DIPLOMARBEIT / DIPLOMA THESIS

Titel der Diplomarbeit / Title of the Diploma Thesis

„Synthesis of highly functionalised asymmetric quaternary carbon centres from α-substituted cyanoacetates and activated bromides under phase-transfer catalysis conditions"

verfasst von / submitted by

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Preamble

Acknowledgement

Foremost I want to thank my supervisor ao. Univ.-Prof. Mag. Dr. Michael Widhalm for the opportunity to work with him and learn from him. He not only gave me the chance to better my skills as a scientist but also deepen my love for chemistry.

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Thank you Christian Knittl-Frank, BSc MSc and Dr. Katharina Pallitsch, Bakk. MSc for your big help in writing this thesis and your patience with my many questions.

I would also like to thank my colleagues and friends for their patience and motivation through this time. I cannot name you all but I could not have done this without you.

To my parents, for without them this amazing experience could not have been possible. I love you very much.

List of Abbreviations

cat catalyst

COSY correlation spectroscopy

d doublet

DCM dichloromethane

DIBAL diisobutylaluminium hydride

DMF dimethyl formamide

e.e. enantiomeric excess

ESI electrospray ionization

EtOAc ethyl ethanoate

GC gas chromatography

HMBC heteronuclear multiple bond correlation

HMQC heteronuclear single quantum coherence

HPLC high performance liquid chromatography

HRMS high resolution mass spectrometry

m multiplet

MPLC medium pressure liquid chromatography

NMR nuclear magnetic resonance

NOESY nuclear overhauser enhancement spectroscopy

PE petroleum ether

PTC phase-transfer catalysis

q quartet

r.t. room temperature

RCM ring closing metathesis

s singlet

t triplet

TBAB tetrabutylammonium bromide

THF tetrahydrofuran

TLC thin layer chromatography

TMS tetramethylsilane

TOF time of flight

tol toluene

UV ultraviolet

Contents

Chapter 1
Introduction

1.1 Amino acids

α-Amino acids are organic molecules and part of the compound class referred to as amino acids. This group of compounds includes all compounds carrying a carboxylic acid and an amine functional group. However, compounds that carry acidic functional groups like sulphuric and phosphoronic acids $(R_3N^+-(R^1R^2C-)_n\,SO_3^-; R_3N^+-(R^1R^2C-)_n\,P(OH)O_2^-)$ are included in the definition of α-amino acids.[1] During the course of this work I will generally focus on α- and β-amino carboxylic acids. These comprise an carboxylic acid, an amine and one or two side chains of varying types (Figure 1.2).
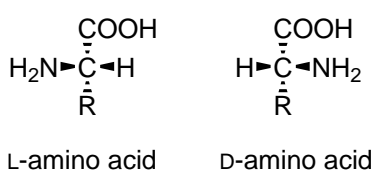
Figure 1.1 | General structure of α-amino acids
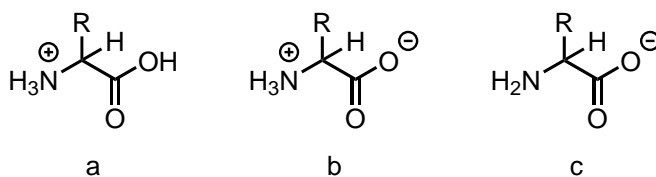
Figure 1.2 | Different ionic forms of α-amino acids

Figure 1.1 clearly shows amino acids with different substituents at the α-carbon atom next to the carboxylic acid can exist as two enantiomers. Yet, this is an inaccurate representation because amino acids do not occur as uncharged molecules. Depending on the pH α-amino acids can present as one of three forms (Figure 1.2). In case of a pH below the pK_a of the carboxylate, the amino group is protonated (a); above the pK_b of the amino group, the acid is deprotonated (c) and if the pH is between these two pK values, the amino acid is present in its zwitterionic form – carrying both a negative and a positive charge (b).

The configuration of α-amino acids often goes along with distinct properties or biological activities for the two enantiomers. The enantiomers of free amino acids show for example different characteristics of taste. L-prolin for instance is described as sweeter than D-prolin.[2]

Amino acids can be further divided into two categories: natural and synthetic. The former are compounds that are of biogenic nature and can be either proteinogenic or non-proteinogenic. Proteinogenic α-amino acids are the main building blocks of proteins. Proteinogenic means

that these amino acids are capable of being used in ribosomal synthesis. Whereas the latter are compounds of secondary metabolic origin found in fungi, bacteria, animals and plants with varied functions. Today, around 800 natural α-amino acids have been discovered and their number is still steadily growing.[3,4] However, only 20 of those α-amino acids have a role in protein bio-synthesis.
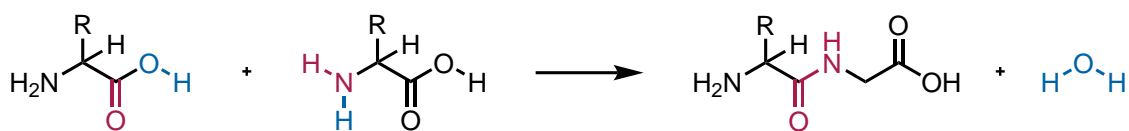
Scheme 1.1 | Formation of the peptide bond

Peptides and proteins are distinguished through the number of linked amino acids. Oligopeptides refer to chains up to ten amino acids, polypeptides to chains longer than ten amino acids and proteins usually contain chains over 100 amino acids. Both peptides and proteins are generated by amide/peptide bond formation from amino acids (Scheme 1.1).

Usually, proteinogenic amino acids only occur in their L-configuration to form proteins. These L-configured, chiral molecules induce the formation of a right-handed α-helix form of proteins.[1] However, free natural proteinogenic and non-proteinogenic α-amino acids can also be D-configured. Both L- and D-forms are fundamental for diverse biochemical processes in all organisms including the human's. Amino acids like arginine, glutamine and glutamate (in L-configuration) play important roles in signalling pathways and are therefore essential for regulating gene expression, nutrient metabolism, oxidative defence and intracellular protein turnover.[5]

Natural α-amino acids are manufactured in huge amounts and used as food additives and as cheap starting materials for the synthesis of other, more complex chiral molecules. Up to now thousands of synthetic α-amino acids, not found in nature, have been synthesised in chemical laboratories. There is also a high demand for non-natural, specifically labelled amino acids or derivatives of the latter. Thus, there are several known synthetic strategies to generate such new α-amino acids. Possible synthetic procedures to access racemic α-amino acids include the Strecker synthesis (Scheme 1.2) or the Erlenmeyer synthesis via oxazolone (Scheme 1.3). However, usually single enantiomers are desired which are accessible by optical resolution of racemates or asymmetric syntheses (Section 1.2).
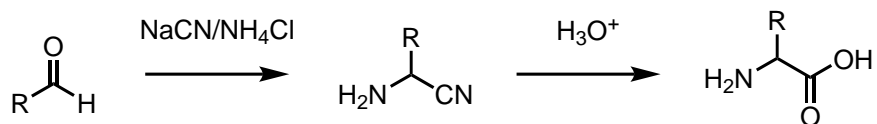
Scheme 1.2 | Strecker synthesis to access racemic α-amino acids
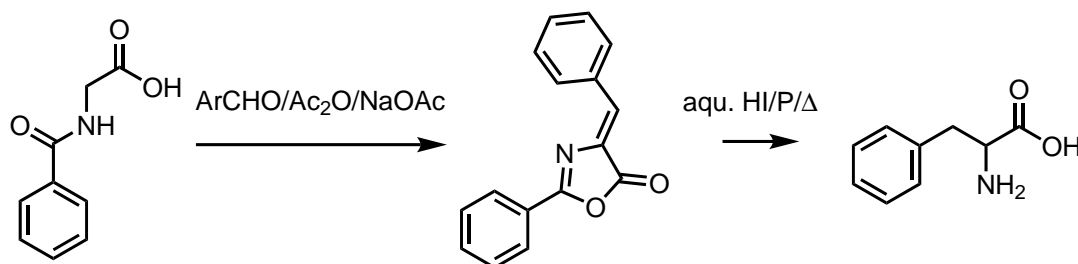
Scheme 1.3 | Erlenmeyer synthesis to access racemic α-amino acids

Racemic α-amino acids can be resolved to give pure enantiomers. The separation of enantiomers can be achieved by derivatisation with an optically active reagent, followed by separation of the diastereomers by crystallisation and removal of the derivatisation agent. Another possibility, especially for α-amino acids, is the separation via enantioselective enzymes such as aminoacylases or other hydrolases (Scheme 1.4).[6]
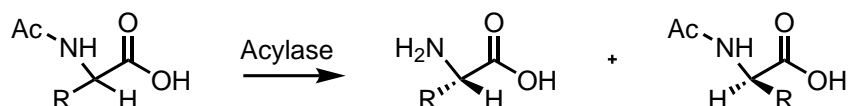
Scheme 1.4 | Optical resolution of α-acyl-amino acid using the enzyme aminoacylase (acylase I)

