaction between the R of the aldehyde and the R^1 of the silyl enol. The corresponding *E*-silyl enol has similar interactions. For the *anti*-adduct there are two interactions between the R of the aldehyde with both the R^1 and R^2 of the silyl enol. For the *syn*-product there is one between the R^1 of the silyl enol and the Lewis acid of the aldehyde. The overall selectivity of the reaction therefore depends both on the geometry of the starting material and the nature of the R-groups and their steric interactions.



Scheme 159: Transition State Model for the Diastereoselectivity in the Aldol Reaction of Silyl Enols.

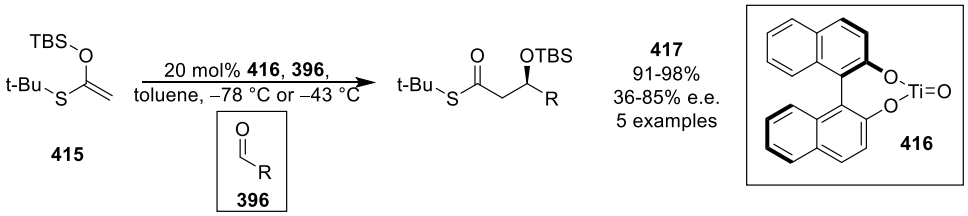
Chiral Lewis Acids

To address such a challenge, in 1986 Reetz developed an enantioselective Mukaiyama aldol reaction based on the use of chiral Lewis acids.[6,44] Using the silyl enol **410a** and a catalytic quantity of sterically hindered chiral Lewis acids, Reetz was able to effect a reaction with the aldehyde **396s** to form the aldol adduct **414** with varied results (Scheme 160).[6] The use of the titanium chloride Lewis acid **411** with a chiral BINOL ligand gave the highest yield of **414** but with almost no enantiocontrol. Pinanediol derived catalyst **412** considerably increased the selectivity but had a detrimental effect on the yield. Borneol based chiral Lewis acid **413** gave a midpoint with regard to yield and selectivity. While none of the examples gave high enough yields or selectivity to be useful it was a significant advance as it showed that chiral Lewis acids could be used in a catalytic manner to exert stereocontrol in Mukaiyama aldol reactions. This led to further research into the nature of the Lewis acid with the aim to increase the enantioselectivity of the reaction.



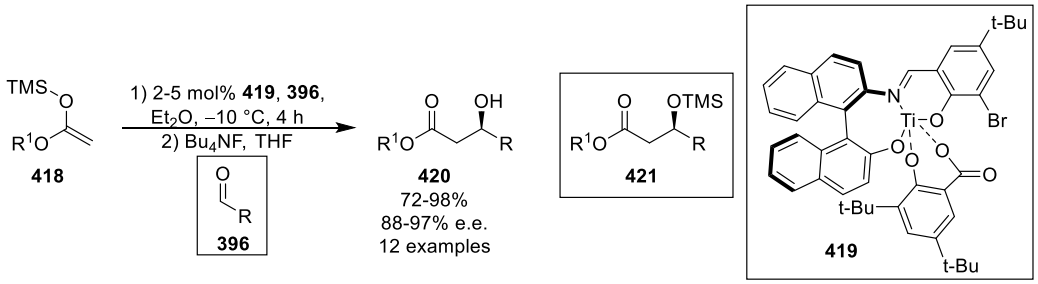
Scheme 160: Reetz's Initial Enantioselective Mukaiyama Reaction Using Chiral Lewis Acids.

Following these ideas, Mukaiyama reported highly enantioselective aldol reactions using a BINOL based titanium oxide catalyst **416**.[45] Using the silyl enol starting material **415** and catalyst **416** the products **417** were formed in exceptional yields with varied enantioselectivity (Scheme 161). Selectivities were around 60% e.e. with the exception of deactivated aldehydes.



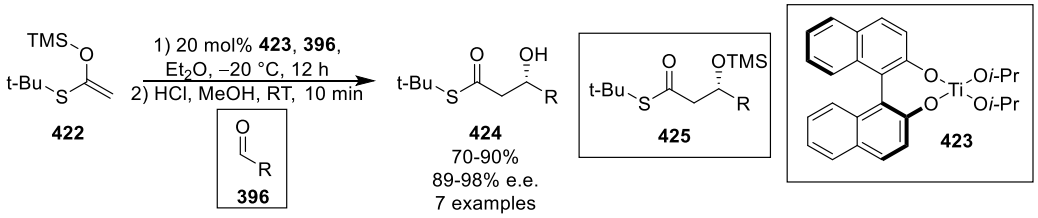
Scheme 161: Mukaiyama's Aldol Reaction Using a Chiral BINOL-Titanium Lewis Acid.

Carriera improved on this by the use of a tridentate ligand in the titanium Lewis acid.[46] Indeed, silyl enols **418** derived from acetates reacted with aldehydes in the presence of the catalyst **419** and directly desilyated to give aldol adducts **420** with high to exceptional yields and enantioselectivites (Scheme 162). The chiral tridentate ligand NOBIN is based on an imine derivative of BINOL and 3,5-di-*tert*-butylsalicylic acid. The initial product in the reaction is the silylated adduct **421** but was unable to be isolated in sufficient quantity.



Scheme 162: Carriera's Mukaiyama Aldol Reaction Using a Lewis Acid with a Chiral Tridentate Ligand.

Keck offered an alternative advancement upon Mukaiyama's initial titanium aldol reaction. His study used a different catalyst and conducted a thorough optimisation to increase the selectivity of the reaction.[47] The catalyst was prepared from BINOL and titanium (IV) isoproproxide and although the structure was unknown a suggestion was made in the form of **423** (Scheme 163), but the possibility of a different structure is conceivable due to the 2:1 ratio between the ligand and metal (using a 1:1 ratio to prepare the catalyst lowered the selectivity and yield). The final reaction conditions using the silyl enol **422** and various aldehydes gave the products **424** after a deprotection step. As with Carreria's methodology, the initial product formed was the silyated aldol adduct, in this case **425**, which due to the lability of the trimethylsilyl group the deprotection step was introduced. The deprotected aldol adducts **424** were obtained in good to excellent yields with good to exceptional enantioselectivity.

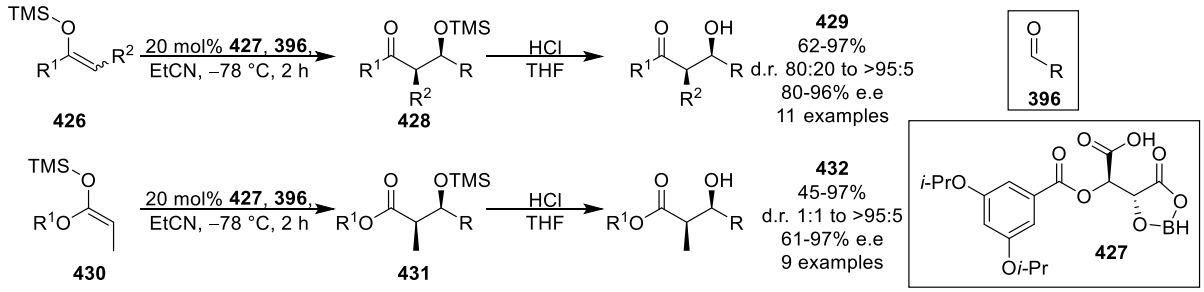


Scheme 163: Keck's Titanium Catalysed Mukaiyama Aldol Reaction.

Various chiral boron compounds have also been used to catalyse the Mukaiyama aldol reaction.[48–52]

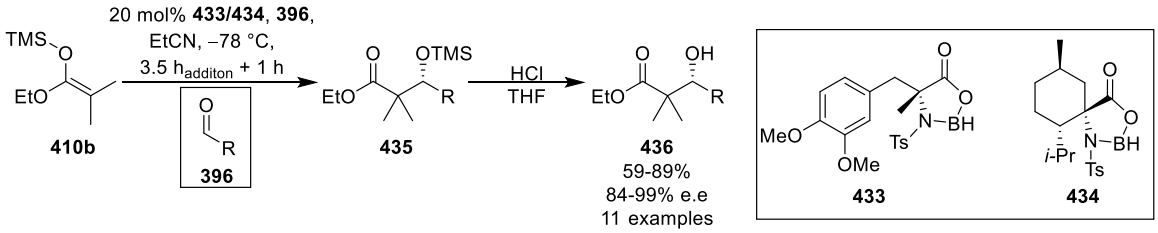
Yamamoto was one of the first to explore chiral boranes as catalysts for the asymmetric Mukaiyama aldol reaction.[51,52] He initially described a reaction of silyl enols **426** derived from ketones with various aldehydes in the presence of the chiral acyloxyborane **427** to install two new stereocentres (Top, Scheme 164).[52] This led to the initial silylated *syn*-aldol adducts **428** which were directly converted to the deprotected adducts **429** after the work-up. Regardless of the isomer of the starting material used the product favoured was still the *syn*-isomer and the selectivity similar in both cases.

He then applied the methodology to silyl enols **430** derived from ester compounds.[51] The products formed, both the initial adduct **431** and the desilylated product **432**, had the same *syn*-configuration as with the alkyl silyl enols. Ethyl or benzyl derived starting materials gave no diastereoselectivity and much lower enantioselectivity (61% and 68% respectively). The nature of the silyl ketene acetal was important therefore, but the aldehyde was also a major influence for selectivity; aromatic aldehydes performed better than aliphatic aldehydes and the best results were seen with α,β-unsaturated aldehydes.



Scheme 164: Chiral Borane Catalysed Mukaiyama Aldol Reaction.

Masamune described a similar procedure using the silyl enol **410b** from methyl isobutyrate.[50] The catalysts used (either **433** or **434**) contained ligands derived from amino acids and were coordinated to the boron through both the amine and carboxylate groups. The reaction again gave majorly the silylated products **435** but often with mixtures of the free aldol **436** so as before a uniform deprotection step was conducted (Scheme 165). The products **436** were obtained in moderate to excellent yields with high to exceptional enantiocontrol. The catalysts were generally interchangeable with **434** giving slightly higher selectivity and in one case a lower yield.

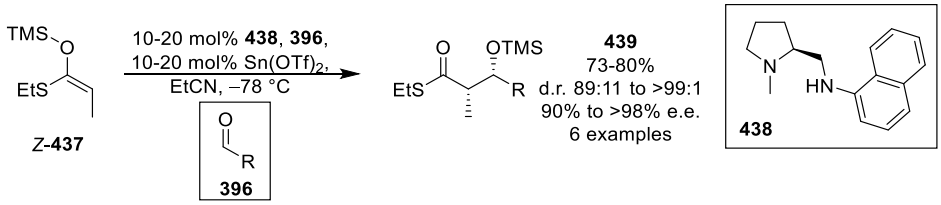


Scheme 165: Masamune's Asymmetric Mukaiyama Aldol of a Silyl Ketene Acetal.

Kiyooka described a similar procedure using a borane derived from valine for the addition of silyl ketene acetals to various aldehydes.[49] Corey used a tryptophan derived borane catalyst to also perform Mukaiyama aldol reactions from various silyl enol nucleophiles.[48]

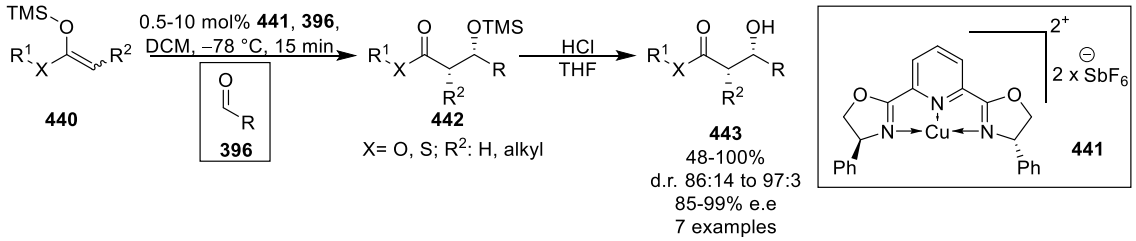
Mukaiyama also developed aldol reactions based on tin(II).[53,54] Starting from tin(II) triflate and a chiral diamine it was possible to produce chiral tin(II) complexes to properly activate the aldehyde. After a comprehensive optimisation of the reaction conditions it was found that the *Z*-**437** isomer of the thioester based silyl enol ether, reacting with 10-20 mol% of the chiral Lewis acid formed from the tin triflate and chiral diamine **438** was the best option (Scheme 166). The yield was high in all cases for

the *syn*-product **439** with selectivity towards the *syn*-aldol adduct ranging from excellent to exceptional with comparable enantioselectivity also. Unlike in the previous Mukaiyama reactions the final product was not the alcohol adduct but the silyl protected aldol adducts.



Scheme 166: Mukaiyama's Catalytic Enantioselective Aldol Reaction.

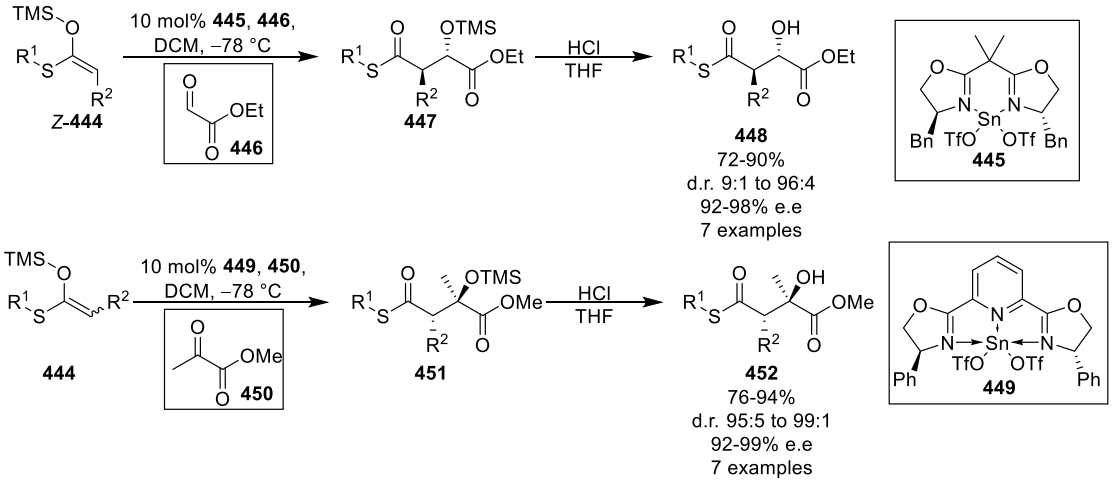
In turn, Evans described two procedures for the enantioselective Mukaiyama aldol reactions with chiral pincer compounds, initially with copper and later with tin(II) catalysts.[55,56] The first reaction of variety of silyl enol reagents **440**, derived from thioesters or ester compounds which when reacted with different aldehydes in the presence of the catalyst **441** gave the *syn*-products **443** after a desilyation of the initial *syn*-adducts **442** (Scheme 167). In the cases where R^2=H the corresponding enantiomer was formed in a purity of 92-99%, whereas when R^2≠H a selectivity towards the *syn*-isomer was observed in all cases with a diastereomeric ratio above 96:4 and enantioselectivity of 95% e.e..



Scheme 167: Evans' Mukaiyama Aldol Reaction Catalysed by a Chiral Copper Pincer Complex.

The methodology was expanded to glyoxylate esters using a bidentate chiral tin complex, and also to the use of ketone electrophiles when a the previous chiral pincer ligand was used.[56] For the reaction with the glyoxylate ester **446**, various thioester derived silyl enol substrates Z-**444** were used in the presence of the tin chiral catalyst **445** (Top, Scheme 168). The resulting aldol adducts **447**, were directly deprotected to give the free aldol adducts **448** in high to excellent yields. Interestingly the selectivity was towards the *anti*-aldol adducts **448** in excellent to exceptional diastereo- and enantioselectivity.

After an optimisation of the chiral ligand, to give chiral tin catalyst **449**, the reaction was expanded to use ketones as the electrophile and creating a quaternary chiral centre at the β-position (Bottom, Scheme 168). In this case the silyl enols **444** were reacted with the pyruvate ester **450** to give the *anti*-products **452**, after the deprotection of the initial adduct **451**. Interestingly using an analogous copper catalyst, the selectivity was completely reversed towards the *syn*-aldol adduct.

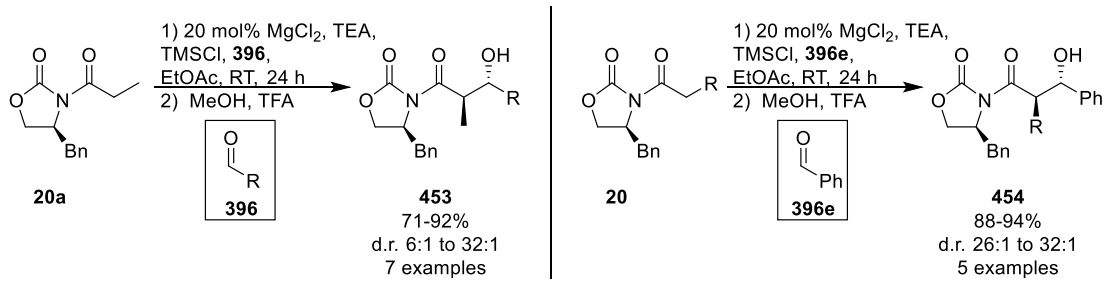


Scheme 168: Evans' Mukaiyama Aldol Reactions with Chiral Tin Catalysts.

Direct Aldol Reactions

As explained in the Introduction, the concept of direct reactions is a highly important one in organic chemistry. The ability to have all of the reagents present at the beginning of the reaction offers a mechanistic simplification which means the reactions are easy to conduct in the laboratory. If reagents are required to be activated then being able to do so in the same reaction flask offers a simple solution and one which, if the reagent is unstable, can offer improved yields and selectivities. Therefore applying this concept to aldol reactions, the starting material, aldehyde, metal complex, base, Lewis acid and any additives are placed in the flask at the same time. The source of chirality can be either from the starting material as a chiral auxiliary or other chiral element, but more commonly it is in the form of a chiral metal catalyst or pre-catalyst.

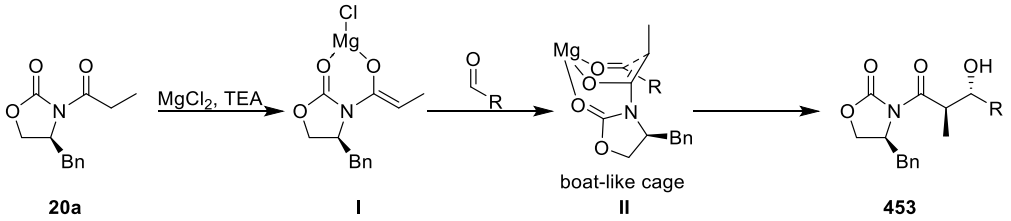
In the early 2000's Evans investigated the direct aldol reactions catalysed by structurally simple Lewis acids. The first advance he reported in this field was the use of catalytically generated magnesium enolates from chiral oxazolidinones.[57] The oxazolidinone **20a** reacted with aldehydes **396** in the presence of magnesium chloride and triethylamine to give the *anti*-aldol products **453** (Left, Scheme 169). The magnesium enolate was generated *in-situ* and reacted with the aldehyde in a direct-type reaction. The use of trimethylsilyl chloride protected the resulting aldol adduct which allowed the magnesium to dissociate from the product allowing the Lewis acid to be used in a sub-stoichiometric quantity; this protecting group was then removed in the work-up. The methodology was also expanded to various starting materials **200** using benzaldehyde (**396e**) to give aldol adducts **454** in excellent to exceptional yields and selectivities (Right, Scheme 169).



Scheme 169: Magnesium Catalysed Anti-*Aldol Reactions of* N-*Acyl Oxazolidinones. Left: Varying the Aldehyde; Right: Varying the Starting Material Side Chain.*

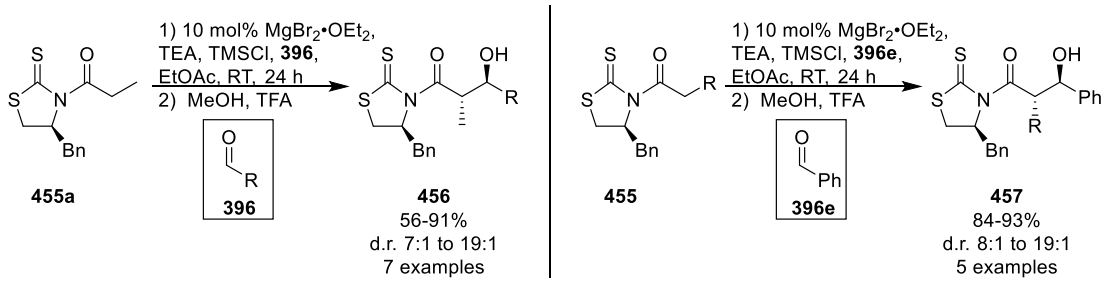
Interestingly the *anti*-selectivity is not due to an *E*-enolate as one might expect in light of the previous work, but originates from the use of a chelated *Z*-enolate (**I** in Scheme 170). In a later paper Evans

suggested the formation of boat-like transition states using magnesium *Z*-enolates to explain this difference in selectivty.[58] In this particular case a boat-like cage transition state **II** is formed due to the coordination of the magnesium to not only the aldehyde carbonyl but also that of the chiral auxiliary (Scheme 170). This gives the Evans *anti*-relative configuration of **20**.