Amino acids have a very broad reactivity range. Aside from reactions of the side chain of the amino acids, reactions of the amino and carboxyl group are often carried out using very similar and reliable procedures for most amino acids (Scheme 1.5). Reactions of the amino group, the carboxy group or both groups can be performed. Acylation (a), sulphonylation (b) and thioacylation (c) represent reversible reactions of the amino group, whereas the Schiff base formation (d) is an irreversible process. Esterification (e) and acyl halide formation (f) (that can be converted into L-α-acylamido-ketones (g)) are possible reactions of the carboxy group. An example of a reaction involving both, the amino and the carboxy group, is the azalactone formation (h).[1]
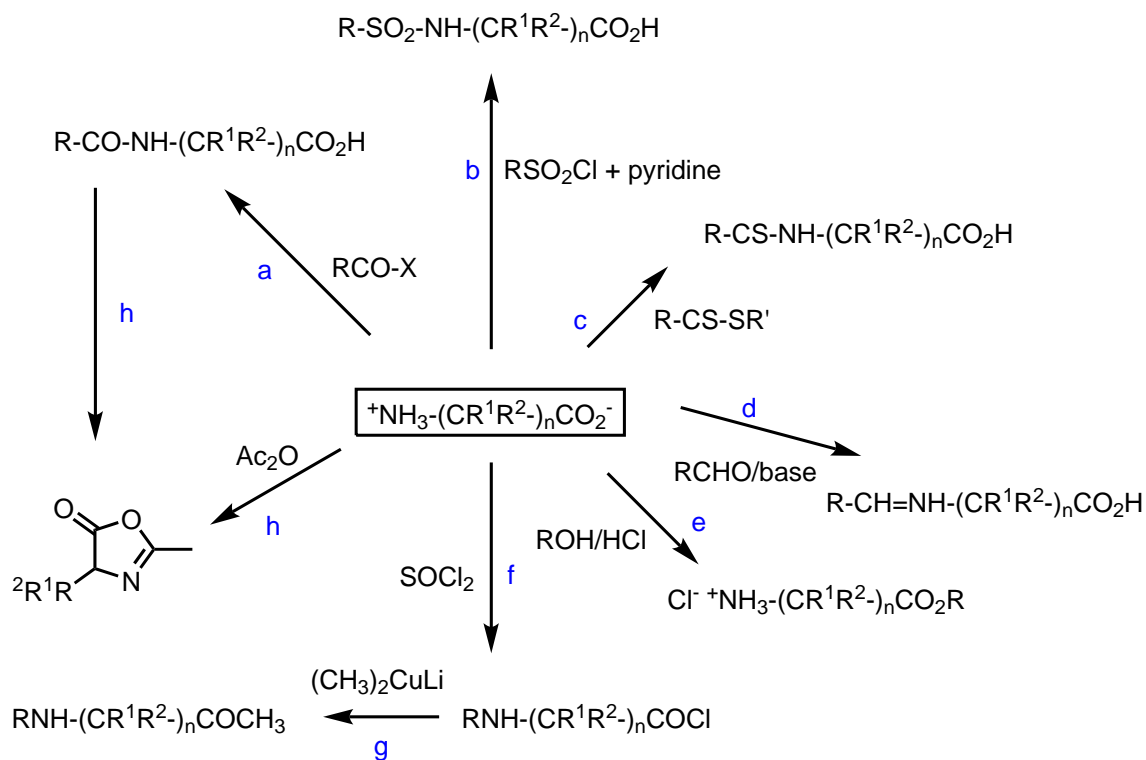
Scheme 1.5 | Selected standard reactions of amino acids

It is known that there are amino acids that carry their amino and carboxy functions on different carbons of their molecular framework. These β-, γ- or higher amino acids have been found in nature as well though they are less common than α-amino acids. Aspartic acid or glutamic acid can be classified as either α- or β-amino acid or α- or γ-amino acid respectively (see Figure 1.3).

Figure 1.3 | ʟ-α/β-Aspartic acid and ʟ-α/γ-glutamic acid

Figure 1.4 | β-Alanine

Some of these naturally occurring higher amino acids can be found as free amino acids, in peptides or as other derivatives. They too exhibit extraordinary biological activities and therefore a scientific interest is displayed.[1,7]

1.2 Asymmetric synthesis

Chiral compounds cannot be superimposed unto their mirror image. This trait is fundamental to many three-dimensional objects. When this applies, two for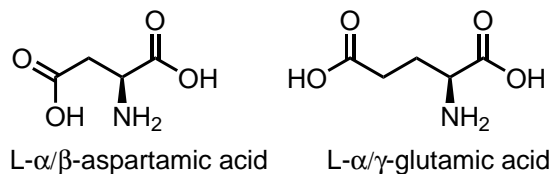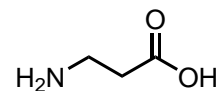ms are possible and they are called *enantiomers*. Enantiomers share the same physical and chemical properties like their boiling point, solubility, nuclear magnetic resonance (NMR) spectra, infrared spectroscopy (IR) and chromatographic retention behaviour. The only property where they differ from each other (and achiral compounds) is *optical activity*. This is the ability to rotate the plane of planar-polarised light which can be interpreted as the consequence of the interaction between the chiral compound and polarised light. Enantiomers rotate the planar-polarised light in opposite directions – the enantiomer which rotates in a clockwise direction is called the (+)-enantiomer whereas the one which rotates counter clockwise (equal but opposite direction under the same conditions) is referred to as the (-)-enantiomer.
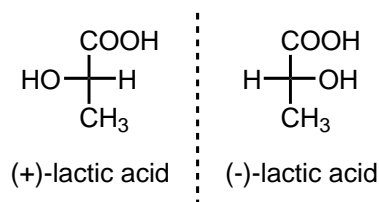
Figure 1.5 | Mirror images of lactic acid

Diastereomers occur when a compound has two or more chiral centres. In case of n chiral centres 2^n stereoisomers exist. The following applies: two stereoisomers cannot be enantiomers and diastereomers to one another at the same time; for one specific molecule there can only be two enantiomers but multiple diastereomers (Figure 1.6).

Asymmetric synthesis refers to reactions that ideally form single enantiomers or diastereomers from prochiral precursors or racemic substrates. Otherwise described as enantioselective synthesis the main objective is the formation of enantiomers in unequal amounts. At best, a high enantiomeric excess is achieved for one stereoisomer.

There are many ways in which this goal can be achieved and the methods range widely depending on the reaction type. Asymmetric hydrogenation, oxidation, epoxidation, carbonylation, hydrosilylation or special reactions like Michael additions, Mannich and Strecker reactions are just a few possibilities that can be achieved via asymmetric synthesis.[8–10] The synthetic protocol for transformations that can be conducted in an asymmetric manner often require
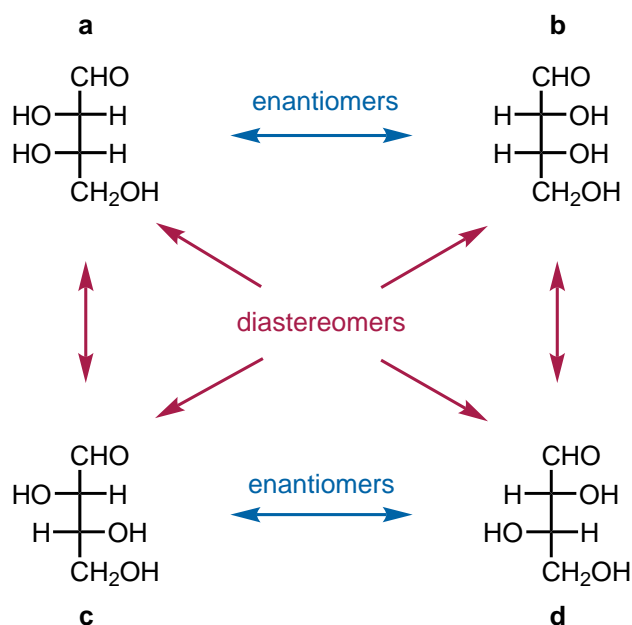
Figure 1.6 | a) L-Erythrose, b) D-erythrose, c) L-threose, d) D-threose as examples for diastereomers and enantiomers

catalysts of various types: enzymatic and metal-based ones and organocatalysts.[3,8,9] In this thesis the focus lies on the latter since the catalysts used herein are of organic nature. In the following sections a few examples of research objectives are presented.

The importance and scientific interest in asymmetric compounds lies not only in the synthesis of amino acids as discussed in Section 1.1. Nature presents us with many biologically active chiral compounds that scientific research tries to replicate. The chemistry of medicine for instance has increased the usage of chiral drugs using single enantiomers, also in regards to the scientific research for agriculture and foods the use of asymmetric synthesis is expanding.[11,12]

1.3 Organocatalytic synthesis

1.3.1 Asymmetric phase-transfer catalysis

An attractive reaction protocol, termed phase transfer catalysis (PTC) has found wide practical application as it is operationally simple, requires mild reaction conditions, safe and environmentally benign solvents and reagents, and can be conducted also on large scale.[9,13] PTC was originally developed to perform simple reactions where substrate and reagent are present in different phases (aqueous, organic or solid). This requires a catalytic amount of a species acting as a carrier between phases. It was later adapted for asymmetric synthesis. In this regard, there

are generally three steps that make up the PTC process: first, the substrate is deprotonated in the interface between two layers (liquid-liquid L/L or solid-liquid S/L); second, the anion is extracted into the bulk organic phase due to the forming of an ion pair with the catalyst; third, a new chiral centre in the product is created by face selective alkylation of the ion pair (Scheme 1.6).
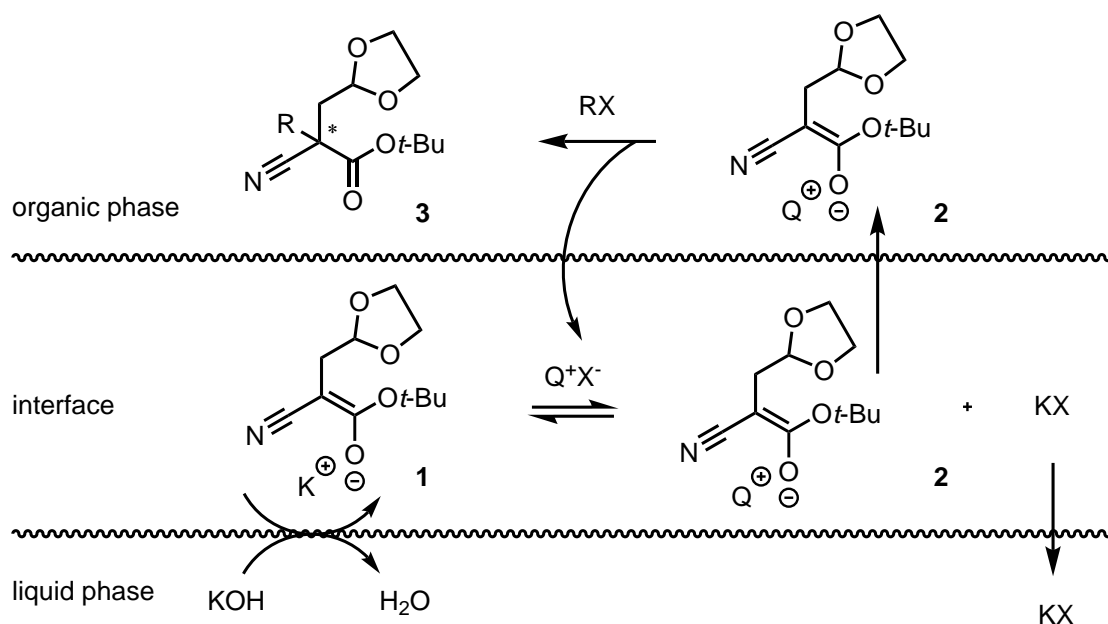
Scheme 1.6 | Mechanism of an exemplary asymmetric liquid-liquid PTC reaction with Q^+X^- representing the catalyst