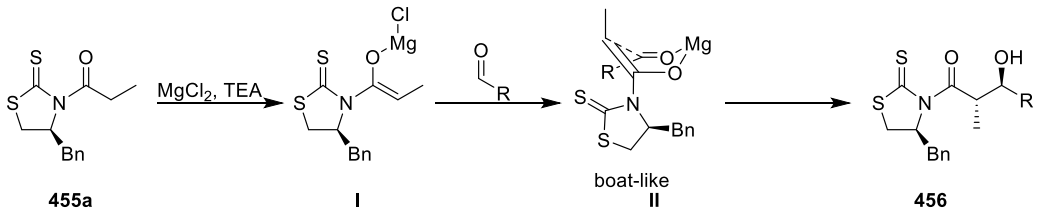
Scheme 170: Mechanistic Representation of the Magnesium Catalysed Aldol Reaction of Oxazolidinones Showing the Z-Enolate and Boat-like Cage Transition State.

This method was later expanded to the use of thiazolidinethione chiral auxiliaries which again gave *anti*-aldol products, but in this case non-Evans *anti.*[58] The analogous **455a** gave the *anti*-aldols **456** (Left, Scheme 171). Different starting materials **455** were then subjected to the reaction with benzaldehyde (**396e**) to give the *anti*-aldols **457** (Right, Scheme 171).



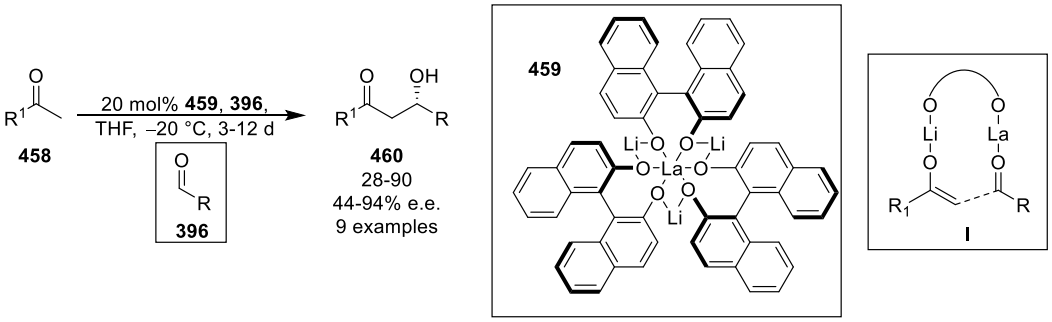
Scheme 171: Magnesium Catalysed Anti-Aldol Reactions of N-Acyl Thiazolidinethiones. Left: Varying the Aldehyde; Right: Varying the Starting Material Side Chain.

This selectivity can again be explained by a boat-like transition state involving a magnesium *Z*-enolate. In this case the thionyl group does not coordinate to the magnesium, forming the simpler enolate **I** (Scheme 172). This then forms a boat-like transition state **II** unlike with the oxazolidinone which formed a cage due to the extra coordination to magnesium. This allows the auxiliary to position itself to reduce steric interactions and places the C4-Bn group on the side of the enolate (instead of on the side of the methyl group as in Scheme 170). While the boat-like transition state still favours the *anti*-configuration for the aldol adduct, the positioning of the chiral auxiliary creates an *anti*-relationship with the methyl substituent. This therefore leads to the Evans *anti*-product **456** when using the chiral N-acyl thiazolidinethione **455**.



Scheme 172: Mechanistic Representation of the Magnesium Catalysed Aldol Reaction of Thiazolidinethiones Showing the Z-Enolate and Boat-like Transition State.

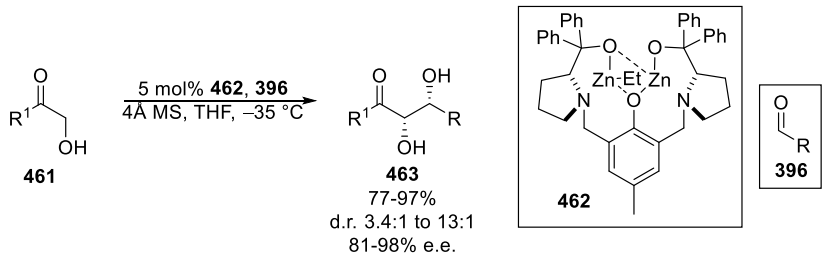
Alternatively, the origin of the stereocontrol may be placed on the Lewis acid. Shibasaki investigated in the late 90's the use of a chiral lanthanide based catalysts for methyl ketones aldol reactions.[59] The reaction of the alkyl or aryl ketones **458** with aldehydes in the presence of the lanthanum catalyst **459** produced the aldol adducts **460** in low to excellent yields and enantioselectivities (Scheme 173). The free lithium alkoxide acts as a Bronsted base and forms the enolate species and at the same time the lanthanum metal acts as a Lewis acid activating the aldehyde substrate as seen in the intermediate **I**. While in some cases the yield or selectivity was low, in general the results were good. A large excess of the ketone and long reaction times were necessary however to achieve reasonable yields.



Scheme 173: Enantioselective Aldol Reaction of Ketones Using a Chiral Lanthanum Catalyst.

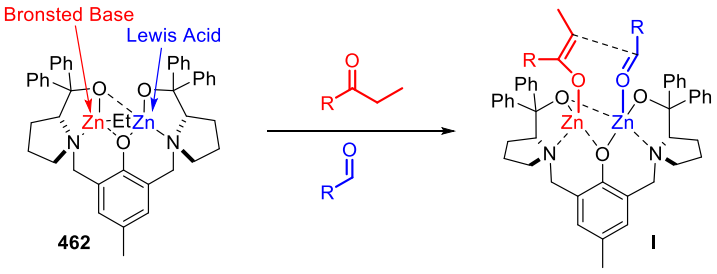
His research in this area also continued with various methodologies described with various catalysts based on different metals and ligands being used. Shibasaki published aldols catalysed by barium,[60,61] zinc,[62–64] calcium,[65] copper,[66–69] nickel,[70] and magnesium.[71]

Parallel studies by Trost in aldol reactions using a dinuclear based complex **462**, with two zinc atoms bridging three oxygens present in the Prophenol ligand also proved successful. As explained in the introduction, using this catalyst he was able to perform highly selective aldol reactions (Scheme 174).[72] This reaction has been studied expansively and is now applicable to a wide variety of substrates and electrophiles with various catalyst systems.[73]



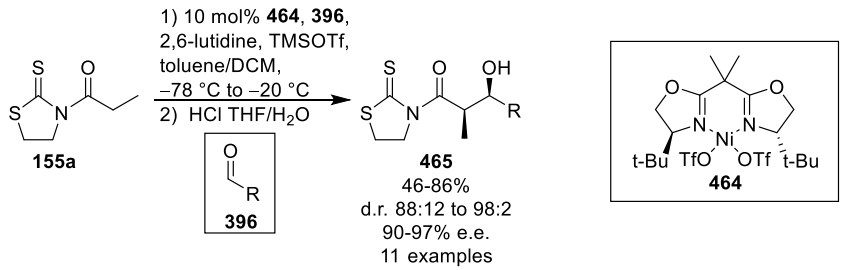
Scheme 174: Trost's Asymmetric Aldol Reaction Using a Dinuclear Zinc Catalyst.

In this reaction the zinc atoms act separately with one being a Bronsted base centre where the enolate is bound to and the other being a Lewis acid centre where the aldehyde is coordinated and activated (Scheme 175). This forces the enolate and aldehyde into close proximity with the orientation controlled by the chiral ligand, which is what accounts for the stereocontrol of the reaction.



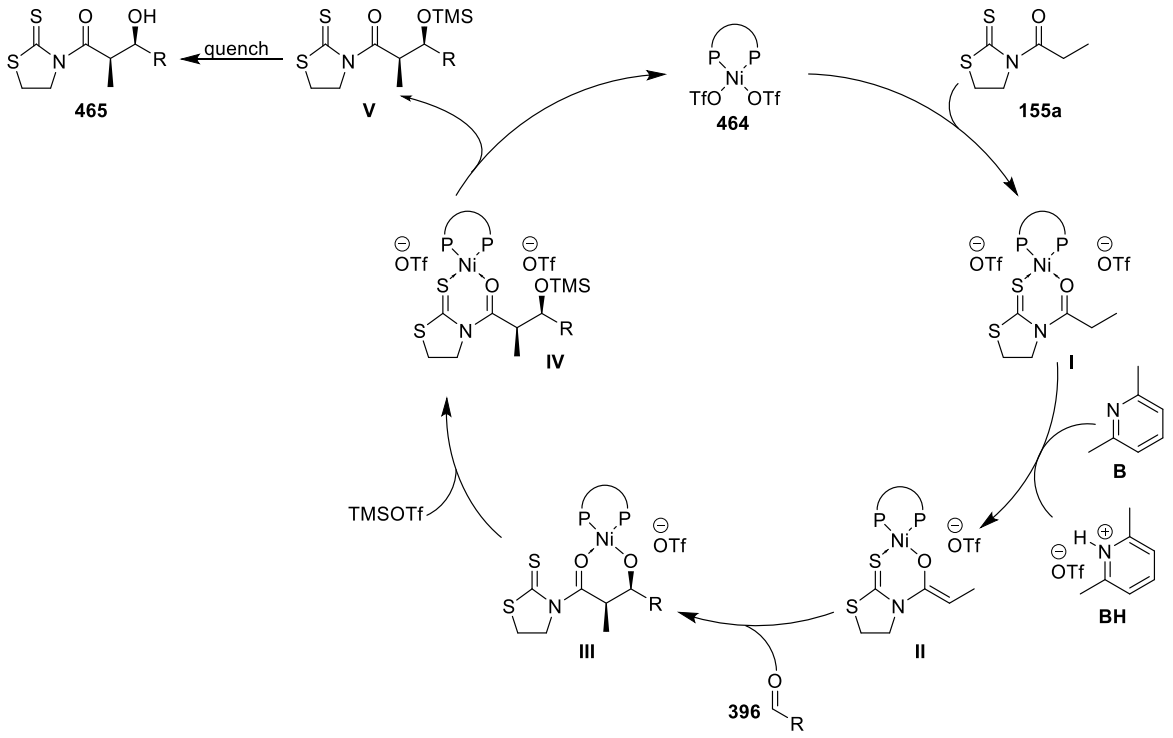
Scheme 175: Mechanism of Action of Trost's Dinuclear Catalyst.

After his success with chiral auxiliary based aldol reactions catalysed by magnesium salts, Evans then moved to the use of catalytically generated chiral enolates from achiral starting materials using a chiral metal catalyst.[74] In this context, the achiral, *N*-acyl thiazolidinethione **155a** was reacted in the presence of the chiral nickel(II) catalyst **464** to give the *syn*-aldol adducts **465** in yields ranging from low to excellent (Scheme 176). The stereoselectivity ranged from high to exceptional and the enantioselectivity was over 90% in all cases.



Scheme 176: Evans' Asymmetric Syn*-Selective Aldol Reaction using a Chiral Nickel(II) Catalyst.*

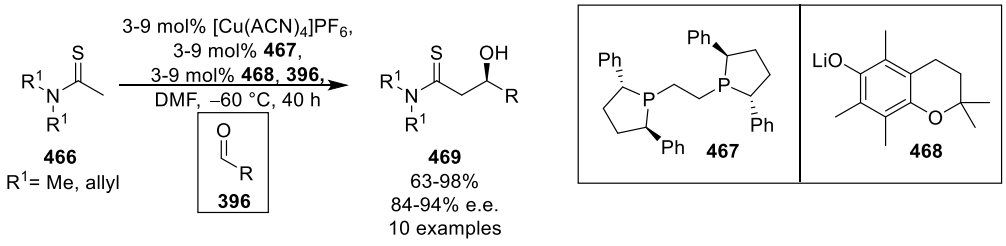
While not completely clear what role the trimethylsilyl triflate had in the reaction, Evans proposed it was most likely to liberate the catalyst in a silylation reaction similar to that shown to release the magnesium catalyst using a silyl chloride in his previous methodology.[57,58] The initial product was then similarly deprotected to release the free aldol adduct. Therefore, the proposed catalytic cycle is shown below in Scheme 177. First, the catalyst **464** interacts with **155a** to form the chelated adduct **I**. This is then deprotonated to give the *Z*-enolate **II**, which reacts with the aldehyde to give the *syn*-aldolate **III**, this is then silylated by trimethylsilyl triflate to give the coordinated protected aldol adduct **IV**. This then allows for the dissociation of the catalytic species **464** which re-enters the catalytic cycle and also frees the silyl aldol **V**. In the quench performed in acidic conditions the silyl protecting group is removed and the free aldol adduct **465** is obtained.



Scheme 177: Proposed Catalytic Cycle for the Asymmetric Syn*-Aldol Reaction.*

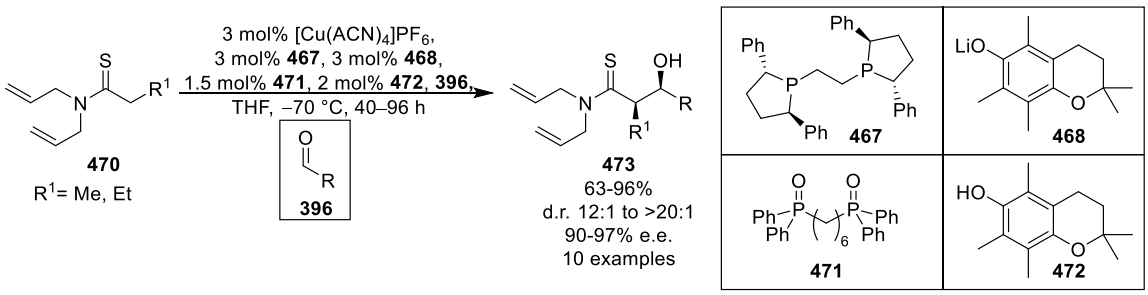
Although Evans does not draw a transition state for the formation of the aldol adduct, he does suggest it could be a cyclic chair-like transition state as the selectivity matches with the expected result of such a transition state.

Following this idea about scaffolds, Shibasaki explored the use of amides. First, he assessed the use of thioacetamides as starting materials for direct aldol reactions catalysed by a chiral copper catalyst to afford the aldol product **469** with generally excellent enantioselectivity.[75] Either the dimethyl or diallyl thioacetamide **466** reacted in the presence of a copper(I) salt, a chiral di-phosphine ligand **467** and a lithium base **468** to give the products **469** (Scheme 178). The thioamide scaffold allowed the formation of the copper enolate in remarkably mild conditions capable of undergoing highly selective, direct, catalytic aldol reactions.



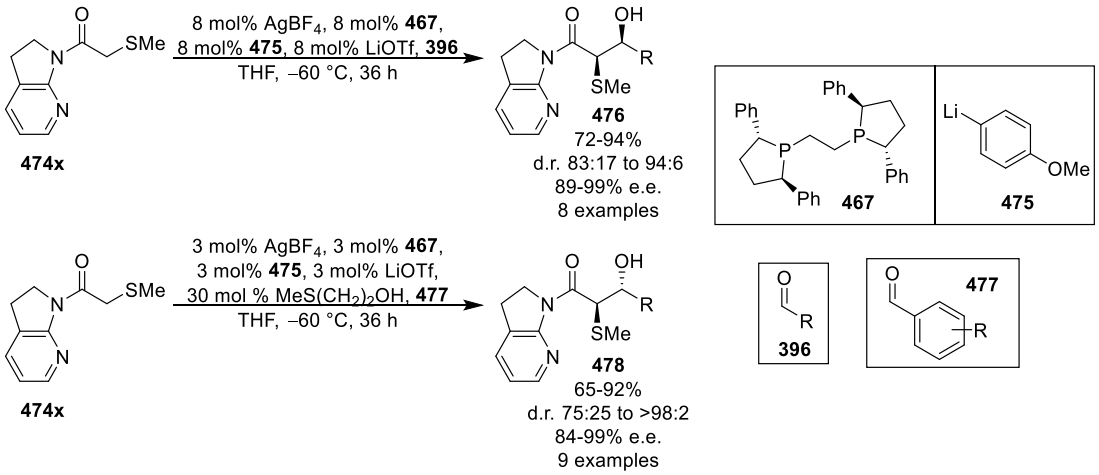
Scheme 178: Shibasaki's Aldol Reaction of Thioacetamides with a Chiral Copper (I) Catalyst.

This methodology was expanded to diallyl thioamides **470** (Scheme 179). These reactions gave the *syn*-aldol adducts **473** containing two new stereocentres with high diastereoselectivities and excellent enantiocontrol. The added complexity of containing a α-alkyl group required an additional phosphine oxide **471** as a hard Lewis base and the alcohol **472** as a proton source to achieve good yields.



Scheme 179: Syn-*Selective Aldol Reactions of Thioamides with a Chiral Copper(I) Catalyst.*

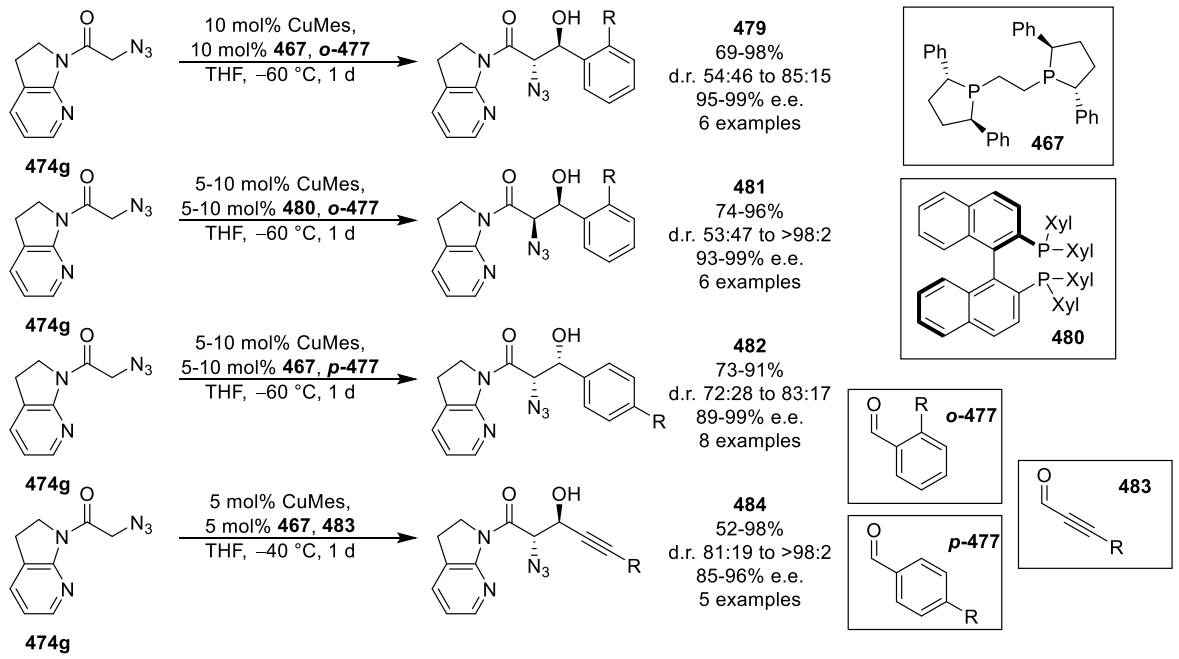
This research led Shibasaki to develop achiral scaffolds as platforms to conduct selective and catalytic aldol reactions. Combining parts from his last two methodologies, the chiral diphosphine **467** with silver catalysis and a α-sulphanyl substrate reported that the 7-azaindoline amides **474x** underwent highly stereoselective aldol reactions (Scheme 180).[76] Interestingly the selectivity of the product depended on the type of aldehyde used for the reaction; aliphatic aldehydes gave the *syn*-aldol adducts **476** (Top, Scheme 180), whereas aromatic aldehydes led to the *anti*-product **478** (Bottom, Scheme 180); the configuration of the α-stereocentre was the same in both cases. The yields were good to exceptional and the selectivity ranged from high to exceptional in both enantio- and diastereoselectivity.



Scheme 180: Shibasaki's First Use of an Achiral Scaffold in the Enantioselective Aldol Reaction.

Due to the curious reversal of the selectivity Shibasaki further investigated the aldol reaction of aromatic aldehydes and α-azido 7-azaindoline **474g** using copper catalysis.[77] Aldol reaction of **474g** with *ortho*-substituted aromatic aldehydes ***o*-477** in the presence of the chiral ligand **467** gave the *anti*-aldols products **479** with variable results (Top, Scheme 181). Aldehydes containing an electron withdrawing group performed the which indicates that the electronic character of the substituent R is crucial for the stereoselectivity.

These examples were repeated in the same conditions with a different chiral ligand (the xylyl-BINAP **480**) which gave the *syn*-aldol adducts **481** in comparable yields, in some cases with less catalyst (Centre Top, Scheme 181). These results show that the selectivity of the reaction using the same electron-withdrawing substituted *ortho*-aldehydes can be tuned towards a particular diastereoisomer by changing the ligand. Notably, the stereocentre which was affected by the change in ligand was the α-position. In both cases the enantioselectivity was above excellent.