There are many variables that influence the outcome of the reaction (the preference or prevention of e.g. side reactions or the formation of the unwanted enantiomer): temperature, solvent, base, type of PTC process (L/L or S/L), structure and functional groups of the catalyst, concentrations of the various compounds and the stirring rate. Various reaction types can be accomplished via PTC if the proper catalysts are used. These reaction types include C–C bond formations, reduction reactions, oxidation reactions as well as C–N, C–O and C–S bond formations. C–C bond formations, for instance, are fundamental transformations in organic chemistry. There are many methods to extend carbon frameworks like Aldol, Diels-Alder, Grignard, Mannich, Michael and Wittig reactions – to just name a few. In recent years chemical research increased the use of PTC conditions for such reaction mechanisms.[13,14]

The first efficient non-racemic phase-transfer catalyst (Figure 1.7) was developed by the Merck Group in 1984 for the enantioselective synthesis of (+)-indacrinone (MK-0197).
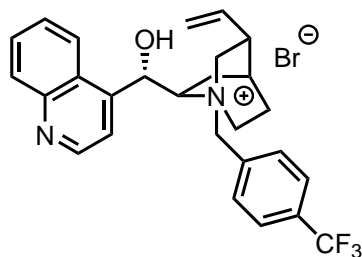
Figure 1.7 | First phase-transfer catalyst cinchoninium bromide, 1984
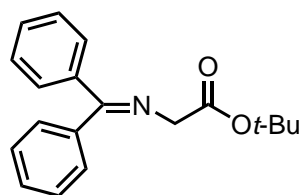
Figure 1.8 | Glycine Schiff base

Earlier works in PTC only produced enantiomeric excess of 15 % whereas with *N*-(4-trifluoromethylbenzyl)cinchoninium bromide 95 % yield and up to 92 % e.e. could be achieved.[15]

O'Donnell and co-workers managed a successful alkylation of the glycine Schiff base in Figure 1.8 via a similar *N*-benzyl cinchoninium halide five years after the Merck report.[16]

Over a decade after the groundbreaking work by the Merck group further progress was reported by Lygo and Corey who independently refined the cinchona alkaloid-derived catalysts.[17,18] This opened new possibilities for the application of phase-transfer catalysis. The group of cinchonidine and cinchonine derived catalysts was even further extended in following years by changing substituents. A few examples are listed below in Figure 1.9
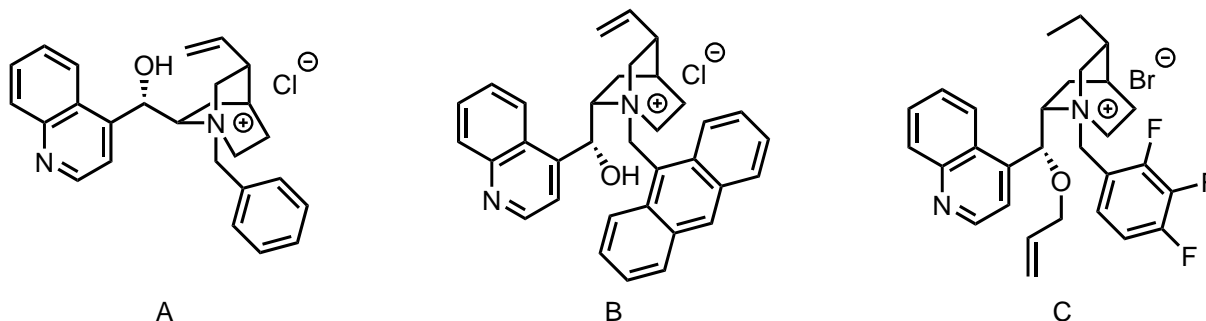
Figure 1.9 | Examples of cinchonine and cinchonidine derived catalysts: A,[16] B,[17] C[19]

The interest for asymmetric synthesis of α-amino acids has always promoted the development of new phase-transfer catalysts. This process can be tracked in the utilisation of the above mentioned glycine Schiff base (Figure 1.8).

Another research objective regarding PTC was its large-scale application. Reusable catalysts obviously present clear advantages. An example are the resin-supported ammonium salts prepared by Nájera (Figure 1.10). Cinchonidine and cinchonine have been alkylated at the N-atom with a Merrifield resin (cross-linked chloromethylated polystyrene) and as such it is used as an easily separable catalyst.[20]
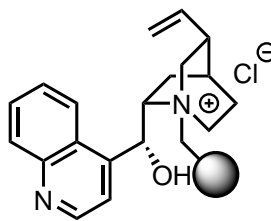
Figure 1.10 | Resin-supported ammonium salts

Regarding reusable catalysts it also has to be noted that solid-phase synthesis (use of polymer-bound substrates like the one in Figure 1.10) has advantages over liquid-phase synthesis.[21]

Furthermore, it shall be said that nowadays many other different organocatalysts are applied for PTC. One of such a group – binaphthyl derived phase-transfer catalysts – are utilised in the course of this thesis. More details on their effects are discussed in Section 1.3.4.

1.3.2 Enantioselective Michael addition via phase-transfer catalysis

An enantioselective approach to Michael additions is one example for the research objectives of asymmetric synthesis in general. One possible realisation is the use of organocatalysts in a PTC environment. In relation to the previous chapter Michael additions of the glycine Schiff base (Figure 1.8) will be discussed herein.

The development of (highly) enantioselective Michael additions via phase-transfer catalysis has been studied for about two decades. On that account, researchers have designed and improved new organocatalysts and tested variable parameters (solvents, reagents, temperature, reaction time etc). In regards to the aforementioned glycine Schiff base, popular Michael acceptors are methyl, ethyl and (*tert*-)butyl acrylates as well as 2-cyclohexenone.
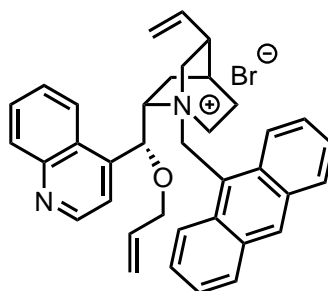
Figure 1.11 | Organocatalyst for enantioselective Michael addition (Corey)

In 1998 Corey[22] developed a catalyst for Michael additions with the glycine Schiff base (Figure 1.11). An example thereof is illustrated in Scheme 1.7. This particular reaction achieved excellent yield (88 %) and 99 % e.e. Optimised reaction conditions for the PTC were identified (−78 °C, 10 mol % of the organocatalyst, solid CsOH x H$_2$O, CH$_2$Cl) by Corey and applied for all analogue experiments of this case study.
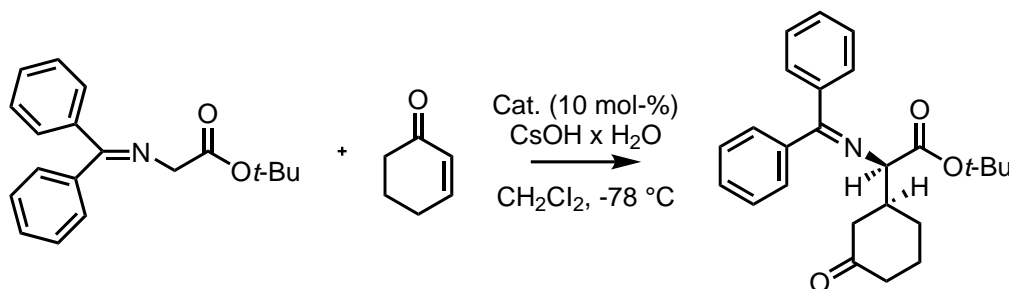
Scheme 1.7 | Reaction scheme of glycine Schiff base with 2-cyclohexenone

Arai et al.[23] built another organocatalyst (Figure 1.12) for similar Michael additions (see Scheme 1.8) in 2002. This particular catalyst comprises a spiro ammonium salt and was derived from diethyl tartrate. They also achieved outstanding results up to 90 % yield and 77 % e.e.
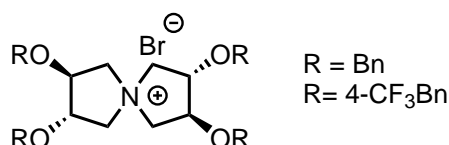
Figure 1.12 | Organocatalyst for enantioselective Michael addition (Arai et al.)

The best results were acquired with Et$_2$O or *tert*-butylmethylether as solvent, CsOH x H$_2$O (10 mol %) as base, 2.5 to 10 mol % of the catalysts and low temperatures of −40 to −78 °C. The reaction times range from 26 to 70 h.
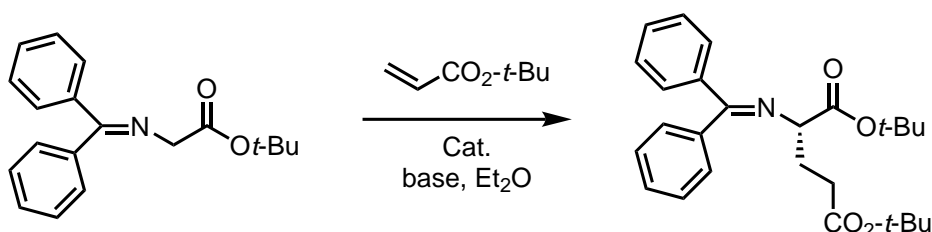
Scheme 1.8 | Reaction scheme of Michael addition via PTC (Arai et al.)

Extensive work on enantioselective Michael additions via PTC has also been done by Shibuguchi et al..[24] They used methyl acrylate as acceptor and glycine Schiff base enolate

as donor. As organocatalyst they designed a two-centre catalyst derived from tartrate with a variety of ketal moieties and aromatic parts. With the possibility to vary substituents at three positions, this catalyst type can be tuned to specific requirements (Figure 1.13).