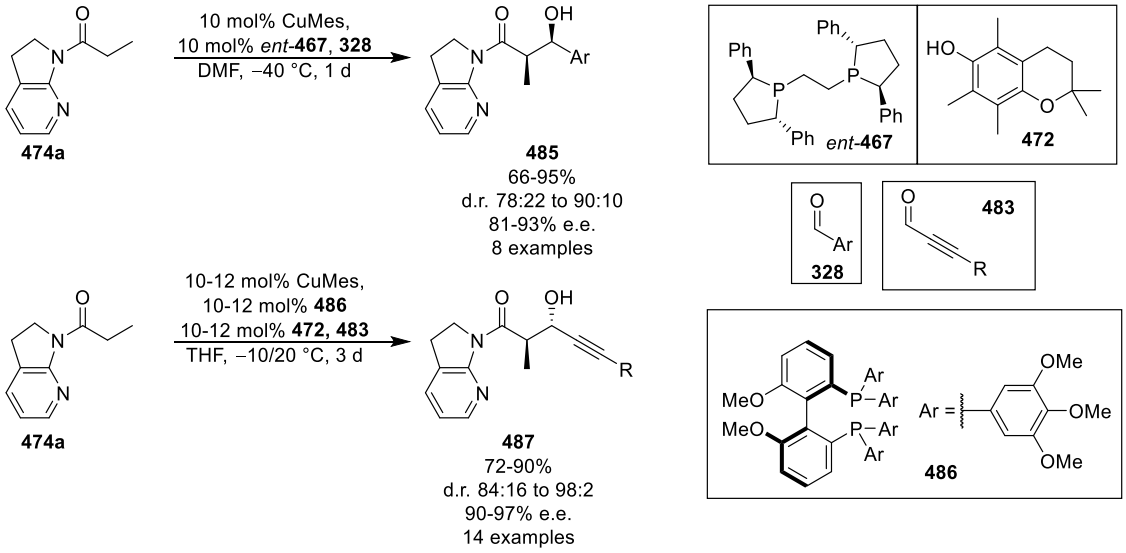
Scheme 181: Shibasaki's Aldol Reactions of α-Azido Substrates with Aromatic and Propargylic Aldehydes.

Using non *ortho*-substituted aldehydes, namely non-substituted or *para*-substituted aldehydes ***p*-477**, in the original conditions the results were again different (Centre Bottom, Scheme 181). In this case the *syn*-isomer **482** with an opposite Cβ stereocentre in respect to **481** was obtained in comparable yields. The selectivity ranged from good to high for the *syn*-isomer with the lowest enantioselectivity being 89% and five examples being over 95%. Benzaldehyde, 2-napthaldehyde and the heteroaromatic 3-thiophenecarboxaldehyde gave some of the lower diasteroselectivities (72:28 to 78:22) but with exceptional enantioselectivity (98-99%). The remaining results were obtained with *para*-substituted aldehydes generally with electron-withdrawing groups; however, one example with an electron-donating group (methyl) and with fluoride which gave similar results suggests that in the *para*-position the nature of the substituent was not as important as in the *ortho*-position.

Finally, the reaction was also conducted with propargylic aldehydes **483** (Bottom, Scheme 181). The reaction conditions were almost identical to those of the initial reaction with a slight increase in the temperature. The selectivity was high to exceptional towards the *anti*-product **484** with enantioselectivity averaging 90%. The substituent of the alkyne was of minimal importance for the selectivity, but aliphatic substituted alkynes did give a lower yield, with the other products being isolated in higher than 90% yields.

This work highlights both the difficulty found in aldol reactions with regards to the selectivity, especially with uniformity in the reaction, and also the potential to tune the aldol reaction towards one product through the manipulation of various factors, mainly the catalyst.

The methodology was then expanded to *N*-propanoyl **474a** using both aromatic and propargylic aldehydes.[78] The reaction of **474a** with aromatic aldehydes **328,** without *ortho*-substituents, in the presence of the chiral ligand *ent*-**467** led to the *syn*-aldol adduct **485** in high to exceptional yields (Top, Scheme 182). The selectivity towards the *syn*-isomer ranged from good to excellent with some of the lowest values being obtained with heteroaromatic aldehydes. Both electron-donating and electron-withdrawing substituents were tolerated with similar results. The product corresponds with the isomer expected when using the enantiomer of the ligand **467** used in the previous study (see Bottom Centre, Scheme 181).

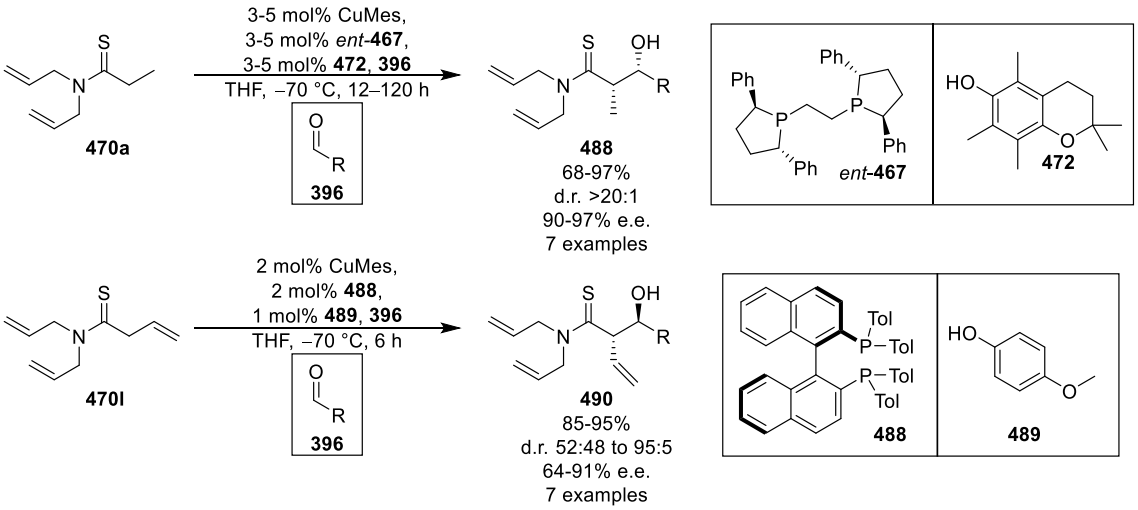


Scheme 182: Aldol Reaction N*-Propanoyl 7-Azaindoline with Aromatic and Propargylic Aldehydes.*

In this case propargylic aldehydes **483** required both an augmentation of the temperature, the addition of the additive **472** as a proton source and the use of the ligand **486** to achieve comparable results (Bottom, Scheme 182). The diastereoselectivity ranged from high to exceptional towards the *anti*-product **487** with excellent to exceptional enantioselectivity depending on the R substituent (Scheme 182). Alkyl (R= hexyl) substituted aldehyde gave considerably lower selectivity (d.r. 62:38), whereas the highest selectivity was seen when using a silyl terminal group. With the absence of an additional coordinating group the postulation of the interaction of the substrate was headed towards the coordination of the carbonyl and the nitrogen of the scaffold to the metal, suggesting that the previous methodologies may have also favoured this coordination.

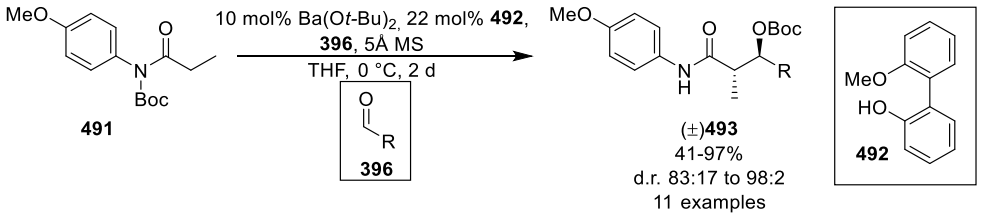
The investigation into the reaction without an achiral scaffold was also recently conducted using diallyl amide substrates.[79] The diallyl starting materials **470** are reminiscent of some of Shibasaki's earlier work in direct, asymmetric, catalysed aldol reactions (see Scheme 178, Scheme 179, Page 229).[75,80] Using **470a**, copper mesylate, the chiral ligand *ent*-**467** and the phenol **472** as a proton source the *syn*-product **546** was formed in good to exceptional yields (Top, Scheme 183). The selectivity was absolute for the *syn*-isomer with no trace of the *anti*-analogue being found and the enantioselectivity ranged from excellent to exceptional. This represents a substantial simplification compared to Shibasaki's original work and improves on the results (see Scheme 179).[80]

When a starting material containing a terminal double bond in the acyl chain (**470l**) and a different ligand (**488**) was used the selectivity of the reaction was reversed and the *anti*-product **490** was favoured (Bottom, Scheme 183). Whilst the yields were excellent, the selectivity was moderate with all but one example being lower than 73:27. When the diphosphine *ent*-**467** was used the selectivity was again switched to the *syn*-aldol adduct. Although the results are not as promising, they do show again the high dependence of selectivity on the chiral ligand when an open transition state is present in the mechanism.



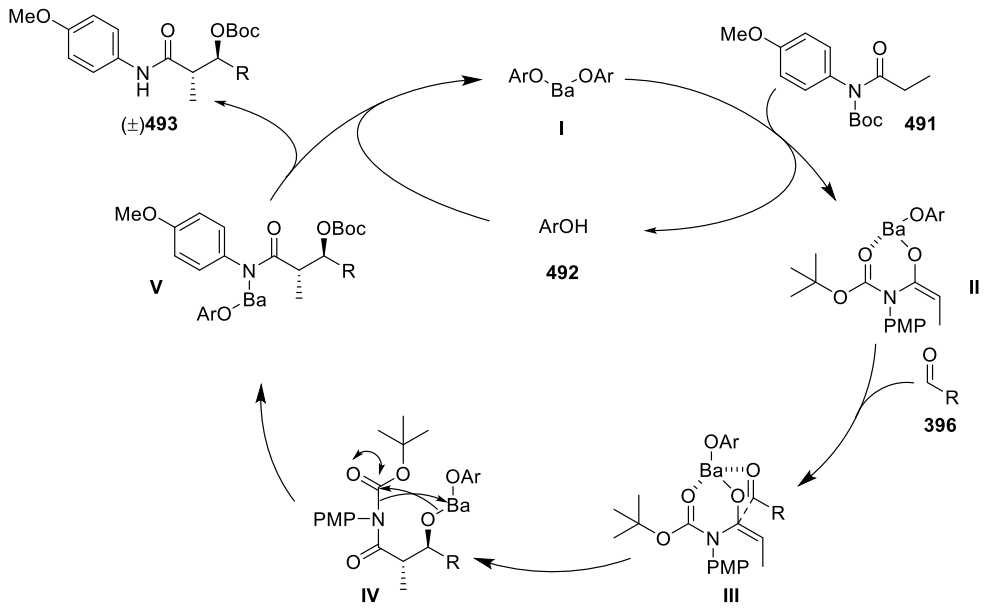
Scheme 183: Shibasaki's Aldol Reaction of Diallyl Amide Substrates.

Kobayashi developed a diastereoselective *anti* aldol reaction from *N*-aryl-*N*-Boc amide **491** catalysed by an achiral barium alkoxide (Scheme 184).[81] Using a barium catalyst with the phenol **492** and Boc/PMP protected *N*-acyl amide **491** the Boc protected *anti*-aldol adducts (±)**493** were obtained with low to exceptional yields and good to exceptional selectivity (Scheme 184). Due to the non-chiral ligand used, the mixtures were racemic. Removing the only alkyl aldehyde used (hexanal) the yields were all above 71% suggesting the aromatic or α,β-unsaturated aldehydes, which composed the rest of the scope, were better suited to the reaction. The lowest selectivity was seen when using cinnamaldehyde while the rest gave over 90:10 selectivity towards the *anti*-product.



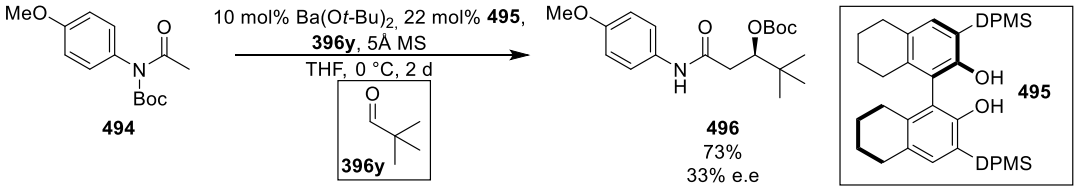
Scheme 184: Racemic Anti-*Selective Aldol Reaction of* N-*Acyl Amides Catalysed by a Barium Complex.*

The catalytic cycle for the reaction is shown in Scheme 185. First the barium catalyst **I** interacts with the amide **491** to form the barium enolate **II**, releasing a molecule of phenol **492**. The enolate then coordinates to the aldehyde **396** to give the complex **III**. This then forms the initial adduct **IV** which spontaneously transforms to the adduct **V** through intramolecular Boc transfer (exchanging with the barium complex). This then interacts with the previously formed phenol to release the product (±)**493** and regenerate the catalytic species.



Scheme 185: Catalytic Cycle of the Barium Catalysed Aldol Reaction.

Once the methodology was established an asymmetric version was also attempted which took advantage of the chiral ligand **495**. Acetamide **494** reacted in the presence of a BINOL-like chiral catalyst with pivaldehyde **396y** to afford the product **496** in a high yield but with a very low enantioselectivity (Scheme 186). Although the enantioselectivity was considerably lower than to be useful it shows again that the asymmetric direct aldol reaction of amide-type substrates is possible



Scheme 186: Enantioselective Acetate Aldol Catalysed by Barium.

Although the enantioselectivity was considerably lower than to be useful it shows again that the asymmetric direct aldol reaction of amide-type substrates is possible.

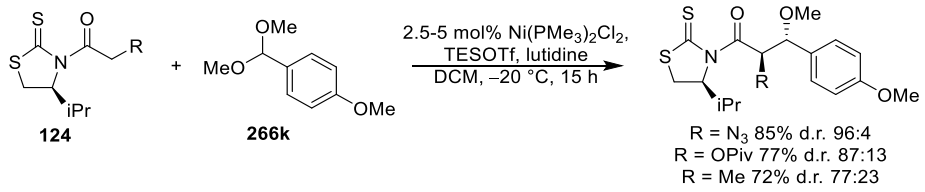
Development of Our Aldol Methodology with Incorporated Silyl Protection

Direct Aldol Reactions in Our Group

While our experience with titanium mediated aldol reactions where the selectivity is determined by the chirality of the starting material is vast, [38,39,82–84] our experience with direct asymmetric catalysed aldol reactions was minimal. However, it was a field we were keen to explore using our chiral nickel-based catalysis developed during this PhD thesis.

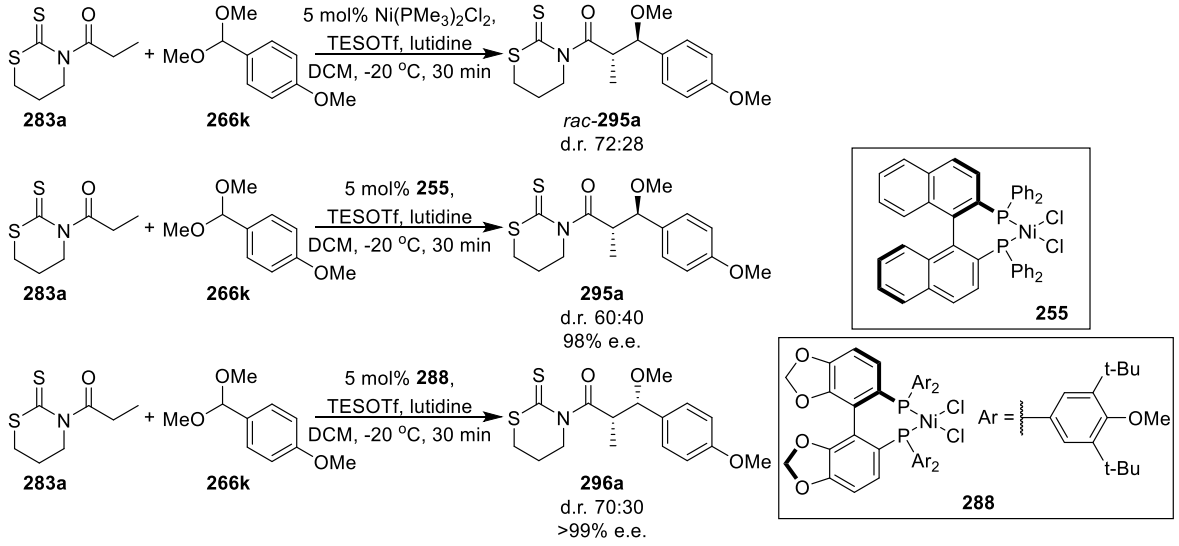
Our group had previously described additions of chiral *N*-acyl thiazolidinethiones to acetals catalysed by achiral nickel(II) complexes, which has been explained in detail in Chapter 3 (Scheme 110).[85–88]. . Initially the reaction of *N*-propanoyl thiazolidinethione (R: Me in Scheme 110) was explored by Juanma Romo in his PhD Thesis,[87] and was later expanded to the α-azido and α-pivaloyloxy counterparts (R: N_3 and OPiv respectively in Scheme 110), which gave better selectivity.[86,88] As explained in the previous Chapter the electrophile is activated to form an oxocarbenium cation which then reacts in an aldol-like manner to give the β-methoxy products with an *anti*-selectivity. This is a direct reaction, but the

selectivity comes from a chiral auxiliary which is something we wished to avoid in our new aldol methodology.



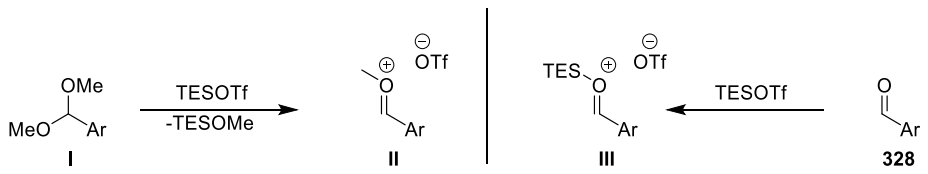
Scheme 187: Reaction of N*-Acyl Thiazolidinethione **239** with Dimethyl Acetal **268a**.*

Our closest reaction to a direct asymmetric aldol reaction we have developed was mentioned in Chapter 3 and is related to the above reaction but without the use of a chiral auxiliary.[89] The reaction involved our six-membered achiral thiazinanethione scaffold developed in Chapter 3 which was used in its propionic acylated form (**283a**). This then reacted with the dimethyl acetal **266k** in the presence of a nickel catalyst, organic base and a silyl-triflate Lewis acid to give the products **295**/**296** depending on which catalyst was used (Scheme 188). The achiral catalyst (to prepare the racemate) and Tol-BINAP complex **255** both favoured the *anti*-product **295** which the much bulkier DTBM-SEGPHOS complex **288** favoured the *syn*-isomer all with moderate diastereoselectivity and exceptional enantioselectivity when the chiral complexes were used. While we are still investigating the full scope and optimisation of the use of acetals in the direct addition reactions, we believed this example could pave the way for a direct asymmetric aldol reaction.



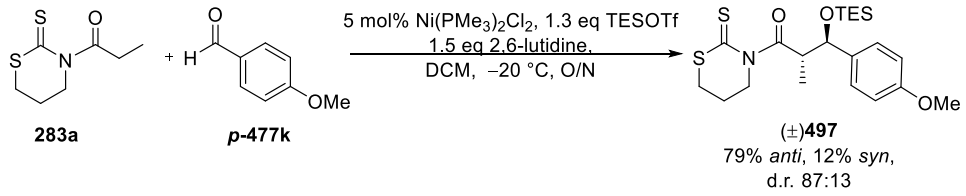
Scheme 188: Nickel (II) Catalysed Reaction of Dimethyl Acetals.

The active electrophilic species is the oxocarbenium ion **II** formed from the acetal reagent **I** by the abstraction of a methoxy group by the Lewis acid (Left, Scheme 189). We thus hypothesised that aromatic aldehydes **328** may be activated in a similar manner to create a new reactive species **III** (Right, Scheme 189), which according to the isolobal principle should react in an aldol-like reaction.



Scheme 189: Left: Activation of Acetal Substrates; Right: Proposed Activation of Aldehyde Substrates.

To our pleasure, the initial test of the reaction led to the formation of a silyl protected aldol adduct. Using our newly developed thiazinanethione scaffold starting material **283a** and *para*-anisaldehyde ***p*-477k** in the presence of a nickel (II) complex the *anti*-aldol adduct (±)**497** was obtained in a high yield with an additional quantity of the *syn*-isomer (Scheme 190). Although our first test was conducted with an achiral nickel complex, we observed high diastereoselectivity towards the *anti*-product. We also obtained the protected aldol adduct directly which removed the need for an additional protection step. We then moved to conduct a full optimisation of the reaction conditions, achiral stating material, chiral ligands, followed by an examination of the reactions scope and mechanistic details. These results can be found in the following draft paper.



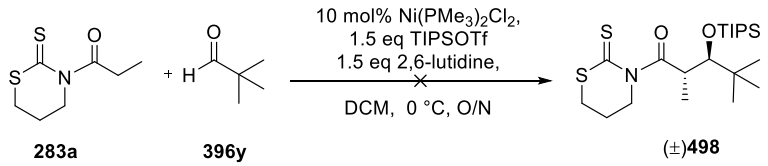
Scheme 190: Initial Test of Our Direct Asymmetric Aldol Reaction with Simultaneous Silyl Protection.

Application to Other Electrophiles

After our success of developing an aldol reaction using aromatic aldehydes, we aimed to broaden the scope of the reaction by applying the same methodology to other classes of aldehyde. Our interest was first aimed at aldehydes with different levels of unsaturation at the α-position. We thus investugated single, double, and triple bond examples of aldehydes to probe their compatibility with the new methodology. We attempted first to use the final conditions described in the following draft paper with subsequent optimisation if necessary.

Aliphatic Aldehydes

Due to the possibility of deprotonation at the alpha position of the activated electrophile (seen in Chapter 3) an aliphatic aldehyde without any α-protons was required. We attempted the reaction with pivalaldehyde (**396y**, Scheme 191) but no product was obtained in relatively forcing conditions. Increasing the temperature and catalyst loading still did not affect a reaction.