R = Me; Et; Pr; Bu; *i*-Bu; *t*-Bu; C$_{14}$H$_{29}$
R' = Me; Et; Pr; Bu; *i*-Bu; H
Ar = -Ph; -Ph-4-OMe; -Ph-4-Me;
    -Ph-4-*i*-Pr; -Ph-4-*t*-Bu; -Ph-4-Oet;
    -Ph-4-OPr
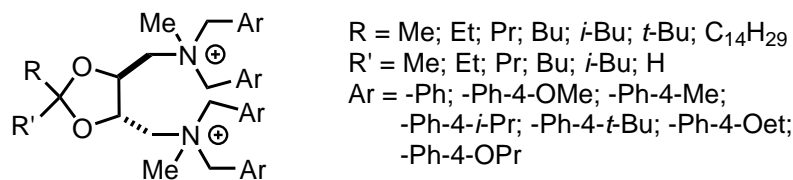
Figure 1.13 | Organocatalyst for enantioselective Michael addition (Shibuguchi et al.)

In their case study they combined different substituents (a list of all substituents for each position is illustrated in Figure 1.13) and achieved good results for yield and e.e. The benzylation of the glycine Schiff base was performed under reaction conditions of 4 °C, argon atmosphere, 10 mol % of the respective catalyst, a reaction time between 1,5 and 4 h and a mixture of 2:7:3 of KOH (50 %), toluene and CH$_2$Cl$_2$ yield of 67 to 94 % and 38 to 68 % e.e. were observed.

1.3.3 Enantioselective Mannich reaction via phase-transfer catalysis

Also asymmetric Mannich reactions have been performed via phase-transfer catalysis in recent years. A few studies that use the glycine Schiff base (Figure 1.8) as the starting material are presented herein.

Ooi et al.[25] investigated the direct Mannich reaction of glycine Schiff base with an α-imino ester (Figure 1.14) under PTC conditions to gain a nitrogen derivative of dialkyl tartrate. The reaction scheme can be seen in Scheme 1.9.
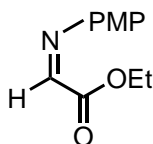
Figure 1.14 | α-Imino ester

Applying the organocatalysts (*R*,*R*)-**C4** and **C5** (Figure 2.2) they were able to achieve yields up to 88 % (syn/anti = 82:18) and 91 % e.e. (syn). In this particular case a big concern lay with the relative configuration since only the syn isomer was of interest. Reaction conditions of −20 °C, 6 h and 17 % aqueous NaOH were identified as optimal.
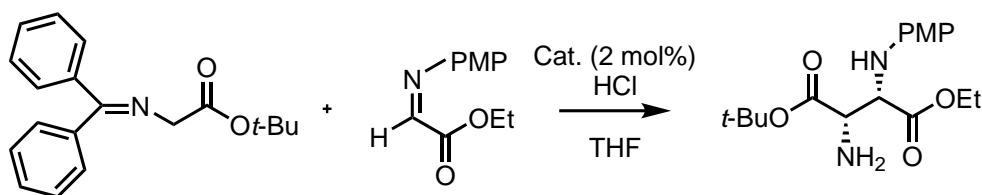
Scheme 1.9 | Enantioselective Mannich reaction according to Ooi et al.

They demonstrated the usefulness of their product by converting it into a precursor of streptolidine lactam (Figure 1.15) which is the core structure of streptothricine antibiotics.[26]
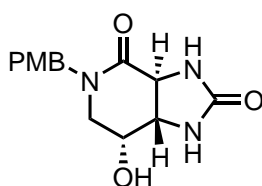
Figure 1.15 | Precursor of streptolidine lactam

The Mannich-type reaction performed by Okada et al.[27] used the phase-transfer catalyst of spiro ammonium salt type (analogue to Figure 1.13) (Scheme 1.10). The best results of 95 % yield (syn/anti = 95:5) and e.e. of 82 % (syn) were achieved at −45 °C and a reaction time of 48 h. They reported a subsequent synthesis of an optically pure tripeptide (Figure 1.16) to demonstrate the synthetic utility of their product.

R = -C$_6$H$_4$-4-OMe
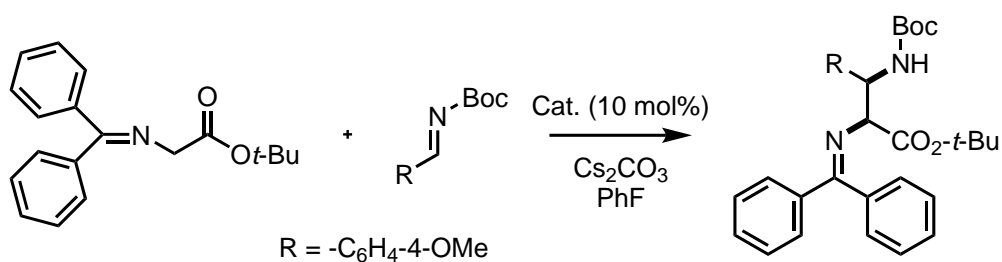
Scheme 1.10 | Enantioselective Mannich reaction according to Okada et al.
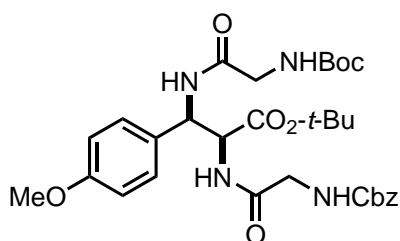
Figure 1.16 | Tripeptide synthesised by Okada et al.

1.3.4 Binaphthyl-derived phase-transfer catalysts

In 1999 the Maruoka group developed spiro ammonium salts derived from commercially available (*R*)- or (*S*)-1,1'-bi-2-naphthol as organocatalysts.[28] These optically active and rigid molecules are C_2-symmetric compounds, substituted on the 3,3' positions of the binaphthyl unit. With these catalysts a high enantioselectivity can be achieved and they are therefore preferably used for the synthesis of α-amino acids. One of the advantages of these spiro ammonium salts is the high reactivity and enantioselectivity requiring only small amounts of the catalysts (ca. 1 mol%) for alkylation reactions. Catalysts of that type were used herein and can be viewed in Figure 1.17.

When modifying the substituents properly, the catalyst can be adjusted to the optimal conditions required for a specific reaction and substrate. During the course of this thesis the impact of fine-tuning the catalyst will be discussed. In the figure below the catalysts used for this thesis are depicted. Catalysts **C1**, **C2**, **C4** and **C5** were used with (*S,S*)-formation whereas **C3** was applied in (*R,R*)-formation.
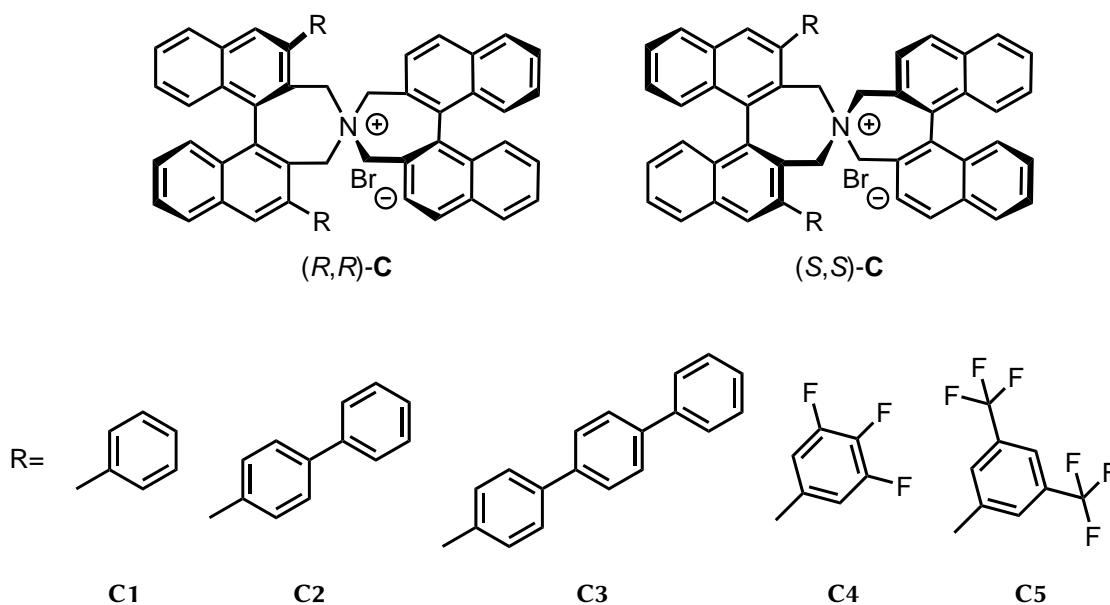
Figure 1.17 | Functionalised spiro ammonium salts as used organocatalysts

Especially **C4** is usually an excellent choice for alkylation reactions due to its high enantioselectivity. Another advantageous feature of **C4** is its capability to catalyse reactions with glycine ester derivatives (see Figure 1.8) with methyl, ethyl and *tert*-butyl groups at the ester moiety to enantiomerically pure products.