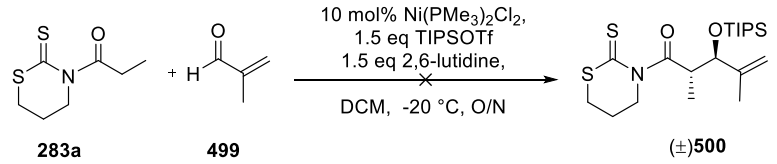


Scheme 191: Failed Attempt Using Pivaldehyde.

We theorised that a proper activation of the electrophile is not achieved in this case. Therefore, without the activation the reaction cannot take place. We therefore moved to α,β-unsaturated aldehydes.

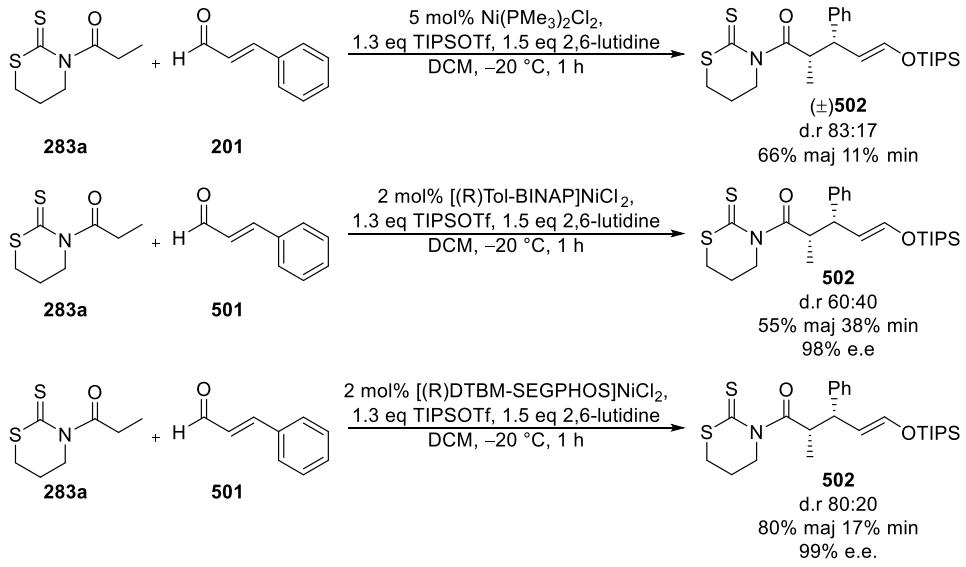
Vinyl Aldehydes

We next investigated vinyl aldehydes which we hoped would be reactive enough to be activated by our Lewis acid. Initially, we examined the reaction with methacrolein (**499**). Unfortunately, we were unable to isolate the expected product **500** under different conditions (Scheme 192). In most cases the electrophile was not recovered suggesting it had reacted. As methacrolein is known to be able to self-polymerise we moved to a more stable vinyl aldehyde to test the reaction.



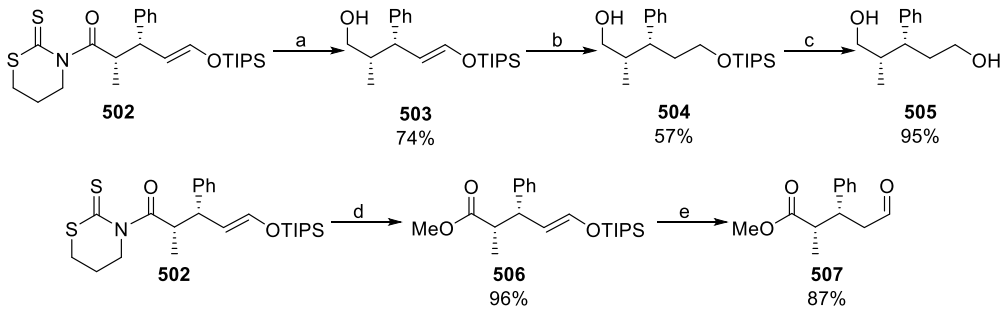
Scheme 192: Test with Methacrolein.

We therefore ran a test with cinnamaldehyde (**501**). To our surprise we found that not only the reaction proceeded but rather than yielding the protected aldol adduct we expected, yielded exclusively the protected Michael product **502** (Scheme 193). The selectivity when using the racemic nickel complex was almost 5:1 but when we moved to using Tol-BINAP the selectivity dropped to 1.5:1. We then decided to run the reaction with the largest catalyst DTBM-SEGPHOS to see if we could illicit a change in the selectivity; interestingly it increased the selectivity towards the major product and not towards the minor as we expected. This led us to believe the major product was in fact the *syn*-isomer as in the previous cases the larger catalyst has been more selective towards the *syn*-products (or less selective towards the *anti*-products). In both cases the enantioselectivity of the major isomer was exceptional and the yields were also excellent for both isomers.



Scheme 193: Reactions with Cinnamaldehyde.

We chose diol **505** to determine the relative configuration of the Michael adduct **502** as both the *anti*- and *syn*-isomers were described (Scheme 194). Removal of the scaffold in reductive conditions yielded alcohol **503**, which was hydrogenated to give **504.** A final deprotection led to the diol **505**. Our NMR data matched with the *syn*-product,[90] therefore confirming our suspicions that the new Michael reaction was *syn*-selective. Unfortunately, the optical rotation was not described for this compound so we could not confirm the absolute configuration in this manner. However, as we have invariably observed excellent control over the α–stereocentre we believe that it should be consistent with the previous reactivity and thus the enantiomer shown in Scheme 194. We are currently working on confirming the absolute configuration.



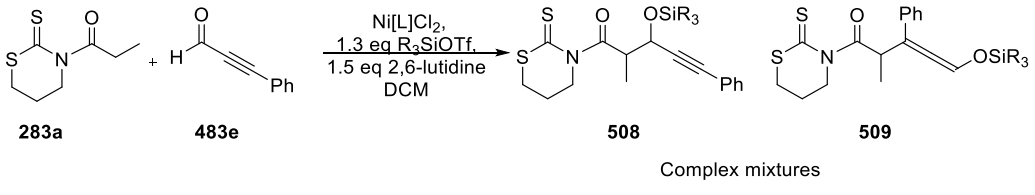
Scheme 194: Removal of the Scaffold and Discovering the Configuration.

Also, as our product was uniquely a protected Michael adduct, we wished to show the versatility of the method by creating another derivative. This time we removed the scaffold through nucleophilic displacement with methanol to give ester **506** followed by deprotection to provide the aldehyde **507**. This allowed us not only to choose the functionality when removing the scaffold as previously demonstrated in our other methodologies but also functionalise the opposite end. We could leave the aldehyde expected from most Michael reactions by first deprotection or by manipulating the product before deprotection access the alcohol functionality. The silyl enol product also has potential for use in other reactions.

Due to the unexpected success of this electrophile we have started a project in the group dedicated to the study of Michael additions which will now focus on expanding the scope and pushing the limits of what we can do with this new chemistry discovered. For this reason, these results do not appear in the following draft paper. We are hoping to maintain or even improve the exceptional selectivity towards both the Michael products and towards the *syn*-isomer. One possibility for this could be to move to the 5-membered scaffold and then to the sulphur/oxygen combination; with both showing less affinity for the *anti*-product in the aldol reactions it would have to be examined under the Michael conditions for the same effect.

Propargylic Aldehydes

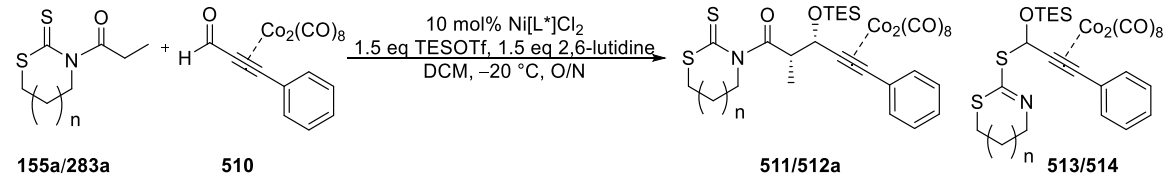
After our success with cinnamaldehyde and creating new reactivity we moved onto looking at propargylic aldehydes, hoping to secure a new electrophilic species for our aldol reaction. We started with phenylpropargylic aldehyde **483e** structurally close to cinnamaldehyde. Unfortunately, our initial tests produced complex mixtures of both the protected aldol adducts **508** and protected Michael adducts **509** (Scheme 195). Changing the conditions, catalyst and Lewis acid could not increase neither the regioselectivity nor the stereoselectivity to a sufficient level (even an 80% regioselectivity with a 4:1 d.r. gives a maximum yield for 64% of the major product).



Scheme 195: Initial Tests with Phenylpropargylic Aldehyde.

In an effort mainly to combat the lack of regioselectivity and remove the possibility of the Michael addition we protected the triple bond of phenylpropargylic aldehyde with cobalt carbonyl.[86,91] This aldehyde solely gave aldol addition (Table 4); but the use of TIPS triflate produced slow kinetics and formation of undesired S-alkylated compounds (10% products and 60% S-alkylation). Thus, we

continued using TES triflate. Whilst the initial selectivity was low, screening of catalysts allowed us to reach 9:1 selectivity (entries 1-3, Table 4). Seeing the diastereoselectivity increased using DTBM-SEGPHOS we inferred that it was towards the *syn*-product **512a** and therefore decided to test the five-membered scaffold. Using the smaller scaffold, we saw a threefold increase: firstly, in the selectivity, which was significantly higher, especially when using the chiral catalysts (entries 4-6). Secondly there was an increase in the conversion to the products **511a**, coupled with a decrease in the alkylation at the sulphur position (**513**). This matched our previous experience that the five-membered scaffold was less prone to alkylation at the sulphur position compared to the six-membered counterpart. Our final conditions allowed us to achieve the final product in consistent yields of around 75% of the major diastereoisomer. Unfortunately, due to the complexation of having a cobalted adduct we were unable to confirm the enantiopurity accurately using HPLC (although it seemed around 95%). Hence, we required a further step to confirm the enantioselectivity of the reaction.

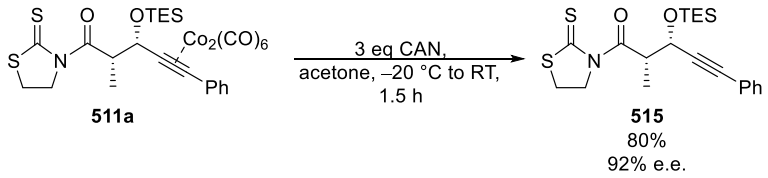


155a/283a **510** **511/512a** **513/514**

Entry	n	Ligand, L*	d.r.	Products (%)	Conv S-Alkyl (%)
1	1	$(PMe_3)_2$	45:55	55	30
2	1	(*R*)-Tol-BINAP	65:35	65	20
3	1	(*R*)-DTBM-SEGPHOS	90:10	20	9
4	0	$(PMe_3)_2$	90:10	50	3
5	0	(*R*)-Tol-BINAP	95:5	75	5
6	0	(*R*)-DTBM-SEGPHOS	98:2	>95 (77)	1

Table 4: Results in the Screening of Scaffolds and Catalysts for the Addition of Cobalted Propargylic Aldehydes.

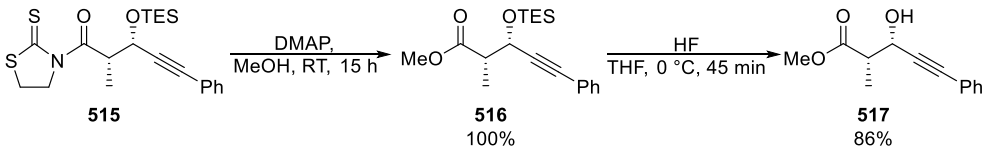
Following our research, we next assessed the removal of the cobalt using cerium ammonium nitrate to give the deprotected triple bond adduct **515** (Scheme 196). With this aldol adduct in hand we were able to ascertain the enantiopurity which was 92%; furthermore, as we saw no creation of a diastereomer from racemisation in the removal we assume the selectivity of the initial adduct is reflected in the decobalted product.



511a **515** 80% 92% e.e.

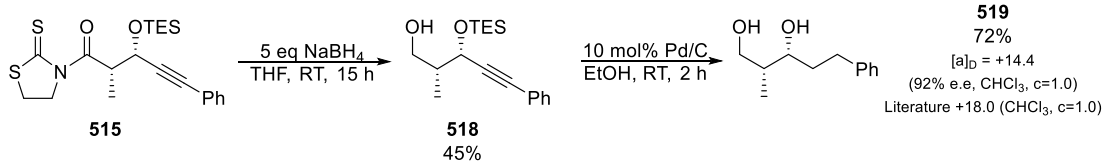
Scheme 196: Deprotection of the Triple Bond.

With the enantioselectivity confirmed we then moved to firmly establish the stereochemical outcome of the reaction. Synthesis of the hydroxyester **517** and comparison to the synthesised *anti*-isomer,[78] showed that the product was correct but was the complementary diastereomer, confirming the *syn*-selectivity of the reaction. This was achieved through the displacement of the scaffold of the decobalted adduct **515** with methanol to give the ester **516**, followed by deprotection with fluoride to give the hydroxy ester (Scheme 197).



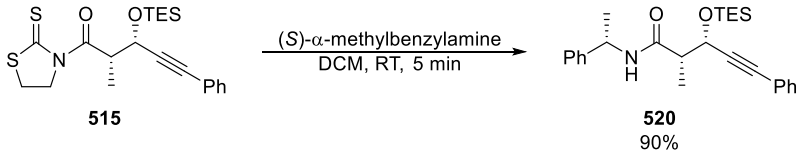
Scheme 197: Confirmation of Relative Stereochemistry.

Looking for a direct confirmation of the relative, as well as the absolute, configuration we performed further transformations on the product **515** to reach a suitable candidate for literature comparison. For this it was necessary to reduce the triple bond and form a saturated compound. Therefore, we first removed the scaffold in reductive conditions to leave the alcohol **518** (Scheme 198). We then performed a hydrogenation to reduce the triple bond which proceeded with concurrent deprotection of the secondary alcohol to give the diol **519**. This molecule matched perfectly with the described *syn*-isomer and we were able to confirm the absolute configuration as the expected enantiomer through comparison of the optical rotation.[92]



Scheme 198: Confirmation of Absolute Stereochemistry.

Finally, we also removed the scaffold using (*S*)-α-methylbenzylamine to produce a chiral amide **520** we could crystallise to perform an X-Ray analysis. We removed the scaffold with enantiopure methylbenzylamine to give the amide **520** which we crystalised and are currently awaiting the crystal structure (Scheme 199).



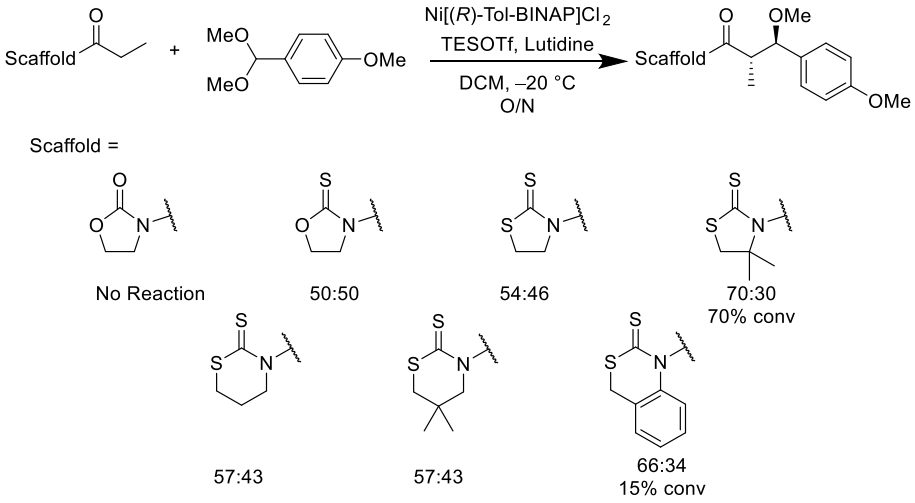
Scheme 199: Scaffold Removal with Chiral Amine.

Once more, due to the success of the electrophile and because we deemed it both sufficiently different and important, we decided to dedicate a project dealing solely with cobalted propargylic aldehydes in *syn*-selective protecting aldol reactions. An investigation into the scope is currently underway along with its potential uses, including a Pauson-Khand reaction using the cobalted adducts. Consequently, the results do not appear in the draft paper.

Acetals as Electrophiles

Owing to our previous experience with acetals in aldol-like reactions both using chiral auxiliaries under stoichiometric as well as catalytic conditions,[85,86,88,89,93–96] we explored the reaction of such electrophiles. In this case however the product would be a β-methoxy derivative and not a silyl-protected adduct. We have run some initial tests in this area which have shown the viability of the reaction although the selectivity needs improvement.

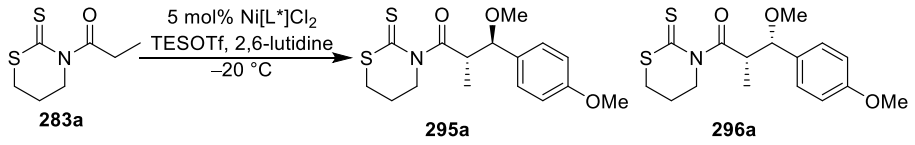
Initially we investigated the effect of the achiral scaffold. Testing various scaffolds gave us a view of the pattern of the effect the achiral scaffold can have on the diastereoselectivty. Below is a summary of the results using Tol-BINAP as the chiral ligand and *p*-anisaldehyde dimethyl acetal as the electrophile (Scheme 200).



Scheme 200: Reaction of Different Scaffolds Using Ni[(R)-Tol-BINAP]Cl$_2$.

The scaffold that gave the best selectivity towards the *anti*-product **295a** without significant effect on the conversion was the simple six-membered thiazinanethione, whereas the scaffold that provided the least selectivity towards the *anti*-product was the oxazolidinethione, the five-membered scaffold containing an endocyclic oxygen atom. Unfortunately, the adducts proved extremely difficult to separate and most we were unable to isolate and characterise, therefore we needed to increase the selectivity to make it easier.

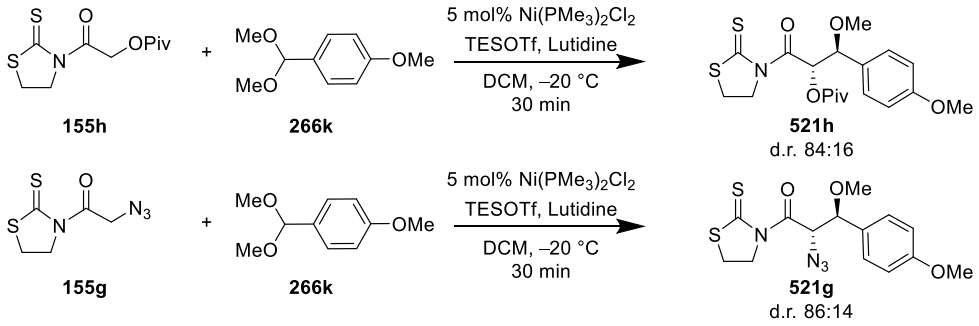
We then tested a variety of chiral catalysts of which the results are shown below in Table 5. Using the achiral catalyst and DIOP provided the highest *anti*-selectivity but low or no enantioselectivity. The BINAP family gave around 1.5:1 selectivity towards the *anti*-product and exceptional enantiocontrol. Finally using the SEGPHOS family we saw a trend away from the *anti*-product and using the DTBM analogue a full reversal towards the *syn*-isomer **296a**.



Entry	Ligand, L*	d.r . (*anti*:*syn*)[a]	e.e[b]
1	$(PMe_3)_2$	72:28	0
2	DIOP	73:27	8
3	(*R*)-BINAP	60:40	98
4	(*R*)-Tol-BINAP	57:43	98
5	(*R*)-Xyl-BINAP	63:37	-
6	(*R*)-SEGPHOS	55:45	-
7	(*R*)-DTBM-SEGPHOS	30:70	>99

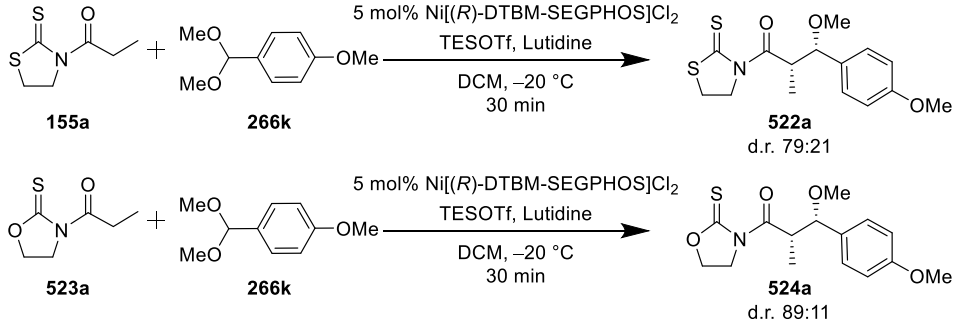
Table 5: Results from the Catalyst Screening, a: Determined by NMR, b: Determined by Chiral HPLC.

We tried to optimise the selectivity towards the *anti*-product through manipulating the starting material. Using the α-oxy and α-azido derivatives (**155h**/**155g**) of the five-membered scaffold and the achiral catalyst gave an increased ratio towards the *anti*-products **521** (Scheme 201). This would then be expected to drop when combined with a chiral catalyst as seen in Table 5.