(S,S)-**A**

(S,S)-**A1** (R=R'=Ph)
(S,S)-**A2** (R=H, R'=Ph)
(S,S)-**A3** (R=R'=3,5-Ph$_2$-C$_5$H$_3$)

a | 4,4'- and 6,6'-substituted phase-transfer catalysts

(S,S)-**B**

(S,S)-**B1** (R=R'=3,5-Ph$_2$-C$_6$H$_3$)
(S,S)-**B2** (R=H, R'=3,5-Ph$_2$-C$_6$H$_3$)

b | D$_2$-Symmetrical *N*-spiro type phase-transfer catalysts

(S)-**D**

(S)-**D1** (R=β-Np, R'=H)
(S)-**D2** (R=3,5-Ph$_2$-C$_5$H$_3$, R'=H)
(S)-**D3** (R3,5-Ph$_2$-C$_5$H$_3$, R'=Ph)

c | Conformationally flexible *N*-spiro type phase-transfer catalysts
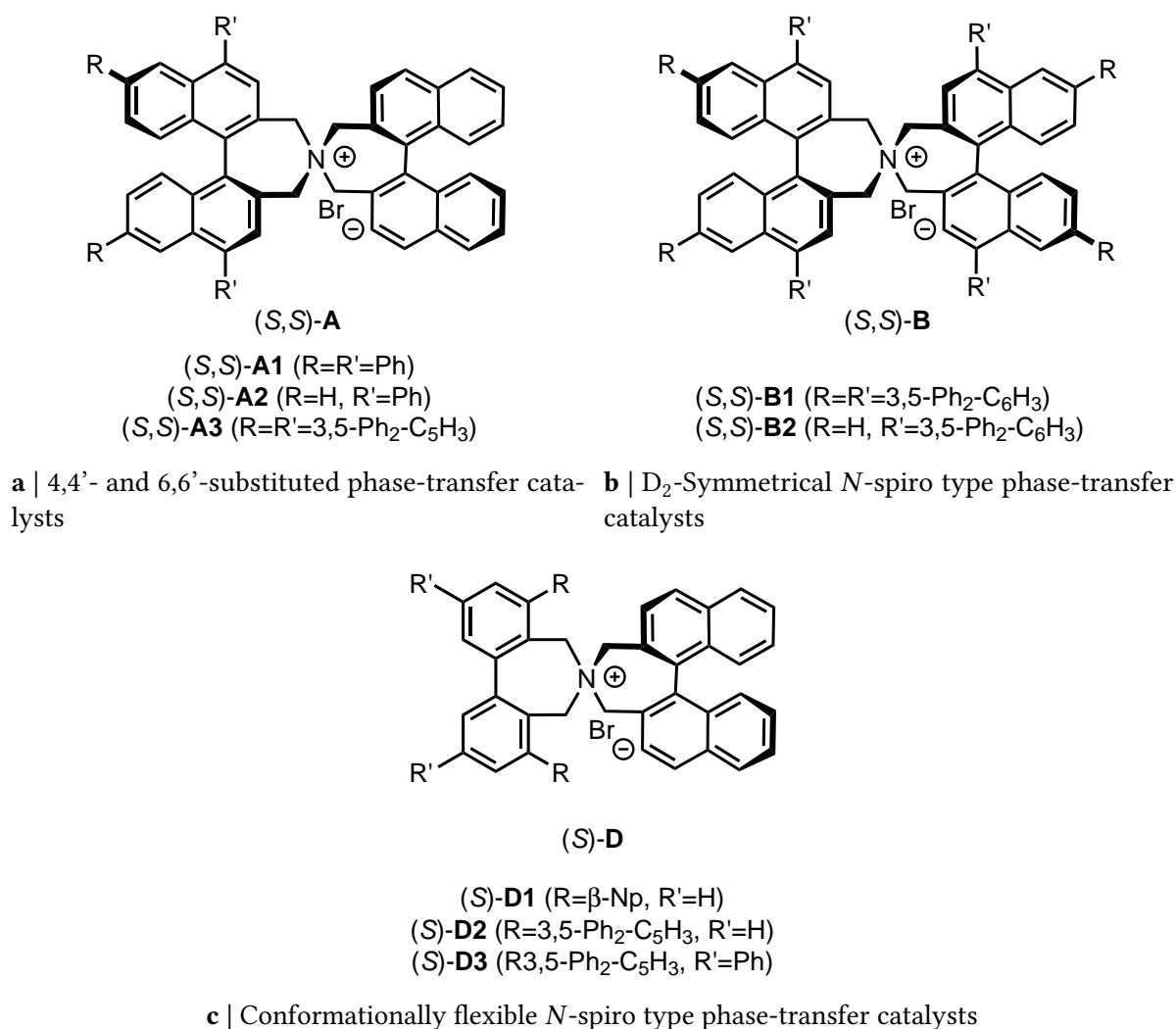
Figure 1.18 | Selected derivatives of binaphthyl-derived phase-transfer catalysts

Maruoka et al. further expanded the scope of these spiro ammonium salts. They explored effects of 4,4'- and 6,6'-substituents instead of 3,3'-substituents (Figure 1.18a). Additionally, they designed D_2-symmetrical *N*-spiro type catalysts as to evade the separate synthesis of the different binaphthyl subunits (see Figure 1.18b).[29] Both modifications achieved excellent yields and e.e. for the alkylation of the glycine Schiff base illustrated in Figure 1.8. Outstanding results were also achieved with a more flexible variation of the *N*-spiro type catalysts. Here, two of the naphthyl subunits were replaced by substituted phenyl moieties (Figure 1.18c).

The reason catalysts of the type in Figure 2.2 were used in the course of this thesis, is their simple synthetic access and the straightforward process of fine-tuning.

1.4 Analysis methods

1.4.1 Internal standard: Quantitative NMR analysis

The use of internal standards is a common aid in quantitative analysis. It provides a reference for the determination of an analyte's concentration by adding a defined quantity of a stable known compound as standard to the sample. In order for this procedure to work, the concentration of the analyte and internal standard must be measured simultaneously. It is therefore used in analytic methods like chromatography where an internal standard is used to calculate the calibration and is added to all standard solutions and samples. The most important characteristics of an internal standard are similar chemical traits as the analyte, yet, it is not allowed to react with the analyte and interfere with the analyte's signals.

In case of NMR analysis, a defined amount of the internal standard is mixed with the sample and dissolved in a deuterated solvent. When choosing the right internal standard, it must be guaranteed that the NMR signals of the standard and the analyte do not overlap. When interpreting the NMR spectra, the integral of a suitable signal of the internal standard is calibrated according to its molar amount and number of protons. Since the integrals are calibrated in proportion to mole, the integration ratio of the analyte is now directly proportional to its mole and can be calculated backwards to the respective mass. The number of expressed protons per peak must again be taken into equation.

The advantage of using internal standards for quantitative NMR analysis lies in the improvement of analytical accuracy because it eliminates systematic errors: errors due to multiple weighings and the loss of yield due to purifying methods. This makes the present procedure ideal as the analyte must not be purified. But even if purification has to be performed, an internal standard that can easily be removed should be selected. The reliability of quantitative NMR analysis is mainly dependent on sufficiently good signal to noise ratio, accuracy of performing the integration, and absence of impurities in the integration area.

1.4.2 Shift reagents: Determination of enantiomeric excess via NMR

For the determination of enantiomeric excess the most popular methods nowadays are chiral HPLC and GC. For these methods to work the analytes either have to be UV active (HPLC) or need to be sufficiently stable at higher temperatures (GC). If neither is applicable, a convenient

alternative is the use of chiral shift reagents. The basic idea is genius in its simplicity: Enantiomers cannot be distinguished via NMR but diastereomers can. When adding an enantiopure rare earth complex (often a camphor derivative forming a stable chelate with lanthanides) to enantiomers this will form diastereomeric complexes where corresponding signals are shifted from their original position. The degree of shift depends on the (relative) stability of diastereomeric complexes. The integration ratio of corresponding signals is directly proportional to the relative concentration of enantiomers in the sample. This method provides significant and solid results (±1 %) if the shift differences are more than 0.01 ppm.

The shift reagent used for this thesis was the Eu(III) salt Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].
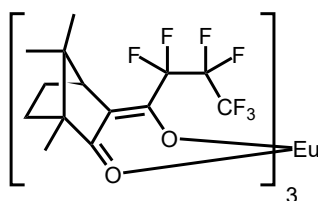
Figure 1.19 | The shift reagent Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]

1.5 Aim and scope of the thesis

The scientific interest in chiral molecules in particular in amino acids has been expressed in the previous sections. The intention of the present work was to synthesise quaternary carbon centres similar to those present in amino acids in an asymmetric fashion. With cyanoacetate **1** as starting product a β-amino acid functionality is inherent (Scheme 1.11). Different substituents could be introduced to form highly functionalised compounds that could be interesting for further synthetic purposes.

One substituent at the α-position is a ketal group, a protecting group that is stable under basic conditions but can easily be removed if desired. The second substituent should be varied and is either a benzyl **3**, allyl **4**, crotyl **5**, propinyl **6**, *N*-protected amino methyl phthalimid **7** group which is planned to be introduced using corresponding bromides. The synthesis of these compounds will be attempted under phase-transfer catalytic conditions in order to obtain the target compounds in non-racemic form. The different binaphthyl-derived phase-transfer catalysts presented in Section 1.3.4 will be used and their efficiency regarding yield

and enantioselectivity will be optimised. Parameters to be varied are: inert gas or standard atmosphere, temperature, reaction time, type of base and type of catalyst.

The focus of this thesis lies in the synthesis of these shown target compounds. Sequence reactions and studies of their reactivities are beyond the scope herein.
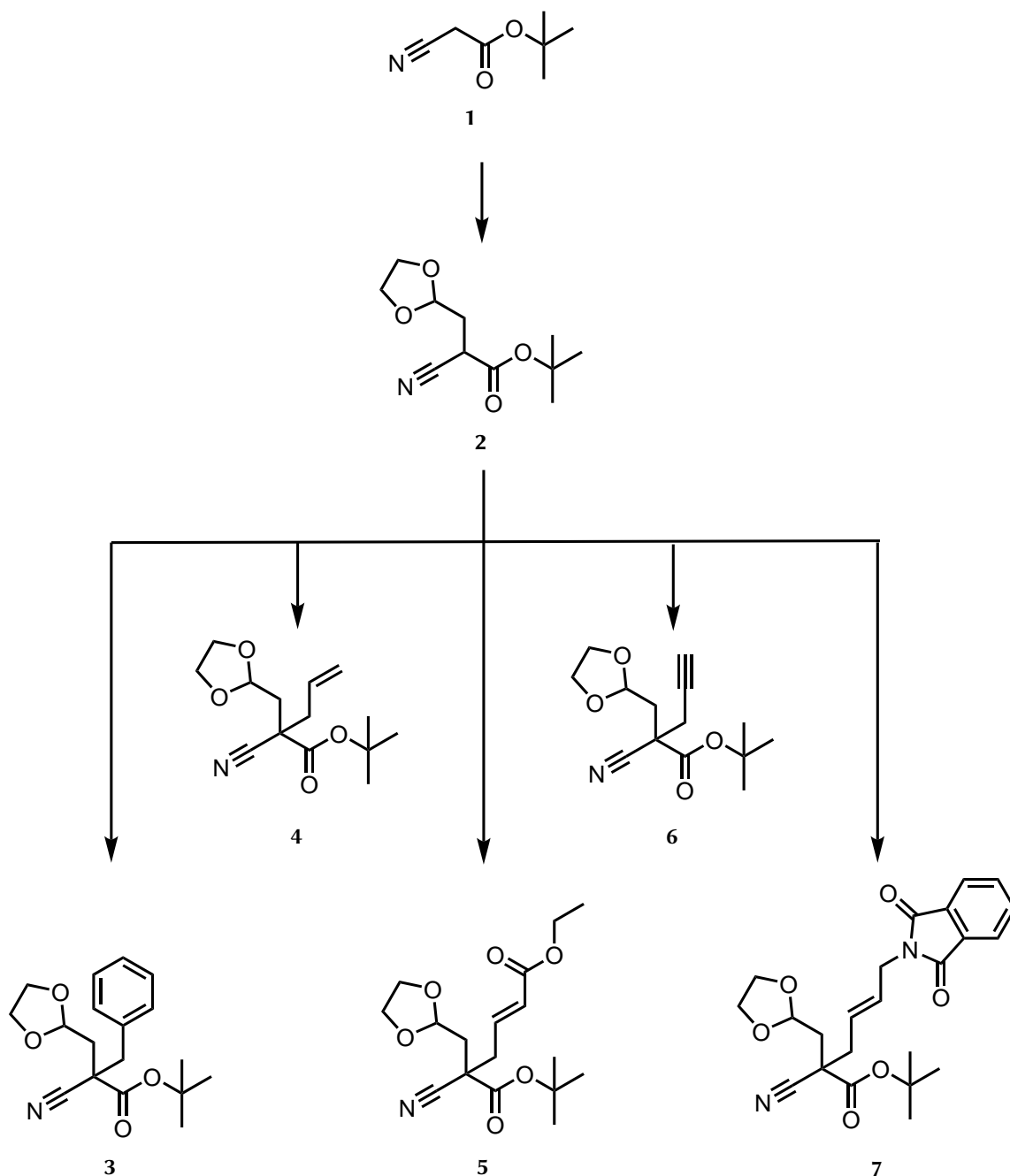
Scheme 1.11 | Highly functionalised asymmetric quaternary carbon centres obtained from α-substituted cyanoacetates

Chapter 2
Results and Discussion

2.1 Methylation and benzylation

Before the five target compounds (see Scheme 1.11) could be prepared an adequate procedure has to be established in order to introduce the first substituent at the α-position in a larger scale. Various reactions using halogenated reagents such as methyl iodide and benzyl bromide were tested in order to find a suitable protocol that can later be applied for the introduction of the ketal group. Since methyl and benzyl groups are very stable and thus highly unreactive for all subsequent synthetic purposes, a ketal group seemed better suitable due to its simple deprotection reaction.
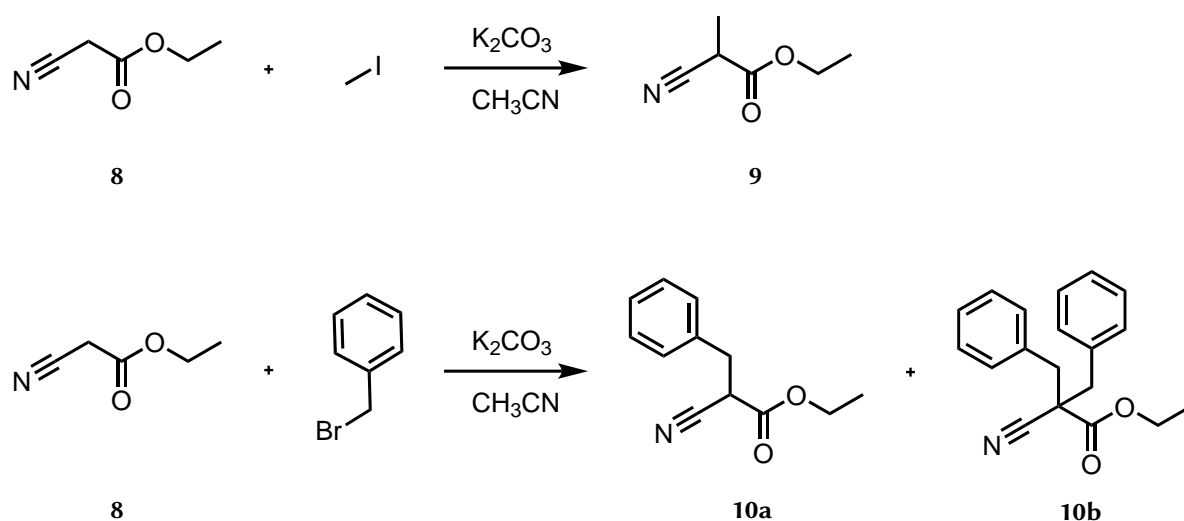
Scheme 2.1 | Methylation and benzylation of **8**

According to previous studies, the methylation of **8** to **9** (Scheme 2.1) via PTC in CH_3CN and with K_2CO_3 as catalyst should yield 41 % of product[30] but for unknown reasons only 19 % yield could be obtained. The procedure was performed in analogy to the benzylation method for the synthesis of **10a**. Unfortunately, only a small amount of **10a** was detected via NMR and could not be isolated from the di-substituted product **10b** and the substrate **8**.

For the next experimental phases we switched to *tert*-butyl esters which are known to be more stable than ethyl esters. Therefore the substrate **8** was replaced by **1** as we suspected the

low product yield to be partly due to decomposition of the starting material. Therefore, the *tert*-butyl cyanoester **1** seemed the better choice as substrate.

A different methylation approach – using NaH to deprotonate the substrate in THF under argon atmosphere – was attempted with no improvement (14 %).[31] In the hope that better yields for the mono-substituted product **12a** could be obtained with a more bulky substituent, the procedure was carried out using benzyl bromide instead of methyl iodide. And indeed, 28 % of the mono-benzylated product **12a** together with 15 % of the di-substituted product **12b** were formed.
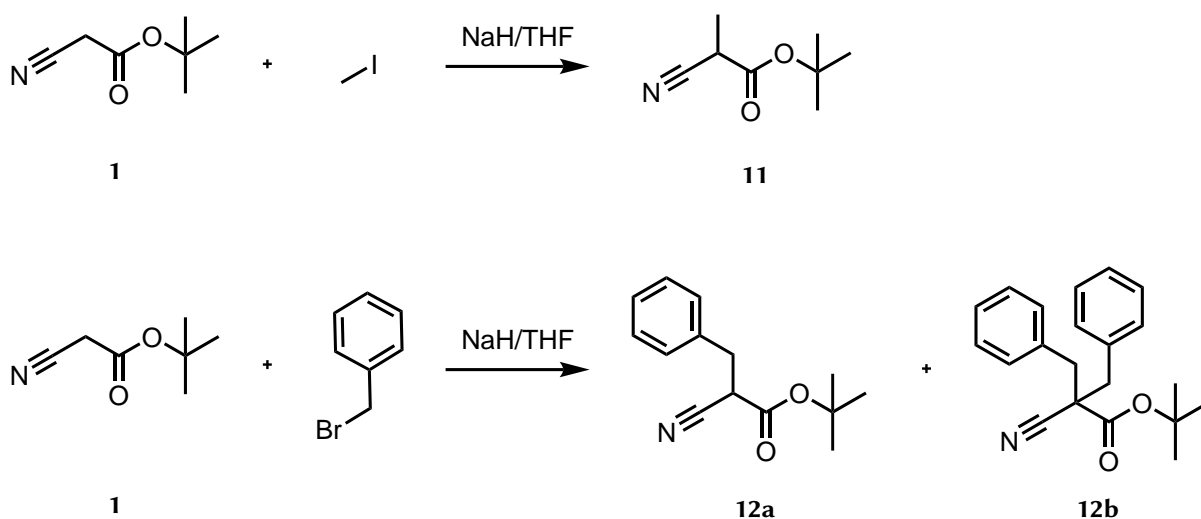
Scheme 2.2 | Methylation and benzylation of **1**

The purification was rather time consuming, especially for compounds **9** and **11** since they are not UV active. Therefore, the content of the individual fractions obtained by MPLC had to be visualised using TLC stains (in this case KMnO$_4$) to find the desired products.
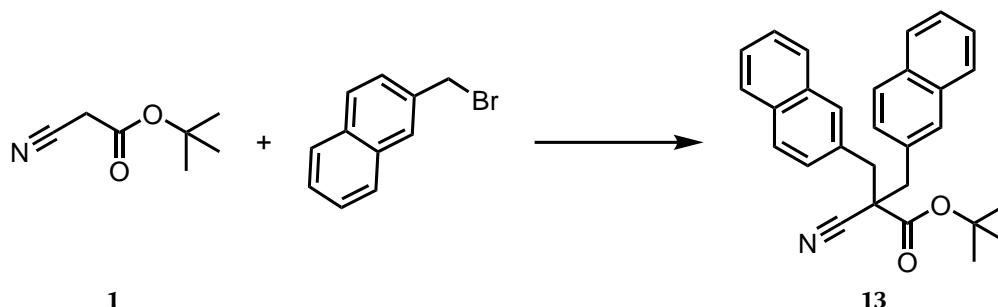
Scheme 2.3 | Naphthylation of **1**

With the hope that still more bulky reagents would further increase the yield of the mono-substituted product, substrate **1** was reacted with 2-bromomethyl naphthalene using the already

described methods: PTC with TBAB (in toluene) as a catalyst and NaH in THF. Disappointingly, both procedures led only to the di-substituted product **13** and no further synthetic experiments were pursued (Scheme 2.3).