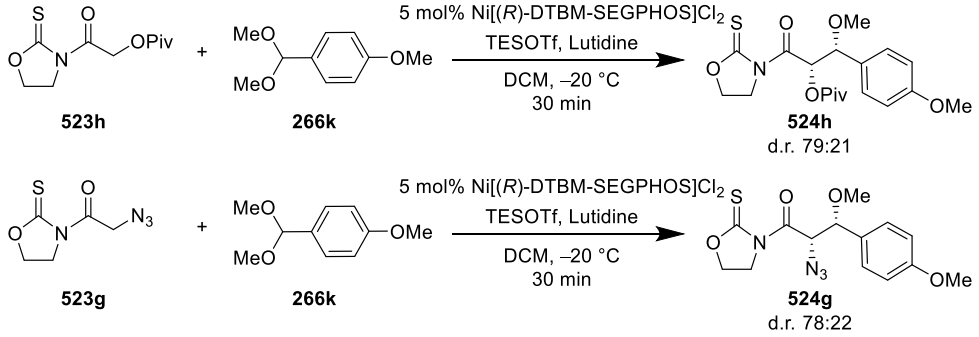
Scheme 201: Test with OPiv and Azide Chains and Dimethyl Acetal.

We then tested the best combinations of catalyst and scaffold to achieve the *syn*-product and it resulted in very high selectivity (Scheme 202). Using the thiazolidinethione starting material **155a** and the DTBM-SEGPHOS ligand the selectivity towards the *syn*-product **522a** reached 4:1. This increased to almost 9:1 when the oxazolidinethione starting material **523a** was used in the same conditions.



Scheme 202: Towards Syn*-Selectivity.*

We also were able to achieve the α-oxy and α-azido *syn*-derivatives of **524** with only a small drop in selectivity (Scheme 203).



Scheme 203: Test with OPiv and Azide Chains and Dimethyl Acetal.

Due to the scale of the project and the work left to complete it we have moved the use of acetals to a separate project where we aim to solve the issues in purification of some of the adducts and increase the selectivity towards the *anti*-products. We are also investigating the scope of the *syn*-selective reactions both in terms of different acetals and acyl chains used in the reaction. Due to the nature of these preliminary results they do not appear in the draft paper.

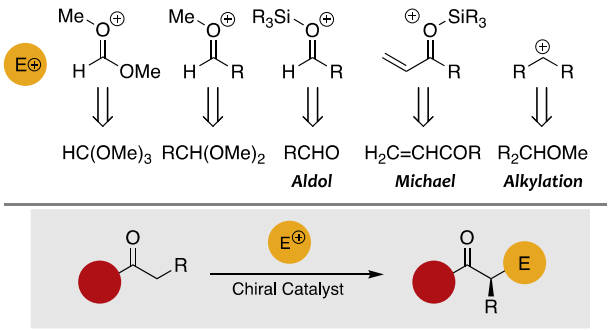
Direct and Enantioselective Aldol Reactions Catalyzed by Chiral Nickel(II) Complexes with Inherent Silyl Protection

Stuart C. D. Kennington, Saul Teloxa, Miguel Mellado, Oriol Galeote, Marina Bellido, Pedro Romea,* Fèlix Urpí,* Gabirel Aullón and Mercè Font-Bardia

Abstract

A new, direct and asymmetric aldol reaction using thiazinanethione scaffolds, aromatic aldehydes, silyl triflates and a chiral nickel(II) complex is described. The resulting *anti*-products are silyl-protected aldol adducts which are obtained with high yields, levels of diastereoselectivity and exceptional enantiocontrol. These adducts can in turn be transformed to a number of enantiopure synthons with wide functionality via the simple removal of the scaffold in various conditions.

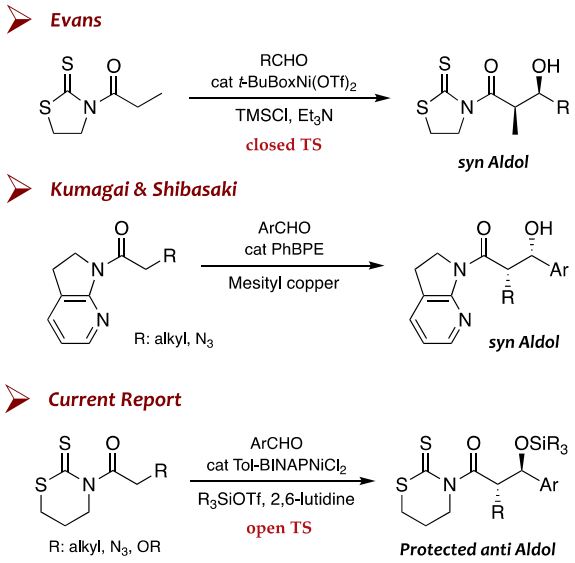
The enantioselective construction of the carbon backbone of chiral molecules has been at the forefront of organic synthesis in the last decades. It is therefore hardly surprising that classical transformations as aldol or Michael reactions or Diels-Alder cycloadditions still hold a prominent position among the most important synthetic methods. In this context, the continuing demand for increasingly more efficient procedures in accordance to the premises dictated by the selectivity and the economy in synthesis has given rise to the development of a number of catalytic methods for the enantioselective construction of carbon–carbon bonds. Unfortunately, the scope of most of them is rather narrow, which hampers further developments and prevents a comprehensive exploitation of their possibilities. Thus, considering the benefits arising from a general approach, we envisaged that metal enolates from a single platform might participate in a wide array of direct, enantioselective and catalytic transformations provided that the appropriate electrophiles were simultaneously generated in the reaction mixture and evolve through similar open transition states (Scheme 1).



Scheme 1.

Keeping in mind such a central tenet and taking advantage of previous reports, we envisaged that activated aldehydes shown in Scheme 1 might react with metal enolates generated catalytically by using appropriate chiral Lewis acid to provide aldol adducts in a highly stereocontrolled manner. With this aim, we have identified *N*-acyl thiazinanethiones as worthy substrates for our purposes and we now describe our findings on direct and highly enantioselective aldol reactions with aromatic aldehydes catalyzed by chiral nickel(II) complexes in which the resultant protected aldol compounds are selectively obtained with a remarkable atom economy. Importantly, this reaction gives access *in a single step* to

protected *anti* aldol adducts and supplements *syn* methods described by Evans, and Kumagai and Shibasaki (Scheme 2). Furthermore, the reaction shows a wide scope on the nucleophilic partner, which also permits to obtain enantiomerically pure and *O*-silyl protected α-amino-β-hydroxy and α,β-dihydroxy derivatives in high yields under mild conditions (Scheme 2).

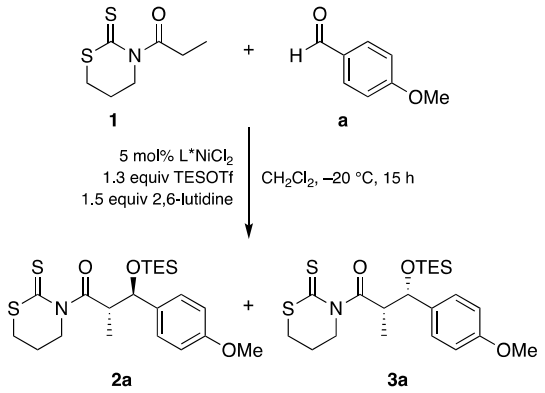


Scheme 2.

Initial tests using *N*-propanoyl derivatives of a broad array of achiral substrates and $(Me_3P)_2NiCl_2$ proved the feasibility of our approach for a direct and stereocontrolled aldol reaction as well as the advantage of thiazinanethione over other heterocyclic scaffolds (for further information, see Table SI1). Following such preliminary experiments, we examined the stereocontrol provided by a number of chiral nickel(II) complexes. It is important to highlight that these complexes are robust, easy to handle and prepare from the corresponding chiral ligands and $NiCl_2$, and that are properly activated in the reaction mixture at the same time that the aldehyde by simple treatment with a silyl triflate. Results summarized in Table 1 shows that *N*-propanoyl thiazinanethione **1** reacts as planned with 4-methoxybenzaldehyde (**a**) in the presence of minute amounts of nickel(II) complexes with the exception of $DIOPNiCl_2$ (entry 2 in Table 1). Indeed, achiral $(Me_3P)_2NiCl_2$ provided a mixture of silyl aldol adducts with remarkable diastereomeric ratio (dr 87:13) from which major *anti* adduct **2a** was isolated with a 79% yield (entry 1 in Table 1), whereas other chiral complexes also catalyzed the desired aldol reaction with full conversion. Interestingly, the steric hindrance

of the chiral ligands plays a key role in the stereochemical outcome of the reaction. Indeed, the chiral DTBM-SEGPHOS diphosphine gave an equimolar mixture of *anti* and *syn* diastereomers (**2a** and **3a** respectively), whereas the less bulky SEGPHOS performed much better and afforded an 80:20 **2a**/**3a** mixture (compare entry 2 and 3 in Table 1); in turn, the enantiocontrol was outstanding and enantiomerically pure (*ee* ≥ 98%) aldol adduct **2a** was isolated in both cases. Furthermore, BINAP family gave much more consistent results, although the stereochemical outcome of the reaction slightly depended on the bulk of the ligand, being the Tol-BINAP ligand the most appropriate in terms of stereocontrol and yield (compare entries 5–7 in Table 1).

Table 1.

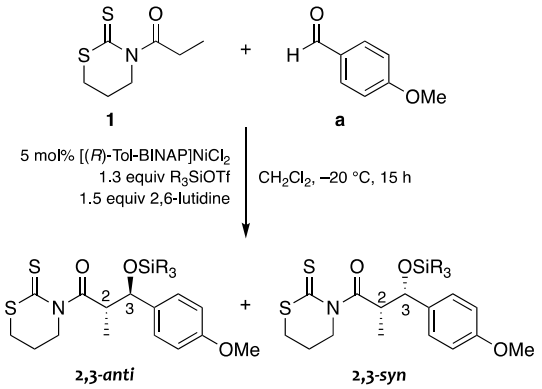


Entry	L*$NiCl_2$	dr (**2a**/**3a**)	*ee* **2a** (%)	Yield **2a** (%)
1	$(Me_3P)_2NiCl_2$	87:13	–	79
2	(+)-DIOP$NiCl_2$	88:12	< 5	< 10
3	[(*R*)-SEGPHOS]$NiCl_2$	80:20	98	67
4	[(*R*)-DTBM-SEGPHOS]$NiCl_2$	49:51	99	43
5	[(*R*)-BINAP]$NiCl_2$	80:20	97	75
6	[(*R*)-Tol-BINAP]$NiCl_2$	80:20	98	76
7	[(*R*)-Xyl-BINAP]$NiCl_2$	83:17	83	71

The impact of the steric bulk of ligands in the reaction led us to explore the influence of the activating Lewis acid. We thus examined the commercially available TMS, TBS, TES, and TIPS triflates. In the racemic reaction with $(Me_3P)_2NiCl_2$, all these silyl triflates but TMSOTf, which produced similar diastereomeric ratios but larger amounts of deprotection, can be used interchangeably with respect to diastereoselectivity and yield. On the contrary,

we observed a significant change of selectivity when [(*R*)-Tol-BINAP]$NiCl_2$ was used instead. As shown in Table 2, diastereoselectivity depends upon the silyl triflate: less bulky TMSOTf and TBSOTf gave lower diastereoselectivity than TESOTf, whereas the bulkier TIPSOTf increased the diastereomeric ratio up to 85:15 (compare entries 1–4 in Table 2). In turn, enantiocontrol was excellent for all these groups (see Table 2).

Table 2.

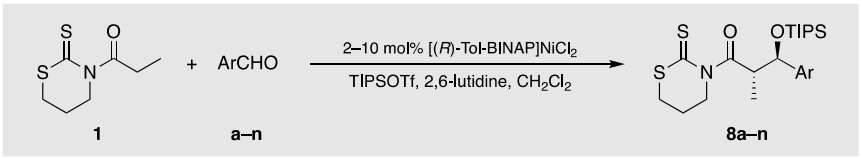


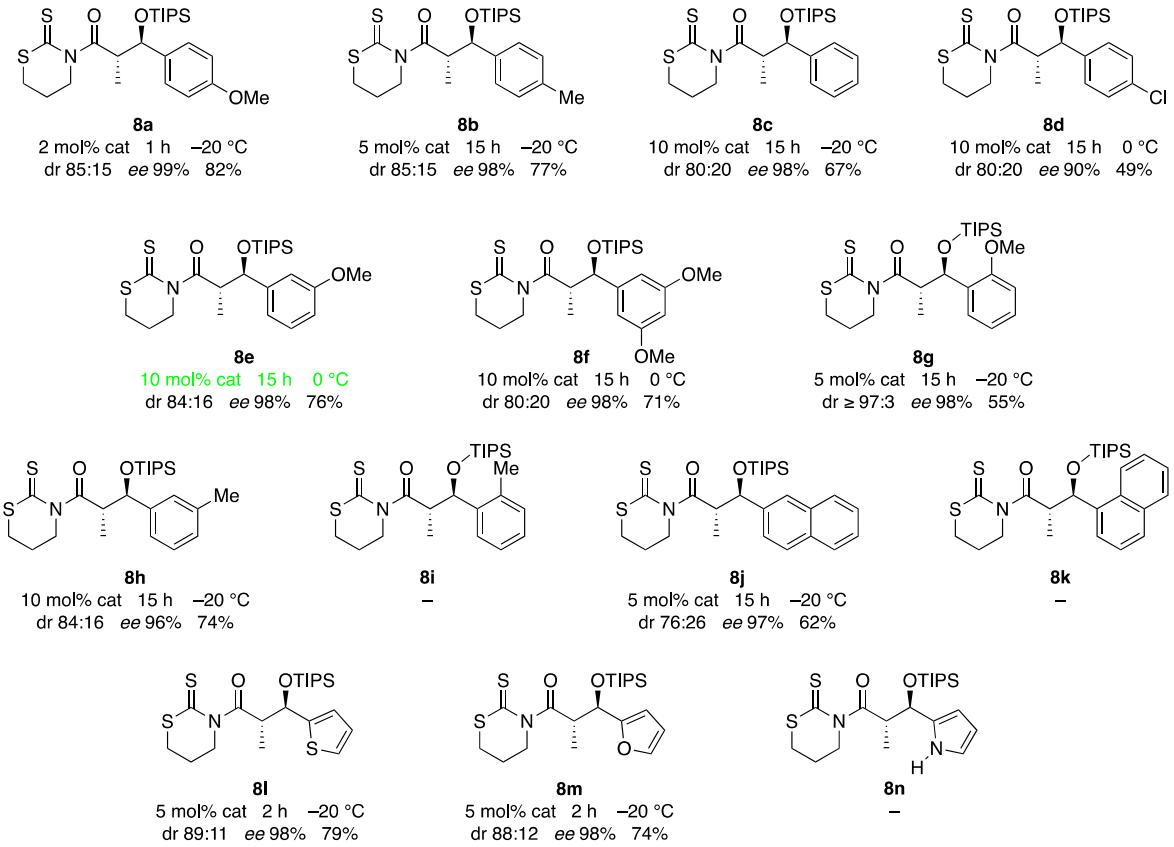
Entry	R_3SiOTf	Major *anti* Adduct	dr (*anti*/*syn*)	*ee* (%) *anti*	Yield (%) *anti*
1	TESOTf	**2a**	80:20	98	76
2	TMSOTf	**4a**	73:27	nd	nd
3	TBSOTf	**6a**	75:25	98	67
4	TIPSOTf	**8a**	85:15	99	82

We finally evaluated other variables. The temperature had, as expected, a modest positive effect on the diastereomeric ratio when cooled to –40 °C but duly decreased the rate of reaction, so we maintained –20 °C as the reaction temperature. Finally, it is worth noting that decreasing the catalyst loading to 2 mol% also gave complete conversion and identical results in only 1 h, which makes much simpler the experimental procedure.

With the reaction conditions firmly established for 4-methoxybenzaldehyde (**a**), we moved to evaluate the scope of the reaction with other aromatic aldehydes. Results summarized in Table 3 prove that the reaction is sensitive both to the electronic character and the steric bulk of the substituents of the aromatic aldehyde.

Table 3.



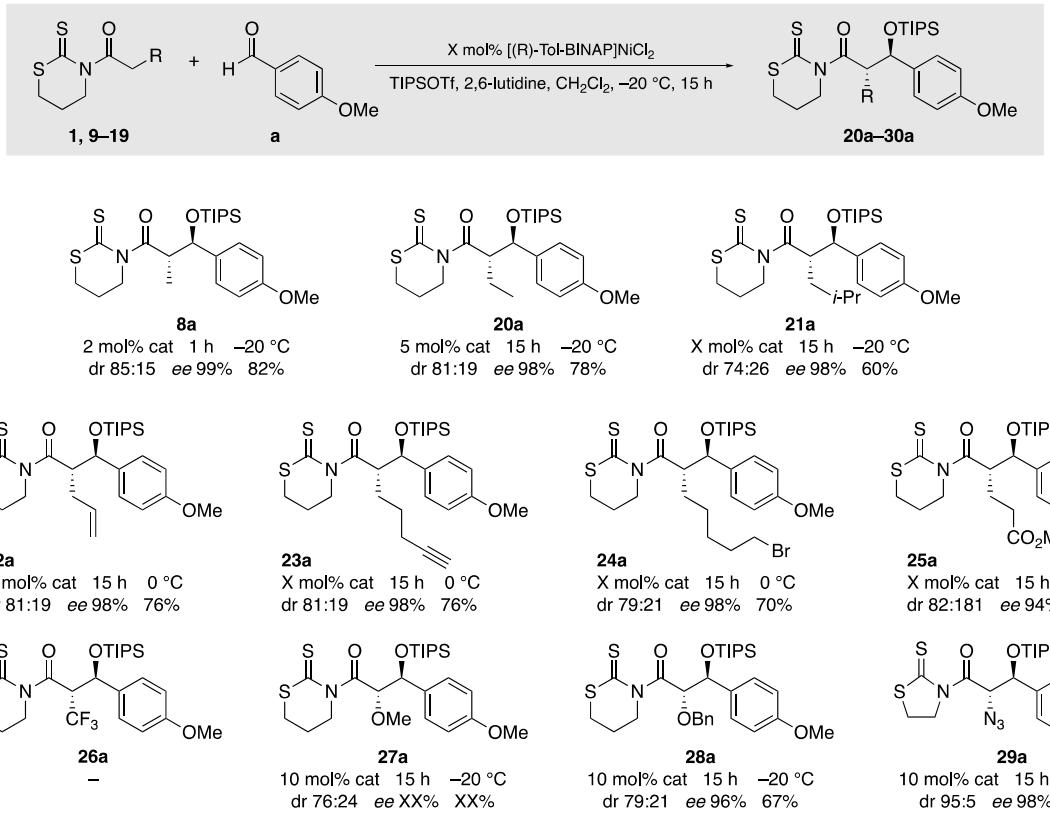


Indeed, electron donating groups at the *para* position enabled highly stereocontrolled aldol reactions (dr 85:15 and *ee* ≥ 98% for **8a** and **8b**) and permitted the isolation of the enantiomerically pure and TIPS-protected *anti* adducts in high yields (77–82%). Model benzaldehyde (**c**) required the increase of catalyst loading to attain similar results but the more deactivated 4-chlorobenzaldehyde (**d**) only provided TIPS–protected *anti* adduct **8d** with a modest 49% yield owing to an incomplete reaction and the formation of a by–product arising from the attack of the nucleophilic exo sulfur atom to the activated aldehyde. Other isomers of 4-methoxybenzaldehyde (**a**) were also assessed with satisfactory results. As expected, the 3-methoxy and the 3,5-dimethoxy benzaldehydes (**e** and **f** respectively) turned out to be less reactive but gave the corresponding *anti* aldol adducts **8e** and **8f** smoothly at 0

°C with a 10 mol% loading of the catalyst. More surprisingly, 2-methoxybenzaldehyde **g** only needed for the use of 5 mol% of the catalyst and led to the protected aldol **8g** as a single stereoisomer (dr ≥ 97:3 and *ee* 98%) in 55% yield. In turn, parallel aldol reactions of alkyl and aryl *meta* substituted aldehydes **h** and **j** also proceeded efficiently, but the *ortho* substituted counterparts **i** and **k** turned out to be completely inactive and did not afford at all the desired adducts **8i** and **8k**. These results indicate that bulky groups close to the reacting carbonyl group hinder the approach to the enolate, whereas we speculate that the outstanding results from 2-methoxybenzaldehyde (**g**) may be due to the formation of a chelated oxocarbenium intermediate. Finally, pyrrole derived aldehyde **n** was completely unsuitable but other aromatic aldehydes containing π-electron rich heterocycles as **l** and **m** turned out to be highly reactive and the corresponding *anti* aldol adducts **8l** and **8m** were isolated in high yields after 2 h by using a 5 mol% of the nickel(II) complex.

Once the feasibility of the enantioselective *anti* aldol transformation had been demonstrated, we addressed the scope of the reaction with regard of the substituents on the acyl group. We thus examined the addition of a number of *N*-acyl thiazinanethiones **9–19** to 4-methoxybenzaldehyde (**a**). Once again, the results shown in Table 4 demonstrated the key role of steric bulk on the stereochemical outcome of the aldol reaction. In this respect, although the enantioselectivity is steadily excellent along the *N*-acyl thiazinanethiones **9–11** containing simple R alkyl groups, the diastereoselectivity and consequently the yield are eroded from **8a** (R:Me, dr 85:15, 82%) to **21a** (R:*i*-Bu, dr 74:26, 60%) as well as the reaction conditions become more stringent (from 2 mol% to 10 mol% of catalyst respectively). On the other hand, the chemoselectivity is excellent and the presence of common functional groups as alkenes, alkynes, halides, and esters has not a noticeable influence on the aldol reaction, so enantiomerically pure (*ee* 94–98%) protected *anti* adducts **22a–25a** were isolated in good to high yields (62–76%). Finally, it is worth emphasizing that the presence of a strong electron withdrawing CF_3 group at the α-position hinders the reaction, but α-hydroxy and α-azido derivatives afford the corresponding *anti* adducts **27a–29a** in a highly efficient manner, which gives a straightforward access to properly protected *anti* α,β-dihydroxy and α-amino β-hydroxy structures with an undeniable synthetic interest. Particularly, the reaction of the azido thiazolidinethione **19** proved especially successful and afforded the α-azido-β-silyloxy adduct **29a** virtually as a single stereoisomer (dr 95:5, *ee* 98%) in 93% yield.

Table 4.



We confirmed the relative and absolute configuration of the products via the synthesis and analysis of derivatives. The major product was confirmed as the anti-adduct with the αS,βR configuration with a crystal structure of the methylbenzylamide derivative **31** (Figure 1).

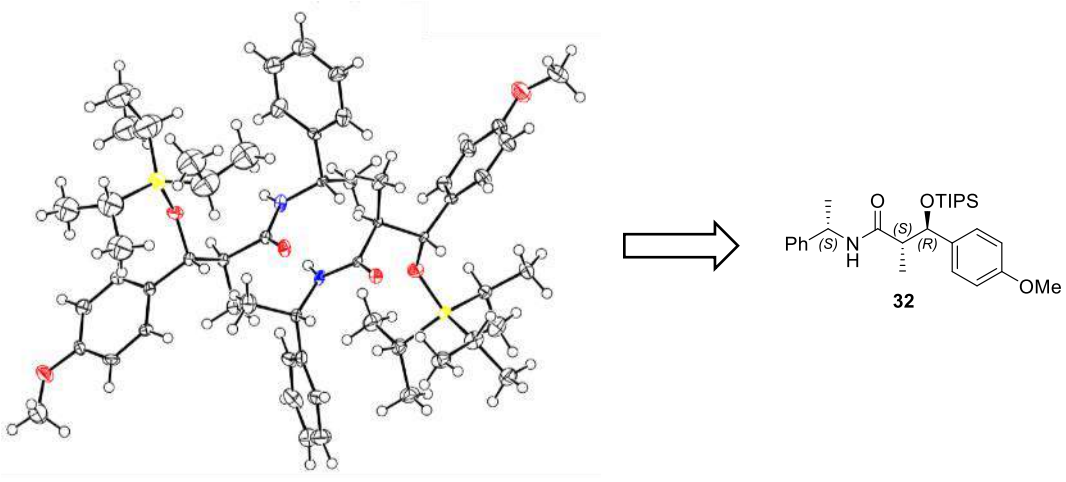
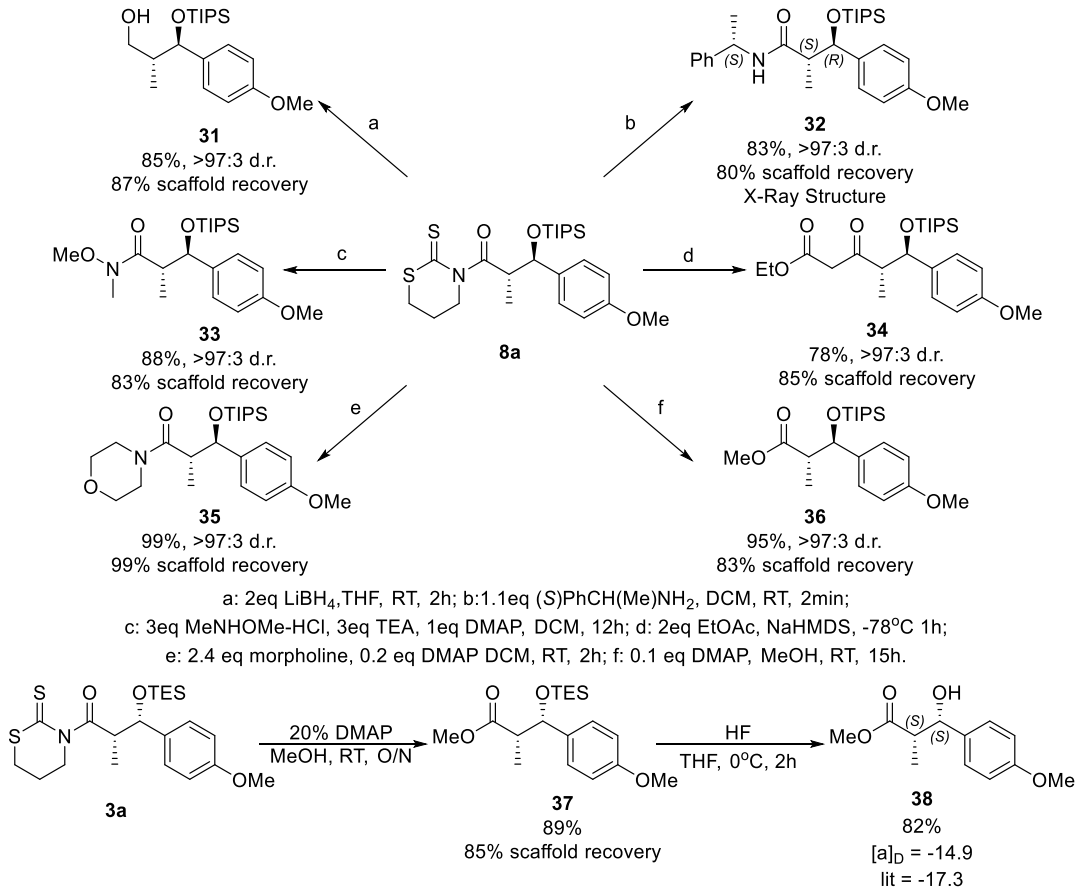


Figure 1.

The derivative was prepared via the simple nucleophilic displacement of the scaffold from the initial TIPS protected *anti*-aldol adduct **8a** with the amine in only 2 minutes with the recuperation of the liberated scaffold. The minor product was confirmed as the αS,βR *syn*-product via chemical correlation of the hydroxy methylester **38**. The adduct was synthesized by first removing the scaffold from the TES protected *syn*-aldol product **3a** with DMAP in methanol and then deprotection of the resulting methyl ester **37** with hydrofluoric acid to give hydroxyester **38** in a 73% overall yield (Bottom, Scheme 3).

The anti-aldol addition product **8a** was also further transformed into other enantiopure derivatives of synthetical interest. The alcohol **31** was synthesized using sodium borohydride in wet THF with a yield of 85% (eq a). The Wienreb amide **33** was made with a high yield via the displacement of the scaffold with methylmethoxyamine chloride (eq c). The sodium enolate of ethyl acetate was used to remove the scaffold to form the β-keto ester **34** in a high yield (eq d). In turn the morpholine amide **35** was prepared using morpholine in DCM in only 2 hours with a yield of 99% (eq e). Finally, as with the syn product, the methyl ester was prepared using the same methodology of DMAP/MeOH to yield 95% of anti-hydroxyester **36** (eq f).



Scheme 3.

Conclusions

In conclusion we have developed a highly selective protecting *anti*-aldol reaction which can be applied to various aromatic aldehydes including highly deactivated substrates. The high tolerance of starting material side chain functionality allows for the synthesis of a large library of silyl-protected anti-aldol products. These substrates can be easily transformed into a variety of enantiopure synthons.

Conclusions

In this chapter we have developed a new methodology for the asymmetric *anti*-selective aldol reaction of aromatic aldehydes with simultaneous silyl protection of the adduct. We have fully optimised the reaction with regards to the achiral scaffold used, the chiral ligands, Lewis acid, temperature, and reaction conditions. Furthermore, we have expanded the scope of the reaction to various aromatic aldehydes and different acyl chains in the starting material. We have also been able to remove the scaffold to leave different functionality, producing differing synthons from the same initial adduct. We also confirmed the stereochemistry and corroborated the proposed mechanism through supporting theoretical calculations. A draft paper has been presented which is currently being submitted to a top-tier chemistry journal.

Aside from the use of aromatic aldehydes we have further examined the imitations of our new reaction. We have found that in our current conditions we are unable to perform the reaction with aliphatic aldehydes. However, we did have success with α,β-unsaturated aldehydes, which opened new doors and new projects for our chemistry. Indeed, we observed a dramatic change on the reactivity. Interestingly the reaction cinnamaldehyde did not lead to an *anti*-aldol reaction but a *syn*-Michael adduct which our group is now investigating in a separate project. In turn, propargylic aldehydes proved initially unsuitable but the protection of the triple bond with cobalt was key in eliminating the option of a Michael addition and obtaining a highly selective *syn*-aldol reaction. The use of cobalted propargylic aldehydes is also currently under study in our laboratory in a new project. Finally, we have conducted a thorough optimisation of the reaction using dimethyl acetals and parallel intents to both increase the *anti*-selectivity and investigate the scope of the *syn*-selective addition form part of another project currently being undertaken in the group.

So, in this chapter we have not only developed a new, innovative and concise reaction in the form of an asymmetric aldol reaction with simultaneous silyl protection but also paved the way for three new self-contained projects with are currently under investigation.

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Overall Thesis Summary and Conclusions

This thesis focuses on the search for new methodologies for the direct, stereoselective and catalytic formation of carbon-carbon bonds through the formation of chiral nickel(II) enolate species and the application of such methods to the synthesis of natural products. The project starts with the stereocontrol coming from chiral auxiliaries, developed first by Evans and then later by Crimmins and Nagao, following the previous experience and expertise of the research group. These auxiliaries have proved to be a reliable and high yielding option to afford excellent levels of stereocontrol in various reactions. Furthermore, they can be removed after such processes to leave enantiopure synthons. However, they do have their drawbacks, one being the inability of synthesising all of the available stereoisomers from one starting material. To combat this issue, the second part of the thesis is centred around the development of a new methodology based on achiral starting materials (scaffolds) with chiral nickel(II) complexes, which both enable the reaction and control its stereochemical outcome.

In the first Chapter, methods previously developed in the group were applied to the synthesis of a fragment of the marine sponge macrolide Peloruside A, which has shown to have anticancer activity, especially against leukaemia. Three key steps involve reactions based on the use of chiral auxiliaries that had been developed in the group: a nickel catalysed reaction with trimethyl orthoformate, a titanium-mediated acetate aldol reaction, and a titanium-mediated addition of an acetate enolate to an acetal. The overall yield of the synthesis of the target fragment C9-C19 was 24% over 14 steps.

Chapter 2 presents a new reaction based on the addition of enolates, generated from chiral *N*-acyl thiazolidinethiones with an achiral nickel(II) complex, to stable carbocationic salts. This alkylation reaction was first thoroughgoingly optimised and later applied to a large range of substrates with wide success. Moreover, it was applied to a highly challenging electrophile successfully which lead to the discovery of a reversible alkylation process. The products were also transformed via the removal of the auxiliary to leave a variety of functional groups.

In Chapter 3 the stereocontrol is passed from the starting material to the catalyst in an ambitious advancement of the group's chemistry. After an extensive study of potential achiral scaffolds to provide the platform for the reactions and chiral diphosphine ligands to provide the enantiocontrol, we observed the best scaffold was the 6-memberd thiazinanethione structure and the best ligand DTBM-SEGPHOS®. We were able to apply this methodology to the reaction of: trimethyl orthoformate (an oxocarbenium precursor), tropylium tetrafluoroborate (a cationic salt), a diaryl methyl ether (a carbenium precursor), and also a more complex diaryl ketal electrophile with high yields and exceptional control over the one stereocentre formed. Furthermore, using a dimethyl acetal we were able to exert some control over the relative configuration of two stereocentres whilst maintaining exceptional enantioselectivity. Calculations and elucidation of the configuration of the new stereocentre formed support our hypothesis for the mechanism for such a process. We also demonstrated the ease with which the scaffold can be removed and were able to synthesise a wide variety of synthons with differing functional groups. Finally, we were able to scale up and apply the methodology to the synthesis of Peperomin D, a five membered lactone containing two stereocentres.

Finally, in the last Chapter we present a new methodology for the asymmetric aldol reaction of *N*-acyl thiazinanethiones with aromatic aldehydes catalysed by a chiral nickel (II) complex, which involves the simultaneous silyl protection of the adducts. This new reaction proceeds through an open transition state and leads to the *anti*-aldol products. We were able to optimise the reaction to achieve a high diastereoselectivity, exceptional enantioselectivity, and excellent yield. Furthermore, we were able to apply the conditions to various aromatic aldehydes and *N*-acyl thiazinanethiones. Finally, the scope of the reaction was expanded to three different electrophiles, opening new lines of investigation.

In conclusion we have more than achieved the original objectives for the thesis: the development of new reactions based on nickel enolates generated from acylated chiral thiazolidinethiones transferring the chirality from the starting material to develop new asymmetric metal catalysed reactions; and the application both to the synthesis of biologically active molecules.

In this thesis we have:

1. Completed the synthesis of a large fragment of Peloruside A using methodologies based on chiral thiazolidinethiones
2. Developed a new reaction using chiral thiazolidinethiones and stable carbocationic salts
3. Undertook and achieved the goal of the transference of the chirality from the starting material to a chiral nickel(II) complex
4. Developed a comprehensive methodology that was applied to various electrophiles controlling the new stereocentre formed
5. Expanded the methodology to a wide range of starting materials and synthesised various synthons with the resulting products
6. Applied this methodology to the synthesis of Peperomin D
7. Scaled up the methodology
8. Started the synthesis of Lacosamide which was completed by Saul F. Teloxa who was able to also synthesise various derivatives using the same methodology
9. Developed an asymmetric aldol reaction controlling two new stereocentres which gives the *anti*-product with inherent silyl protection
10. Made the initial investigation into the application of this methodology to three different electrophiles, opening new research lines.

Furthermore, these results have been published in four papers so far, two are currently under correction and an additional paper is currently being prepared to be submitted. The continuing research in the project discovered during this thesis, is promising and is planned to be published also upon completion.

Annex

Other Work Published During the Thesis not Related to the Thesis's Project

The following paper was published during the duration of the thesis and whilst it contains work conducted during the thesis's timeframe the work does not form a part of the project to which the thesis is dedicated. Nor does it fit with the topic of the thesis. It may however be of some interest to the reader.

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General and stereoselective aminoxylation of biradical titanium(IV) enolates with TEMPO: a detailed study on the effect of the chiral auxiliary†

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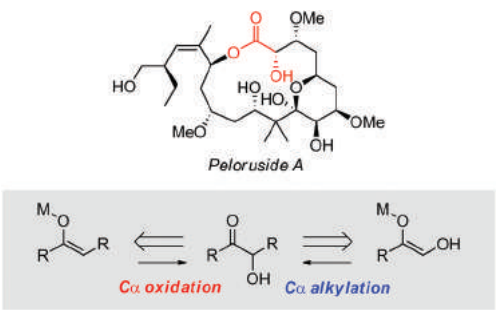
A comprehensive analysis of the influence of the chiral auxiliary on the α-aminoxylation of titanium(IV) enolates with TEMPO indicated that (*S*) 4-*tert*-butyl-1-oxazolidine-2-thione is the most appropriate scaffold to provide a single diastereomer in high yields for a variety of substrates, which converts such a radical reaction into a highly chemo- and stereoselective oxidation.

Introduction

The widespread presence of α-hydroxy carbonylic and carboxylic structures in biologically active natural products has fostered the development of increasingly efficient transformations involving either the asymmetric construction of carbon–carbon or carbon–oxygen bonds from metal enolates to access these structures (Scheme 1).[1]

Particularly, the stereoselective Cα-oxidation of carbonyl bonds has received lasting attention, resulting in a number of procedures based on the treatment of metal enolates with a variety of oxidizing agents like *N*-sulfonyloxaziridines, peroxides, or transition metals.[2,3] Aside from these methods, the emergence of organocatalytic procedures represented a major step forward in the asymmetric synthesis of α-hydroxy carbonylic compounds. Thereby, initial reports on the enantioselective preparation of aminoxylated adducts through addition of aldehydes and activated ketones to nitrosobenzene catalyzed by chiral amines[4] were soon enlarged by the SOMO activation mode concept.[5] This broadly referred to the oxidation of chiral enamines, which provided a cation radical that underwent highly enantioselective reactions. Thus, it presently stands as a milestone in asymmetric transformations involving radical or electronically excited species.[5,6]



Scheme 1 Reactivity of the Cα position of enolates.

Mirroring such achievements, the recognition of the biradical character of titanium(IV) enolates[7] laid the foundations for their use in SOMO-like transformations without the need for a stoichiometric oxidizing reagent. Zakarian proved the feasibility of such a new approach by developing a new photoredox alkylation of titanium(IV) enolates from chiral *N*-acyl oxazolidinones catalyzed by a ruthenium complex.[8] In this context, the commercially available and persistent radical TEMPO was an appealing reagent to trap chiral titanium(IV) biradical enolates and stereoselectively afford the aminoxylated derivatives. TEMPO had been used as precursor of electrophilic reagents for the stereoselective construction of carbon–oxygen bonds.[9] In contrast, its use in radical like reactions was scarce and restricted to non-stereoselective transformations[10] until Zakarian[11] and our group[12] independently developed the asymmetric oxidation of titanium(IV) enolates of a wide range of chiral *N*-acyl oxazolidinones with TEMPO, which provides the corresponding aminoxylated adducts with good yields and diastereoselectivities (Scheme 2).

We have also reported theoretical insights of this TEMPO-mediated oxidation reinforcing the proof of the valence tauto-

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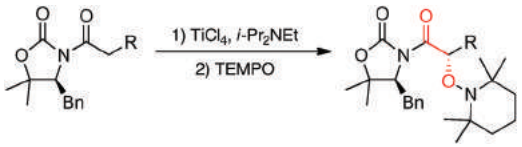
†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds described in the Experimental section. CCDC 1835692. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob01074a

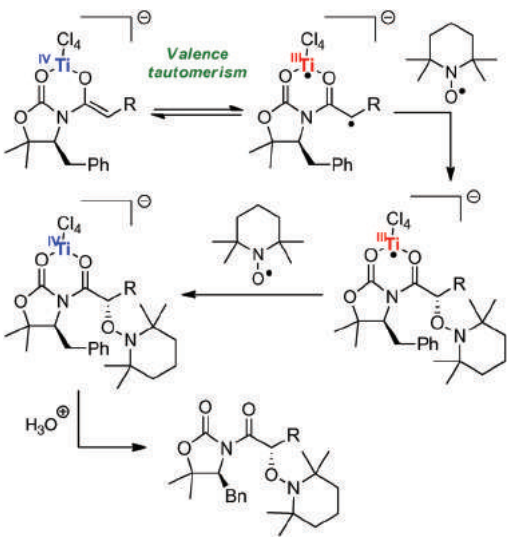


Scheme 2 Stereoselective aminoxylation of titanium(IV) enolates with TEMPO.

merism and the resulting biradical character of titanium(IV) enolates from *N*-acyl oxazolidinones as well as offering a concise explanation of the entire mechanism.[13] Essentially, the process hinges on the radical attack of a first molecule of TEMPO to the Cα position of the biradical form of the titanium(IV) enolate (Scheme 3). This is then followed by a fast oxidation of the resultant titanium(III) complex by a second molecule of TEMPO. Thereby, the high stereocontrol achieved by such transformations may be explained through a chelated titanium(IV) enolate in which the C4-benzyl group favours the approach of the oxidizing agent to the less sterically hindered π-face of the biradical enolate.

Thus, considering the key role played by chiral scaffolds in stereoselective reactions,[14,15] we decided to assess its influence on such oxidations with the aim of identifying other chiral auxiliaries which may able to produce a single diastereomer and be easily removed from the resultant aminoxylated adduct leaving enantiopure synthons. Particularly, we focused our attention on chiral oxazolidinones developed by Evans[16,17] and related five membered heterocycles with a long tradition within stereoselective synthesis (Fig. 1).[18–21]

Herein, we describe a detailed study of the aminoxylation of titanium(IV) enolates derived from a wide array of chiral auxiliaries possessing different oxygen and sulphur patterns and several side chains as well as a further analysis of the scope of the reaction and the final removal of the chiral scaffold.



Scheme 3 Mechanism for the stereoselective aminoxylation of titanium(IV) enolates from chiral *N*-acyl oxazolidinones with TEMPO.

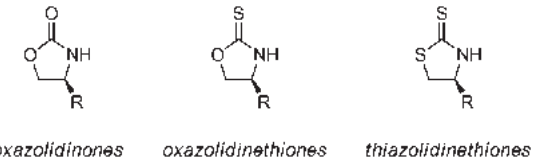


Fig. 1 Five membered cyclic chiral auxiliaries.

Results and discussion

Chiral auxiliary screening

Taking advantage of our own studies on the aminoxylation of titanium(IV) enolates from *N*-acyl oxazolidinones with TEMPO,[12,13] we initially investigated the influence of chiral auxiliaries **1–6** with various combinations of oxygen and sulphur heteroatoms *exo* and *endo* to the heterocycle and bulky groups at C4 (Fig. 2).[22–24] By choosing such a wide range of chiral substrates we envisaged to fully understand the effect both the heteroatoms and the groups at C4 and therefore to find the most effective scaffold for this type of reaction.