The same strategy was applied for the introduction of an *N*-methyl protected phthalimid and a crotyl group (Scheme 2.4). This time DMF was used instead of THF as a solvent. For the formation of **14** *N*-(brommethyl)-phthalimid was used. Ethyl 4-bromocrotonate was used respectively as starting material to generate **15**. Even though the solvent was changed, the obtained yield of the reactions did not differ from the previous observations.
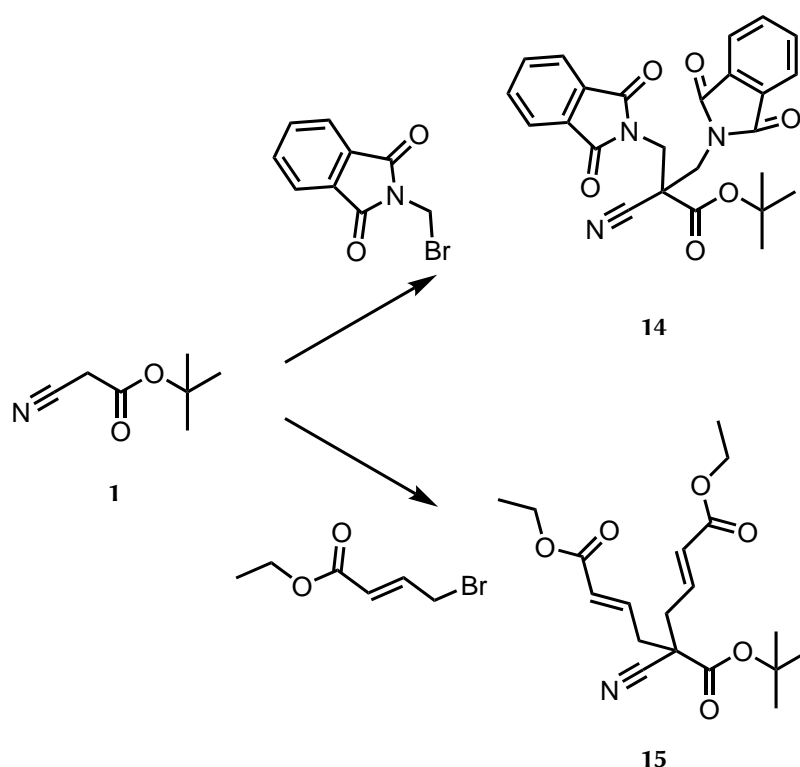
Scheme 2.4 | Synthesis of compounds **14** and **15** starting from **1**

The reactions with *N*-bromomethyl phthalimid and bromo crotonate formed only the di-substituted compounds **14** and **15** as well.
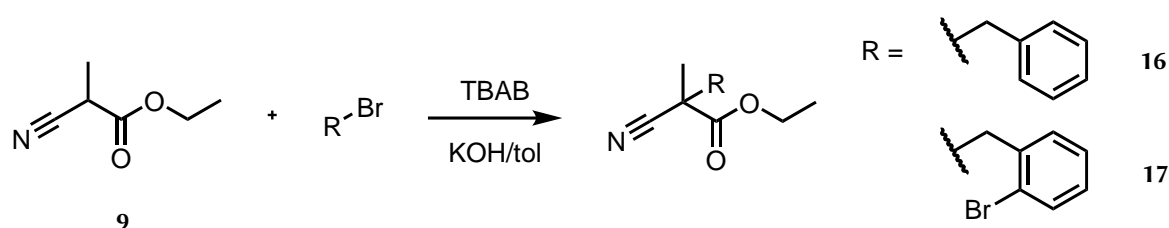
Scheme 2.5 | Substitutions of **9**

Next, we tried to introduce a fourth substituent in the methylated and benzylated compounds **9**, **11** and **12a**. **9** was further substituted with benzyl and *o*-bromo benzyl groups (Scheme 2.5) while an allyl group was introduced to the *tert*-butyl esters **11** and **12a** (Scheme 2.6). These reactions were performed to investigate whether the formation of a quaternary α-carbon is possible for these substrates without the removal of the ester moieties or the formation of other unwanted side reactions.

R = Me **11**
Bn **12a**

R = Me **18**
Bn **19**

KOH/tol
0 °C, Kat.
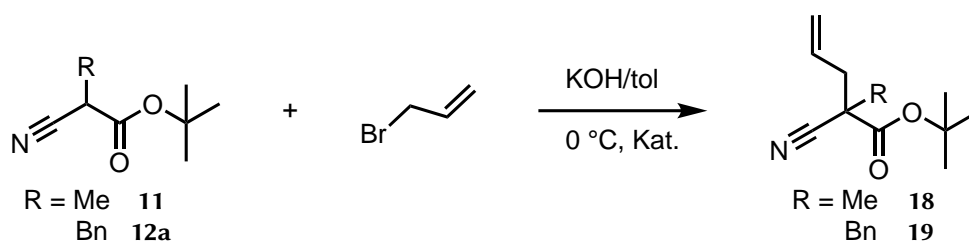
Scheme 2.6 | Formation of a quaternary carbon of **11** via allylation

The analogous reaction was performed with the benzylated *tert*-butyl cyanoester **12a** (Scheme 2.6). These reactions as well as the substitutions of **9** in Scheme 2.5 were performed via PTC and TBAB as an achiral catalyst under argon atmosphere. TBAB is suitable because it is easily available, cheap and only small quantities (1 mol %) are needed.

The reactions of **16**, **17**, **18** and **19** were kept stirring for 4 h and achieved yields from 14 to 62 %. **18** and **19** were synthesised with a reaction time of 2 h to compare the yields under the previous described conditions (4 h). In both cases the yields did not show any substantial differences. Therefore next reactions were stirred for 2 h.

Product	Base	Reaction time	Temperature	Inert gas	Yield (%)
16	KOH	4 h	0 °C	argon	62
17	KOH	4 h	0 °C	argon	44
18	KOH	4 h	0 °C	argon	53
18	KOH	2 h	0 °C	argon	52
19	KOH	4 h	0 °C	argon	14
19	KOH	2 h	0 °C	argon	11

Table 2.1 | Formation of quaternary carbon compounds from **9**, **11** and **12**

In Scheme 2.7 an exemplary ring closing metathesis can be viewed. The reduction of the cyano group was attempted for **18**. **18** was preferred over **19** because larger amounts are easier to synthesise and purify even though it is not UV active. The formation of the di-substituted **12b** complicates the purification of the desired mono-substituted **12a**.
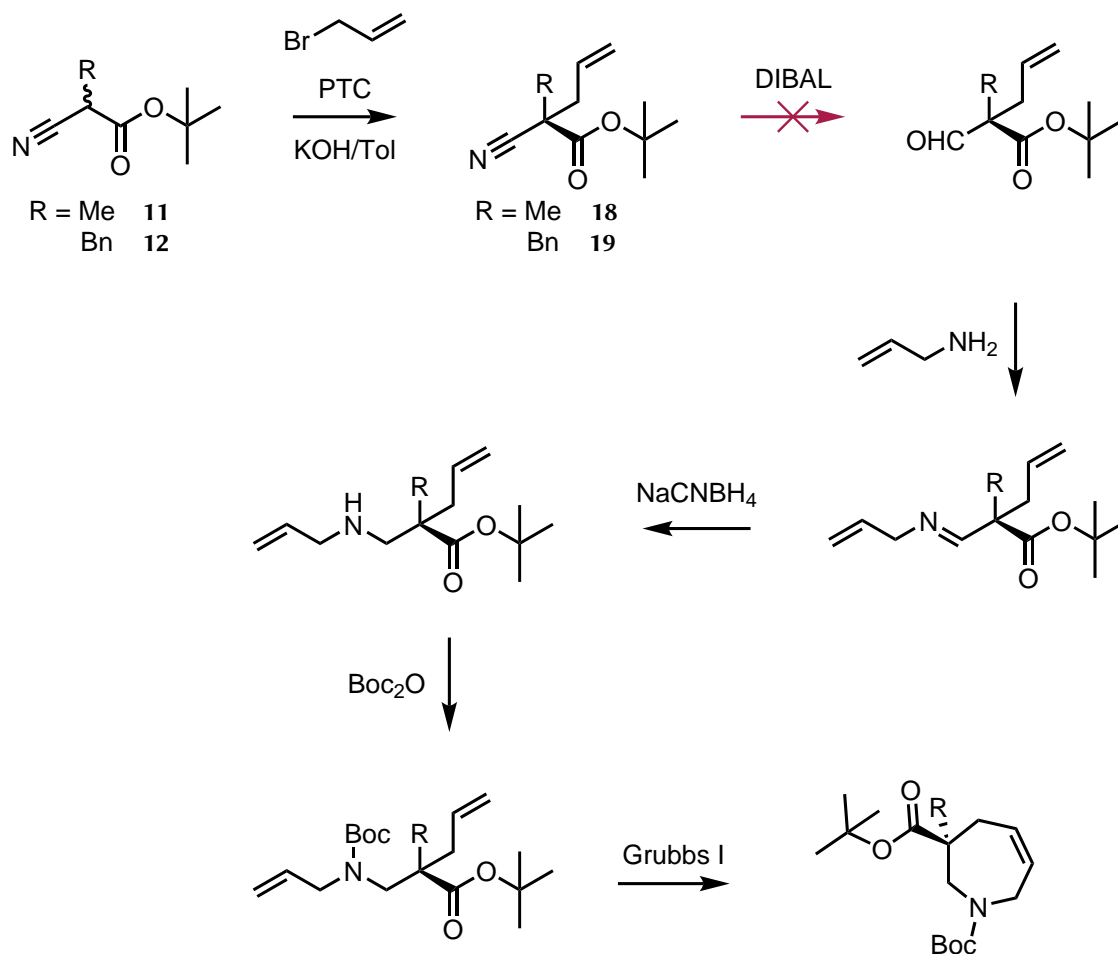
Scheme 2.7 | Planned ring closing metathesis

As the reduction to an aldehyde using DIBAL and work-up with rochelle salt was unsuccessful – which is inexplicable since this is a common procedure in organic synthesis – another approach was attempted: the reduction to a primary amino group with LiAlH$_4$ and AlH$_3$.[32] Again, the conversion was without success. Both attempts showed no traces of the desired products and no pure compounds could be isolated.

2.2 Introduction of the ketal group and new quaternary carbon atoms

Continuing on the pursuit for new functionalised α-chiral β-amino acids, a ketal group was now introduced to **1**. Benzyl and methyl moieties were considered as not particularly interesting in their functionalities which is why the ketal group was chosen. As a protecting group that

can be easily removed with weak acid it is stable under alkaline conditions. If the acetal was removed, the aldehyde could be used for further reactions.
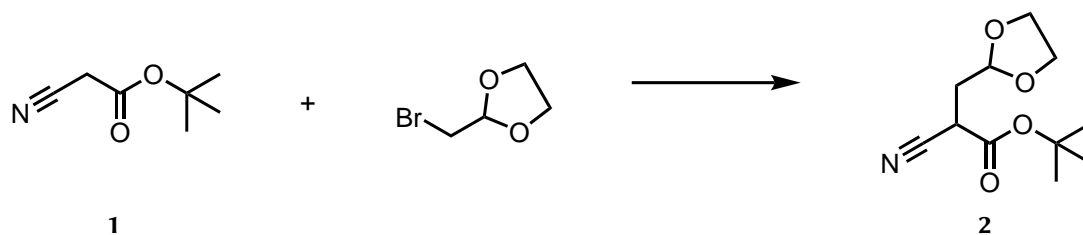
Scheme 2.8 | Synthesis of **2**

Again, NaH and DMF were used to minimise the possibility of a di-substituted product. The mono-substituted compound was synthesised with a yield of 24 %. No di-substituted compound was formed. Some of the substrate **1** could also be recovered after the purification process.