To best analyse the isolated effects of such parameters we conducted the aminoxylation of *N*-propanoyl derivatives **1a–6a** (Scheme 4), easily prepared from chiral auxiliaries **1–6**, under the same conditions, more specifically the optimised conditions reported in our previous report.[12] The results of this preliminary examination summarised in Scheme 3 showed a clear trend. Indeed, substitution of the exocyclic oxygen by sulphur both in the isopropyl and the *tert*-butyl series produced a significant improvement of the diastereoselectivity. Moreover, the bulky *tert*-butyl group turned out to be crucial to obtain a single diastereomer; in all cases moving from isopropyl to *tert*-butyl as the C4 group induced a significant increase in the diastereomeric ratio. Particularly, *tert*-butyl *N*-propanoyl oxazolidinethione **5a** (X: S, Y: O, R: *t*-Bu) and thiazolidinethione **6a** (X, Y: S, R: *t*-Bu) were the most appropriate platforms to carry out a completely stereocontrolled oxidation in high yields.

Having identified the crucial role of the exocyclic heteroatom and the C4 alkyl group, we next evaluated the conse-

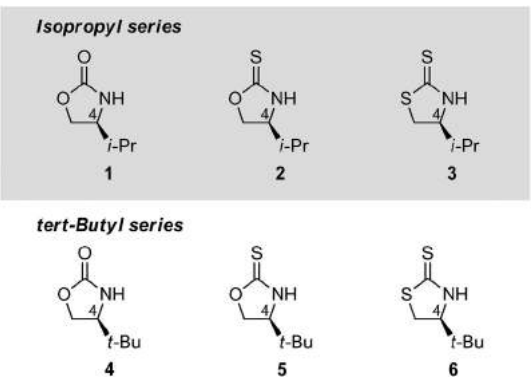
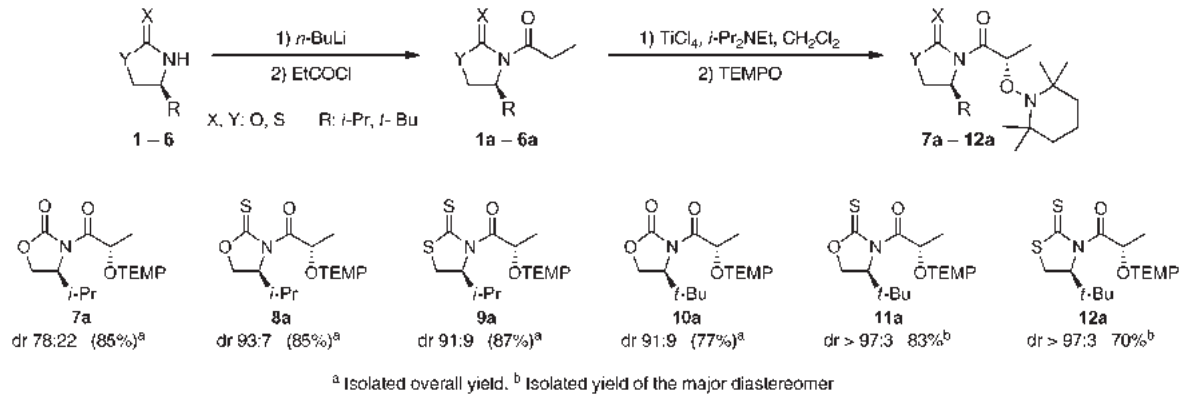


Fig. 2 C4 substituted five membered cyclic chiral auxiliaries.



Scheme 4 Stereoselective aminoxylation of titanium(IV) enolates from *N*-propanoyl C4-substituted chiral auxiliaries **1a–6a** with TEMPO.

quences of placing geminal groups at the C5 position. As we had already described the aminoxylation using chiral auxiliary **14**,[12] in which the oxazolidinone possesses a geminal dimethyl moiety at C5, we next evaluated the outcome of parallel reactions from oxazolidinones and oxazolidinethiones **13–16** shown in Fig. 3.[25]

Thus, *N*-propanoyl derivatives **13a–16a**, easily prepared from chiral auxiliaries **13–16**, were submitted to the previous experimental conditions. The results summarised in Scheme 5 proved the benefit of installing two groups at C5. Indeed, the results from *N*-propanoyl C4 benzyl oxazolidinones **13a** (X: O, R: H) and **14a** (X: O, R: Me) clearly showed that the diastereoselectivity is greatly increased by attaching two geminal methyl groups at C5. Furthermore, the placement of two phenyl groups at this position was also advantageous for the isopropyl oxazolidinethione **15a** (X: S, R: Ph, R^1: i-Pr) since just a single diastereomer **19a** was obtained albeit in a moderate yield (compare **8a** and **19a** in Schemes 4 and 5 respectively). Finally, *N*-propanoyl 5,5-disubstituted oxazolidinethione **16a** (X: S, R, R^1: Ph) demonstrates that a C4 substituent larger than Ph group is required to obtain a single diastereomer (compare **19a** and **20a** in Scheme 5).

All together, these results indicate that only three of the ten different chiral auxiliaries evaluated (oxazolidinethiones **5** and **15**, and thiazolidinethione **6**) give complete control of the newly created stereocentre (see **11a** and **12a** in Scheme 4 and **19a** in Scheme 5). Among all the scaffolds, the *tert*-butyl oxazolidinethione **5** emerges as the most appropriate choice. Certainly, it provides marginally lower yields than the *SuperQuat* auxiliary **14**, but it offers the advantage of giving complete stereocontrol and it is also significantly easier to synthesise starting from readily available *tert*-leucine.‡

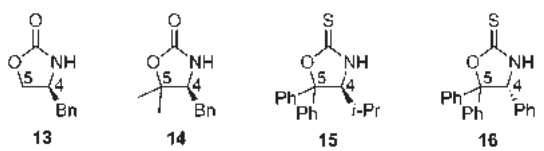


Fig. 3 C4 and C5 substituted chiral auxiliaries.

Scope of the aminoxylation reaction

Since the screening process led us to a new chiral auxiliary, we next reexamined the scope of the radical aminoxylation with TEMPO using this new scaffold. To do this, we varied the acyl group attached to the chiral heterocycle intending to test the impact of sterically hindered R groups as well as others containing various common functional groups. The results summarised in Scheme 6 demonstrated that the simple treatment of titanium(IV) enolates from a wide array of *N*-acyl *tert*-butyl oxazolidinethiones (**5a–g**) with TEMPO afforded a single diastereomer **11** for all the substrates with the exception of α-phenyl derivative **11e**, which was obtained as an equimolecular mixture of two diastereomers in 90% overall yield. Presumably, the higher acidity of the Cα position in *N*-(2-phenylacetyl) oxazolidinethione **5e** precludes its use,[26] in contrast to the high stereocontrol achieved with a parallel reaction from oxazolidinone *SuperQuat* **14**. Importantly, the steric bulk of R nor the presence of a terminal double bond or an ester had a significant influence on the yield. All together, these results highlight the excellent chemo- and diastereoselectivity of the radical-mediated direct oxidation with TEMPO, which permits the obtainment of a single stereoisomer in high yields using straightforward and mild experimental conditions.

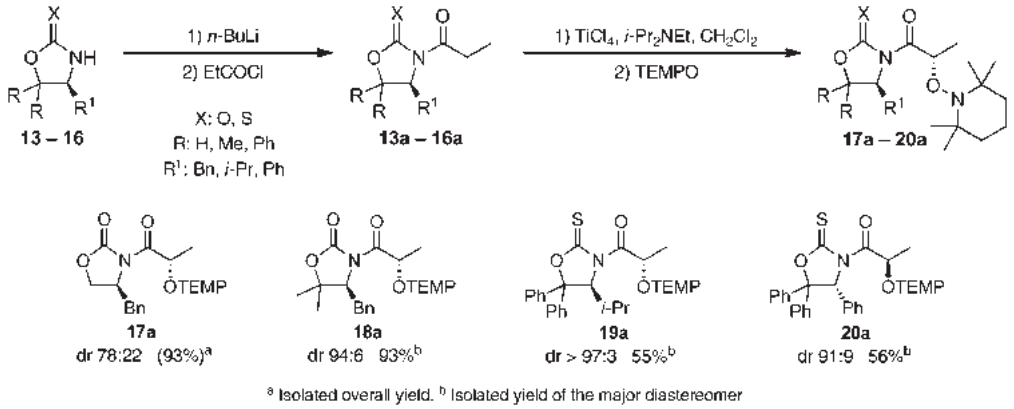
In turn, we took advantage of crystalline properties of adduct **11b** to confirm the configuration of the α stereocentre by X-ray analysis (Fig. 4).§

Removal of the chiral auxiliary

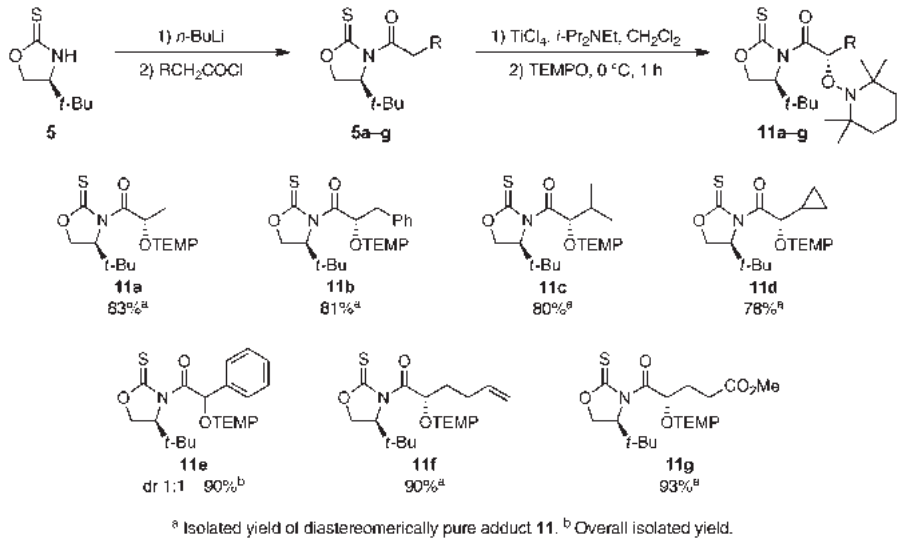
We finally proceeded to investigate the removal of the chiral auxiliary from adducts **11a** and **11b** (Scheme 7) using both the most simple propyl chain and also a more complex example. Initially, we employed $NaBH_4$ to obtain the corresponding

‡ See Experimental section.

§ Crystallographic data for adduct **11b** has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1835692.†



Scheme 5 Stereoselective aminoxylation of titanium(IV) enolates from *N*-propanoyl C4 and C5-substituted chiral auxiliaries **13a–16a** with TEMPO.



Scheme 6 Stereoselective aminoxylation of titanium(IV) enolates from (*S*) *N*-acyl-4-*tert*-butyl-1,3-oxazolidine-2-thiones **5** with TEMPO.

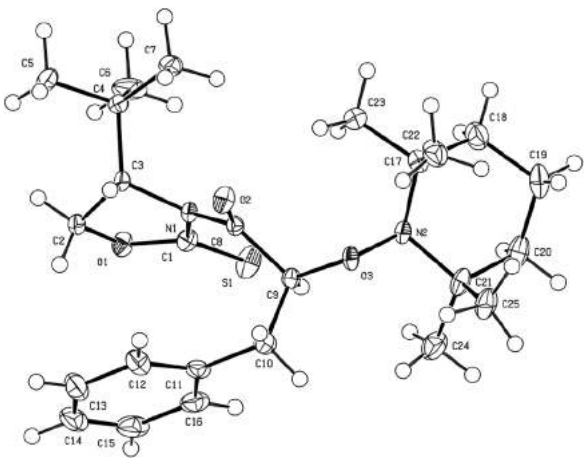
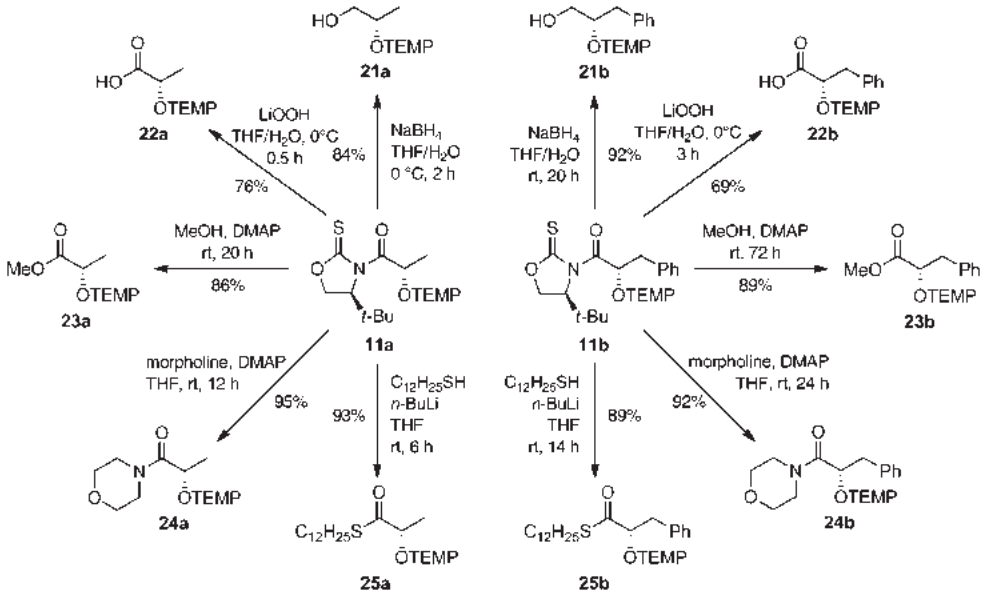


Fig. 4 ORTEP X-ray structure of adduct **11b** (ellipsoid contour probability: 50%).

alcohols **21a** and **21b.** In the case of **11a** the reaction took two hours at 0 °C and yielded 85% of the enantiopure alcohol **21a.** Moving to the more hindered adduct **11b** the reaction required a longer time and at room temperature but also gave an excellent 92% yield of the desired alcohol **21b.** Carboxylic acids **22a** and **22b** were next obtained through common treatment with lithium hydroperoxide in good yields. Methanol was then used to displace the auxiliary and leave an ester. Adducts **11a** and **11b** performed in a similar manner. Both gave excellent yields of methyl esters **23a** and **23b** respectively with **11b** taking longer to complete the reaction. Changing methanol for morpholine allowed us to form amides **24a** and **24b**, again in excellent yields. Finally, displacement of the chiral auxiliary with a thiol to form thioesters **25a** and **25b** also proceeded smoothly and both derivatives were isolated in excellent yields. Remarkably, the recovery of the auxiliary was excellent in all cases, with the minimum amount being 78% and an average recovery of 89% over the ten different reactions.



Scheme 7 Removal of the chiral auxiliary from α-aminoxylated adducts.

Conclusions

In summary, we have comprehensively investigated the role of the chiral auxiliary on the outcome, both in terms of yield and stereocontrol, of the α-aminoxylation of the titanium(IV) enolates from a number of *N*-acylated imide-like derivatives with TEMPO. The 4-*tert*-butyl-1,3-oxazolidine-2-thione auxiliary has been identified as the most appropriate to carry out this reaction since it combines all the favoured characteristics and gives complete control of the newly formed stereocentre with an excellent yield for a wide range of *N*-acylated 4-*tert*-butyl-1,3-oxazolidine-2-thiones. Compared to previous studies that used *SuperQuat*, this is more selective, with a comparable yield and is also much easier to synthesise from commercially available *tert*-leucinol. Finally, straightforward conversion of α-OTEMP adducts affords enantiopure intermediates in excellent yields and with a high recovery of the chiral auxiliary.

Experimental section

General experimental remarks

Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified, when necessary, according to standard procedures. All commercial reagents were used as received. Analytical thin-layer chromatographies (TLC) were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid. R_f values are approximate. Column chromatography were carried out under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Melting points are uncorrected. Specific rotations ($[\alpha]$) were determined at 589 nm and at 20 °C. IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and only the more representative frequencies (ν) are reported. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR); data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (and their corresponding combinations) with coupling constants measured in Hz; when necessary, 2D techniques (COSY and HSQC) were also used to assist with structure elucidation. High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

Synthesis of (*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (5). Neat CS_2 (8.4 mL, 135 mmol) was added to a solution of *tert*-leucinol (5.27 g, 45 mmol) in EtOH (10 mL) at room temperature under N_2. Then, a 2.6 M solution of KOH (26 mL, 67.5 mmol) in 1 : 1 EtOH/H_2O was added and the resulting mixture was heated at reflux for two days. The volatiles were removed and the residue was carefully acidified with 2 M HCl until pH 2. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the organic layers were dried ($MgSO_4$), and concentrated. The resulting solid was purified by column chromatography (CH_2Cl_2) to give 5.50 g (34.5 mmol, 77% yield) of heterocycle **5** as a white solid. Mp: 155–156 °C [lit.[27] Mp: 155.1–155.3 °C]. R_f = 0.65 (CH_2Cl_2). $[\alpha]_D^{20}$ = −11.0 (*c* 1.0, $CHCl_3$) [lit.[27] $[\alpha]_D^{20}$ = −11.6 (*c* 0.92, $CHCl_3$)]. IR (ATR): 3183, 2997, 2960, 1534, 1183 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (br s, 1H), 4.62 (t, J = 9.5 Hz, 1H), 4.46 (dd, J = 9.5, 6.3 Hz, 1H), 3.81 (dd, J = 9.5, 6.3 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 189.6, 71.8, 65.8, 33.6, 20.0. HRMS (+ESI): *m*/*z* calcd for $C_7H_{14}NOS$ $[M + H]^+$: 160.0791; found: 160.0793.

Acylation of 5: synthesis of (*S*)-4-*tert*-butyl-*N*-propanoyl-1,3-oxazolidine-2-thione (5a). A 1.6 M solution of *n*-BuLi in hexanes (2.1 mL, 3.3 mmol) was added dropwise to a solution of **5** (478 mg, 3.0 mmol) in THF (4 mL) at −78 °C under N_2. The reaction mixture was stirred for 10 min and then propanoyl chloride (0.34 mL, 3.9 mmol) was carefully added dropwise. The resulting solution was stirred for 5 min at −78 °C and then allowed to warm to room temperature and stirred for further 1.5 h. The reaction mixture was cooled with an ice-water bath and quenched with sat NH_4Cl (2 mL) and water (5 mL). This mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude reaction mixture was purified by column chromatography (50 : 50 CH_2Cl_2/hexanes) to afford 595 mg (2.8 mmol, 92% yield) of *N*-propanoyl oxazolidinethione **5a** as a colourless oil. R_f = 0.4 (50 : 50 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ = +152.2 (*c* 1.1, $CHCl_3$). IR (ATR): 2967, 1708, 1479, 1402, 1362, 1267, 1179, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.78 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.45 (dd, *J* = 9.5, 1.7 Hz, 1H), 4.34 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.38 (dq, *J* = 18.1, 7.2 Hz, 1H), 3.29 (dq, *J* = 18.1, 7.2 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.94 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.0, 174.9, 69.2, 65.1, 36.1, 31.1, 25.8, 8.9. HRMS (+ESI): *m*/*z* calcd for $C_{10}H_{18}NO_2S$ $[M + H]^+$: 216.1053; found: 216.1058.

General aminoxylation procedure

Neat $TiCl_4$ (121 μL, 1.1 mmol, 1.1 equiv.) was added dropwise to a solution of the acylated chiral auxiliary (1 mmol, 1 equiv.) in CH_2Cl_2 (4 mL) at 0 °C under N_2 and the resultant mixture was stirred for 5 min. Then, i-Pr_2NEt (192 μL, 1.1 mmol, 1.1 equiv.) was added and the mixture was further stirred for 30 min. A solution of TEMPO (328 mg, 2.1 mmol, 2.1 equiv.) in CH_2Cl_2 (0.5 mL + 0.5 mL) was added *via* cannula and the reaction mixture was stirred for 1 h, quenched with sat NH_4Cl (2 mL), and stirred vigorously for 10 min. It was then diluted in water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated to yield the crude product. Column chromatography was then conducted to yield the isolated product.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy) propanoyl]-1,3-oxazolidine-2-thione (11a). Starting from (*S*) 4-*tert*-butyl-*N*-propanoyl-1,3-oxazolidine-2-thione (**5a**, 215 mg, 1.0 mmol) diastereomerically pure adduct **11a** (308 mg, 0.83 mmol, 83% yield) was isolated as a white solid after chromatographic purification (60 : 40 CH_2Cl_2/hexanes). Mp: 130–131 °C. R_f = 0.3 (60 : 40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ = +84.0 (*c* 1.0, $CHCl_3$). IR (ATR): 2970, 2926, 1717, 1178, 1357, 1138, 943, 800, 601 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.57 (q, *J* = 6.8 Hz, 1H), 4.66 (dd, *J* = 7.4, 1.4 Hz, 1H), 4.45 (dd, *J* = 9.5, 1.4 Hz, 1H), 4.28 (dd, *J* = 9.5, 7.4 Hz, 1H), 1.50–1.15 (m, 18H), 1.41 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 186.9, 175.3, 79.4, 69.2, 66.0, 59.6, 40.2, 36.1, 34.0, 26.0, 20.2, 19.3, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{35}N_2O_3S$ $[M + H]^+$: 371.2363; found: 371.2359.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-3-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoyl]-1,3-oxazolidine-2-thione (11b). Starting from (*S*) 4-*tert*-butyl-*N*-(3-phenylpropanoyl)-1,3-oxazolidine-2-thione (**5b**, 291 mg, 1.0 mmol) diastereomerically pure adduct **11b** (361 mg, 0.81 mmol, 81% yield) was isolated as a white solid after chromatographic purification (CH_2Cl_2). Mp: 138–139 °C. R_f = 0.8 (CH_2Cl_2). $[\alpha]_D^{20}$ = +87.0 (*c* 1.0, $CHCl_3$). IR (ATR): 2962, 2922, 2862, 1713, 1479, 1368, 1349, 1308, 1182, 1149 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.15 (m, 5H), 7.00 (dd, *J* = 10.7, 6.0 Hz, 1H), 3.97–3.91 (m, 2H), 3.47 (dd, *J* = 12.6, 6.0 Hz, 1H), 2.92–2.85 (m, 2H), 1.57–1.13 (m, 18H), 0.85 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.3, 175.1, 135.3, 129.6, 128.4, 126.9, 80.8, 68.7, 66.7, 59.9, 40.4, 40.2, 35.9, 34.1, 33.5, 26.1, 20.2, 20.1, 17.2. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{39}N_2O_3S$ $[M + H]^+$: 447.2676; found: 447.2682.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-3-methyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanoyl]-1,3-oxazolidine-2-thione (11c). Starting from (*S*) 4-*tert*-butyl-*N*-(3-methylbutanoyl)-1,3-oxazolidine-2-thione (**5c**, 243 mg, 1.0 mmol) diastereomerically pure adduct **11c** (320 mg, 0.80 mmol, 80% yield) was isolated as a white solid after chromatographic purification (CH_2Cl_2). Mp: 111–112 °C. R_f = 0.7 (CH_2Cl_2). $[\alpha]_D^{20}$ = +97.0 (*c* 1.0, $CHCl_3$). IR (ATR): 2962, 2929, 1698, 1468, 1349, 1301, 1171, 1145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 5.4 Hz, 1H), 4.62 (dd, *J* = 7.3, 1.3 Hz, 1H), 4.44 (dd, *J* = 9.5, 1.3 Hz, 1H), 4.21 (dd, *J* = 9.5, 7.3 Hz, 1H), 2.49–2.36 (m, 1H), 1.63–1.09 (m, 18H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (s, 9H), 0.90 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.6, 173.0, 82.3, 69.2, 66.7, 59.8, 40.4, 36.2, 34.2, 31.7, 26.2, 25.8, 22.4, 22.3, 20.3, 17.9, 17.1, 16.8. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{39}N_2O_3S$ $[M + H]^+$: 399.2676; found: 399.2679.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-2-cyclopropyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)acetyl]-1,3-oxazolidine-2-thione (11d). Starting from (*S*) 4-*tert*-butyl-*N*-(2-cyclopropylacetyl)-1,3-oxazolidine-2-thione (**5d**, 241 mg, 1.0 mmol) diastereomerically pure adduct **11d** (308 mg, 0.78 mmol, 78% yield) was isolated as a white solid after chromatographic purification (95 : 5 CH_2Cl_2/EtOAc). Mp: 107–108 °C. R_f = 0.4 (CH_2Cl_2). $[\alpha]_D^{20}$ = +112.1 (*c* 1.0, $CHCl_3$). IR (ATR): 2958, 2925, 1716, 1483, 1353, 1316, 1182, 1138, 949 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, *J* = 8.4 Hz, 1H), 4.64 (dd, *J* = 7.4, 1.4 Hz, 1H), 4.46 (dd, *J* = 9.5, 1.4 Hz, 1H), 4.26 (dd, *J* = 9.5, 7.4 Hz, 1H), 1.47–1.15 (m, 19H), 0.97 (s, 9H), 0.71–0.56 (m, 2H), 0.54–0.45 (m, 1H), 0.29–0.21 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.0, 172.7, 83.1, 69.1 (×2), 66.1, 64.9, 59.7, 42.3, 40.1, 36.0 (×2), 25.9, 25.7, 17.1, 14.6, 6.8, 4.3, 4.2, 1.4. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{37}N_2O_3S$ $[M + H]^+$: 397.2519; found: 397.2524.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-5-hexenoyl]-1,3-oxazolidine-2-thione (11f). Starting from (*S*) 4-*tert*-butyl-*N*-(5-hexenoyl)-1,3-oxazolidine-2-thione (**5f**, 255 mg, 1.0 mmol) diastereomerically pure adduct **11f** (368 mg, 0.90 mmol, 90% yield) was isolated as a white solid after chromatographic purification. Mp: 94–95 °C. R_f = 0.8 (CH_2Cl_2). $[\alpha]_D^{20}$ = +96.9 (*c* 1.0, $CHCl_3$). IR (ATR): 2966, 2922, 2862, 1716, 1475, 1360, 1327, 1297, 1179, 1134 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.66 (dd, *J* = 7.0, 3.2 Hz, 1H), 5.83–5.71 (m, 1H), 5.02–4.96 (m, 1H), 4.98–4.91 (m, 1H), 4.63 (dd, *J* = 7.3, 1.3 Hz, 1H), 4.45 (dd, *J* = 9.5, 1.3 Hz, 1H), 4.26 (dd, *J* = 9.5, 7.3 Hz, 1H),

2.23–2.11 (m, 2H), 2.02–1.90 (m, 1H), 1.89–1.78 (m, 1H), 1.47 (br s, 6H), 1.18 (s, 6H), 1.16 (s, 6H), 0.99 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 186.9, 173.7, 137.9, 114.7, 81.2, 69.2, 66.5, 40.3, 36.2, 31.1, 27.4, 26.1, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{39}N_2O_3S$ $[M + H]^+$: 411.2676; found: 411.2680.

(*S*)-4-*tert*-Butyl-*N*-[(*S*)-5-methoxy-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-5-oxopentanoyl]-1,3-oxazolidine-2-thione (11g). Starting from (*S*) 4-*tert*-butyl-*N*-(5-methoxy-5-oxopentanoyl)-1,3-oxazolidine-2-thione (**5g**, 287 mg, 1.0 mmol) diastereomerically pure adduct **11g** (413 mg, 0.93 mmol, 93% yield) was isolated as a white solid after chromatographic purification (95 : 5 CH_2Cl_2/EtOAc). Mp: 104–105 °C. R_f = 0.4 (CH_2Cl_2). $[\alpha]_D^{20}$ = +102.5 (*c* 1.0, $CHCl_3$). IR (ATR): 2929, 1731, 1713, 1360, 1320, 1297, 1167, 1142, 934 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.54–4.48 (m, 1H), 4.50–4.45 (m, 1H), 4.45–4.40 (m, 1H), 3.61 (s, 3H), 2.61–2.51 (m, 1H), 2.41–2.30 (m, 2H), 2.20–2.10 (m, 1H), 1.47 (s, 6H), 1.17 (s, 6H), 1.15 (s, 6H), 0.96 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 187.3, 173.9, 173.1, 80.1, 69.3, 66.4, 51.4, 40.0, 35.8, 26.4, 25.9, 25.6, 16.9. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{39}N_2O_5S$ $[M + H]^+$: 443.2574; found: 443.2576.

Removal of the chiral auxiliary

(*S*)-2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)-1-propanol (21a). A solution of **11a** (74 mg, 0.20 mmol) in THF (1.5 mL) was added to a solution of $NaBH_4$ (31 mg, 0.8 mmol, 4 equiv.) in 40 : 1 THF/H_2O (1.4 mL) at 0 °C under N_2 and the resultant mixture was stirred at room temperature for 2 h. The mixture was then diluted with Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), and concentrated. The crude was purified by column chromatography (90 : 10 hexanes/EtOAc) to give 36 mg (0.17 mmol, 84% yield) of pure alcohol **21a** as a colourless oil. The aqueous phase was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 34 mg (90%) of pure auxiliary **5**. R_f = 0.2 (90 : 10 hexanes/EtOAc). $[\alpha]_D^{20}$ = −35.6 (*c* 1.0, $CHCl_3$). IR (ATR): 3376 (br), 2972, 2928, 1453, 1375, 1162, 1131, 1043 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (s br, 1H), 4.38 (dqd, *J* = 9.3, 6.3, 2.2 Hz, 1H), 3.90 (dd, *J* = 11.9, 9.3 Hz, 1H), 3.57 (dd, *J* = 11.9, 2.2 Hz, 1H), 1.60–1.25 (m, 6H), 1.32 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 76.8, 69.3, 61.1, 59.9, 40.2, 39.9, 34.5, 32.6, 20.4, 20.3, 17.2, 16.0. HRMS (ESI): *m*/*z* calcd $C_{12}H_{26}NO_2$ $[M + H]^+$: 216.1958; found: 216.1964.

(*S*)-3-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-1-propanol (21b). A solution of **11b** (58 mg, 0.13 mmol) in THF (1.5 mL) was added to a solution of $NaBH_4$ (31 mg, 0.8 mmol, 6.15 equiv.) in 40 : 1 THF/H_2O (1.4 mL) at 0 °C under N_2 and the resultant mixture was stirred at room temperature for 20 h. The mixture was then diluted with Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (95 : 5 CH_2Cl_2/EtOAc) to give 35 mg (0.12 mmol, 92% yield) of pure alcohol **21b** as colourless oil. The aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 20 mg (95%) of pure auxiliary **5**. R_f = 0.5 (95 : 5 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ = −62.1 (*c* 1.0, $CHCl_3$). IR (ATR): 3303 (br), 2923, 1451, 1359, 1131, 1027, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.18 (m, 5H), 5.67 (br s, 1H), 4.47 (dddd, *J* = 9.4, 7.2, 5.5, 2.0 Hz, 1H), 3.97 (dd, *J* = 11.9, 9.4 Hz, 1H), 3.65 (dd, *J* = 11.9, 2.0 Hz, 1H), 2.72 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.59 (dd, *J* = 13.7, 5.5 Hz, 1H), 1.58–1.42 (m, 6H), 1.47 (s, 3H), 1.30 (s, 3H), 1.12 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.3, 129.4, 128.1, 126.1, 81.2, 67.8, 61.5, 60.0, 40.3, 39.9, 37.6, 34.5, 32.4, 29.7, 20.6, 20.2, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{30}NO_2$ $[M + H]^+$: 292.2271; found: 292.2278.

(*S*)-2-[(2,2,6,6-Tetramethylpiperidin-1-yl)oxy]propanoic acid (22a). A mixture of **11a** (74 mg, 0.20 mmol), 30% H_2O_2 (90 μL, 0.8 mmol, 4 equiv.), and LiOH (10 mg, 0.42 mmol, 2 equiv.) in 3 : 1 THF/H_2O (4 mL) was stirred at 0 °C for 30 min. A sat solution of $Na_2S_2O_3$ (2 mL) was added and the volatiles were removed *in vacuo*. The solution was acidified with 2 M HCl and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (from CH_2Cl_2 to 65 : 35 CH_2Cl_2/EtOAc) to give 27 mg (84%) of pure auxiliary **5** and 35 mg (0.15 mmol, 76% yield) of carboxylic acid **22a** as a colourless oil. R_f = 0.3 (65 : 35 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ = −39.8 (*c* 1.0, $CHCl_3$). IR (ATR): 2974, 2927, 2873, 1720, 1454, 1372, 1359, 1239, 1128, 1077, 935, 783 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (q, *J* = 6.7 Hz, 1H), 1.73–1.63 (m, 5H), 1.54–1.48 (m, 1H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.3, 62.9, 62.5, 39.2, 39.0, 30.9, 30.1, 29.7, 20.9 (×2), 17.0, 16.4. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{24}NO_3$ $[M + H]^+$: 230.1751; found: 230.1759.

(*S*)-3-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoic acid (22b). A mixture of **11b** (89 mg, 0.20 mmol), 30% H_2O_2 (90 μL, 0.8 mmol, 4 equiv.), and LiOH (11 mg, 0.42 mmol, 2 equiv.) in 3 : 1 THF/H_2O (4 mL) was stirred at 0 °C for 3 h. A sat solution of $Na_2S_2O_3$ (2 mL) was added and the volatiles were removed *in vacuo*. The solution was acidified with 2 M HCl and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (65 : 35 CH_2Cl_2/EtOAc) to give 25 mg (78%) of pure auxiliary **5** and 42 mg (0.14 mmol, 69% yield) of carboxylic acid **22b** as a colourless oil. R_f = 0.4 (65 : 35 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ = −68.5 (*c* 1.0, $CHCl_3$). IR (ATR): 2971, 2927, 2870, 1717, 1454, 1372, 1233, 1131, 1027, 751, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.20 (m, 5H), 4.69 (dd, *J* = 8.5, 3.4 Hz, 1H), 3.46 (dd, *J* = 14.6, 8.5 Hz, 1H), 3.14 (dd, *J* = 14.6, 3.4 Hz, 1H), 1.68–1.59 (m, 5H), 1.50–1.44 (m, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.1, 137.6, 129.6, 128.2, 126.5, 80.5, 63.1, 62.8, 39.3, 39.2, 37.6, 31.2, 29.9, 21.0, 20.8, 16.3. HRMS (ESI): *m*/*z* calcd for $C_{18}H_{28}NO_3$ $[M + H]^+$: 306.2064; found: 306.2070.

Methyl (*S*)-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propanoate (23a). A solution of **11a** (74 mg, 0.20 mmol) and DMAP (11 mg, 80 μmol) in methanol (5 mL) was stirred for 20 h at room temperature under N_2. The volatiles were removed and

the resultant residue was diluted in Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (90 : 10 hexanes/EtOAc) to give 42 mg (0.17 mmol, 86% yield) of pure ester **23a** as a colourless oil. The aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 28 mg (88%) of pure auxiliary **5**. R_f = 0.4 (90 : 10 hexanes/EtOAc). $[\alpha]_D^{20}$ = −56.3 (*c* 1.0, $CHCl_3$). IR (ATR): 2931, 1741, 1452, 1374, 1361, 1262, 1243, 1197, 1131, 1078, 973, 941, 788 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (q, *J* = 6.9 Hz, 1H), 3.71 (s, 3H), 1.49–1.38 (m, 6H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.18 (br s, 3H), 1.12 (br s, 6H), 1.02 (br s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.5, 81.6, 60.1, 59.5, 51.4, 40.3, 40.1, 33.6, 32.9, 20.2, 20.0, 18.1, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{26}NO_3$ $[M + H]^+$: 244.1907; found: 244.1901.

Methyl (*S*)-3-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy) propanoate (23b). A solution of **11b** (89 mg, 0.2 mmol) and DMAP (11 mg, 80 μmol) in methanol (5 mL) was stirred for 72 h at room temperature under N_2. The volatiles were removed and the resultant residue was diluted in Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (50 : 50 CH_2Cl_2/hexanes) to give 57 mg (0.18 mmol, 89% yield) of pure ester **23b** as a colourless oil. The aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 30 mg (94%) of pure auxiliary **5**. R_f = 0.5 (50 : 50 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ = −17.1 (*c* 1.0, $CHCl_3$). IR (ATR): 2946, 2911, 1736, 1366, 1166, 1043, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.13 (m, 5H), 4.45 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.50 (s, 3H), 3.25 (dd, *J* = 13.2, 5.5 Hz, 1H), 2.99 (dd, *J* = 13.2, 10.2 Hz, 1H), 1.49–0.99 (m, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 173.1, 136.0, 129.4, 128.3, 126.6, 86.6, 60.6, 59.5, 51.1, 40.3, 40.2, 38.5, 33.5, 32.9, 20.3, 20.1, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{30}NO_3$ $[M + H]^+$: 320.2220; found: 320.2225.

***N*-[2(*S*)-(2,2,6,6-Tetramethylpiperidin-1-yloxy)propanoyl] morpholine (24a).** A solution of **11a** (74 mg, 0.20 mmol), morpholine (69 μL, 0.78 mmol, 3.9 equiv.), and DMAP (14 mg, 0.1 mmol) in THF (2 mL) was stirred for 12 h at room temperature under N_2. The volatiles were then removed and the residue was purified by column chromatography (from CH_2Cl_2 to 90 : 10 CH_2Cl_2/EtOAc) to afford 57 mg (0.19 mmol, 95% yield) of pure amide **24a** as a white solid and 31 mg (97%) of chiral auxiliary **5**. Mp: 57–58 °C. R_f = 0.3 (90 : 10 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ = −3.0 (*c* 1.0, $CHCl_3$). IR (ATR): 2949, 2851, 1644, 1464, 1429, 1233, 1109, 568 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.61 (q, *J* = 7.1 Hz, 1H), 3.77–3.53 (m, 8H), 1.60–1.05 (m, 18H), 1.44 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.3, 83.0, 66.9, 66.6, 59.6, 46.1, 42.1, 40.2, 40.1, 33.9, 33.2, 29.7, 20.6, 20.3, 18.5, 17.0. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{31}N_2O_3$ $[M + H]^+$: 299.2329; found: 299.2334.

***N*-[(*S*)-[3-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy) propanoyl]morpholine (24b).** A solution of **11b** (89 mg, 0.20 mmol), morpholine (69 μL, 0.78 mmol, 3.9 equiv.), and DMAP (14 mg, 0.1 mmol 0.5 equiv.) in THF (2 mL) was stirred for 24 h at room temperature under N_2. The volatiles were then removed and the residue was purified by column chromatography (from CH_2Cl_2 to 80 : 20 CH_2Cl_2/EtOAc) to afford 69 mg (0.18 mmol, 92% yield) of pure amide **24b** as a white solid and 26 mg (81%) of chiral auxiliary **5**. Mp: 148–149 °C. R_f = 0.7 (90 : 10 CH_2Cl_2/EtOAc). $[\alpha]_D^{20}$ = −4.7 (*c* 1.0, $CHCl_3$). IR (ATR): 2930, 1632, 1448, 1239, 1109, 1024, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.17 (m, 5H), 4.73 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.64–3.53 (m, 2H), 3.39 (ddd, *J* = 11.5, 5.5, 3.1 Hz, 1H), 3.32–3.21 (m, 4H), 3.10 (dd, *J* = 12.5, 11.0 Hz, 1H) 3.05–3.00 (m, 1H), 2.74 (ddd, *J* = 11.5, 7.8, 2.9 Hz, 1H), 1.62–1.02 (m, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.1, 136.5, 129.7, 128.4, 126.7, 82.6, 66.5, 66.1, 60.4, 59.5, 46.0, 41.7 40.5, 40.3, 39.0, 33.9, 33.3 20.4, 20.2, 17.1. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{35}N_2O_3$ $[M + H]^+$: 375.2642; found: 375.2651.

***S*-Dodecyl (*S*)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanethioate (25a).** A 1.6 M solution of *n*-BuLi in hexanes (38 μL, 60 μmol) was added to a solution of dodecanethiol (145 μL, 0.6 mmol) in THF (2 mL) at 0 °C under N_2 and the resultant solution was stirred for 15 min. Then, a solution of **11a** (74 mg, 0.20 mmol) in THF (2 × 0.75 mL) was added and the reaction mixture was stirred at room temperature for 6 h. It was diluted with Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (70 : 30 hexanes/CH_2Cl_2) to give 77 mg (0.19 mmol, 93% yield) of pure thioester **25a** as a colourless oil. The aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 30 mg (94%) of pure chiral auxiliary **5**. R_f = 0.2 (70 : 30 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ = −5.8 (*c* 1.0, $CHCl_3$). IR (ATR): 2922, 2852, 1681, 1453, 1361, 1132, 957, 922, 573 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.42 (q, *J* = 6.9 Hz, 1H), 2.85 (t, *J* = 7.4 Hz, 2H), 1.67–0.99 (m, 41H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 203.4, 87.1, 60.5, 59.5, 40.3, 34.4, 33.5, 31.9, 29.6 (×3), 29.5, 29.4, 29.3, 29.1, 28.9, 28.1, 22.7, 20.3, 19.4, 17.1, 14.1. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{48}NO_2S$ $[M + H]^+$: 414.3400; found: 414.3390.

***S*-Dodecyl (*S*)-[3-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)]propanethioate (25b).** A 1.6 M solution of *n*-BuLi in hexanes (38 μL, 60 μmol) was added to a solution of dodecanethiol (145 μL, 0.6 mmol) in THF (2 mL) at 0 °C under N_2 and the resultant solution was stirred for 15 min. Then, a solution of **11b** (89 mg, 0.20 mmol) in THF (2 × 0.75 mL) was added and the reaction mixture was stirred at room temperature for 14 h. It was diluted with Et_2O (20 mL), washed with 1 M NaOH (3 × 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (80 : 20 hexanes/CH_2Cl_2) to give 87 mg (0.18 mmol, 89% yield) of pure thioester **25b** as a colourless oil. The aqueous layer was acidified and extracted with CH_2Cl_2 (3 × 20 mL) to recover 28 mg (88%) of pure chiral auxiliary **5**. R_f = 0.4 (80 : 20 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ = +21.1 (*c* 1.0, $CHCl_3$). IR (ATR): 2921, 2850, 1686, 1451, 1362, 1130, 934, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.16 (m, 5H), 4.53 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.30 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.01 (dd, *J* = 13.5, 9.2 Hz, 1H), 2.74 (t, *J* = 7.3 Hz, 2H),

1.54–0.85 (m, 40H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 201.1, 136.4, 129.7, 128.2, 126.5, 91.4, 40.5, 38.8, 31.9, 29.7, 29.6 (×2), 29.5, 29.4, 29.1, 28.8, 28.4, 22.7, 20.3, 20.2, 17.1, 14.1. HRMS (ESI): m/z calcd for $C_{30}H_{52}NO_2S$ $[M + H]^+$: 490.3713, found: 490.3715.

Conflicts of interest

There are no conflicts to declare.

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