The only drawback of the ketal group as substituent was its purification as the product **2** is not UV active. Like the methylated compounds **9** and **11** a diving reagent ($KMnO_4$) had to be used to locate the wanted product after performing MPLC.

For the fourth substituent the following functional groups were chosen: benzyl, allyl, crotyl, propinyl and phthalimid protected aminomethyl. Their respective activated bromides were used herein. The introduction of these new groups was at first tested with the catalyst TBAB yielding racemic products. The conditions were identical for each reaction: 50 % KOH as the base, toluene as the organic solvent and stirring at 0 °C under argon atmosphere. After all reactions were quite successful with yields from 53 % (**5** and **7**), 59 % (**3**), 94 % (**4**) to 95 % (**6**) the problem of determining the enantiomeric excess was tackled.

Only **3** and **7** are UV active and could therefore be analysed via chiral HPLC. Since the others can not, e.e.-determination with a shift reagents was performed for all products (for reasons of comparability). There is no "recipe" for the application of shift reagents since the necessary quantity depends on the analyte and its concentration; the higher the concentration of the analyte, the more shift reagent is necessary to cause a pronounced shift of monitor protons. Hence, only small amounts of the product were used in the process of determining the e.e. The shift reagent was added in small quantities at a time. Via NMR readings the shifting signals were observed until a sufficient separation of the diastereomeric signals was attained. Since the signals for racemic mixtures have to show a ratio of 50/50 the reliability of the method could be evaluated easily. After establishing conditions for complete separation of signals
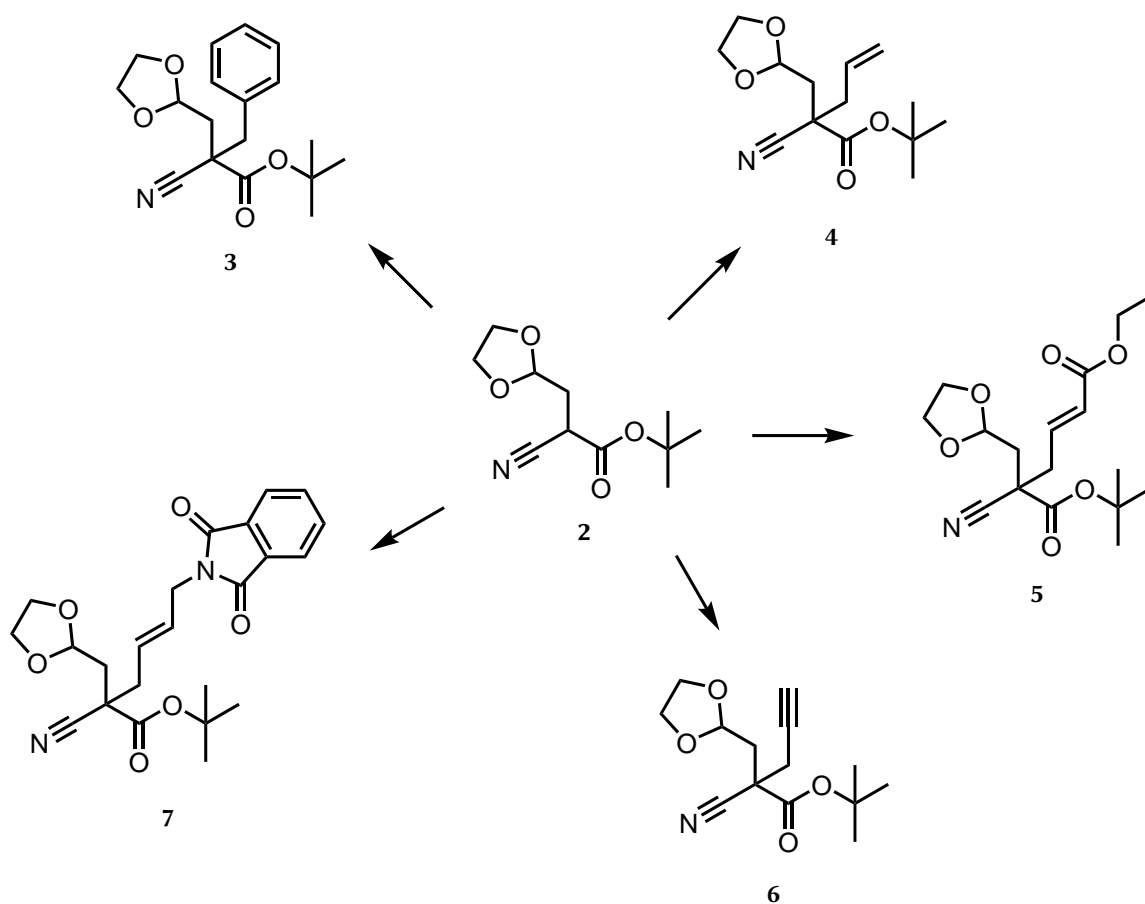
Figure 2.1 | Highly functionalised asymmetric quaternary carbon centres obtained from α-substituted cyanoacetates

of diastereomeric complexes using racemic products, chiral catalysts were applied and the reaction's conditions further improved.

2.3 Optimising enantioselectivity
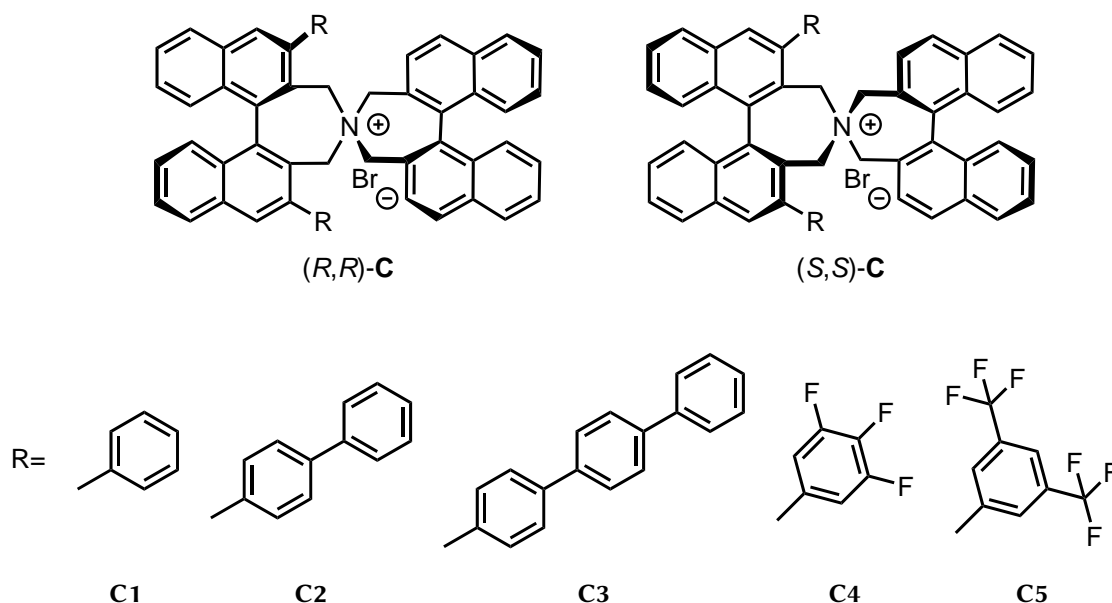
Figure 2.2 | Functionalised spiro ammonium salts as the organocatalysts

Earlier we established that a reaction time of 2 h is sufficient for a complete conversion. The respective yields do not differ as much as a time of 4 h would be justified. Succeedingly, the impact of temperature and inert or atmospheric condition was examined. Using the same catalyst **C1**, **7** was synthesised under the following conditions: a) 2 h, 0 °C and under argon atmosphere, b) 2 h, 0 °C but under normal atmospheric conditions and c) 2 h, at r.t. and under normal atmospheric conditions. The results showed that the yield at r.t. was almost 20 % lower than at 0 °C which is why this condition was not suitable. The enantiomeric excess was not measured. The yield under atmospheric condition at 0 °C did not differ from the yield under argon atmosphere. Since the temperature was the same, there should be no change in enantioselectivity (Table 2.2). Consequently, the following reactions have been carried out for 2 h, at 0 °C and under air. This facilitated the experimental protocol as argon and the degassing process were no longer necessary.

The application of the internal standard as a tool for quantitative analysis also made the purification via MPLC redundant. Since the internal standard did not interfere with neither the NMR signals of the products nor during the measurement of enantiomeric excess, time could be saved by avoiding chromatography.

Product	Base	Reaction time	Temperature	Inert gas	Yield (%)	e.e. (%)
C1						
3	KOH	4 h	0 °C	argon	62	22
4	KOH	2 h	0 °C	-	91	1
5	KOH	2 h	0 °C	argon	68	0
7	KOH	2 h	0 °C	argon	48	2
7	KOH	2 h	0 °C	-	48	2
7	KOH	2 h	r.t.	argon	30	-

Table 2.2 | Yield and enantiomeric excess (in %) using **C1** for **3**, **4**, **5**, **6** and **7**

The catalyst **C1** performed rather poorly for most compounds regarding its enantioselectivity. These syntheses resulted in racemic mixtures (Table 2.2). Under the new standard reaction conditions of 2 h, at 0 °C and under air all five compounds **3**, **4**, **5**, **6** and **7** were now synthesised using the four catalysts **C2**, **C3**, **C4** and **C5** (Figure 2.2). Since the catalysts can be modified as well using different substituents at the 3,3' positions of the binaphthyl unit, there are multiple possibilities of utilising these compounds.

Further electron-donating groups were used to modify the spiro ammonium salts. Biphenyl and terphenyl substituents on the 3,3' positions of the binaphthyl unit form the catalyts **C2** and **C3**.

For **C2** yields of 57 to 93 % and e.e. of 0 to 24 % were achieved as for **C3** yields of 29 to 84 % and e.e. of 2 to 20 % (Table 2.3).

Product	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C2					
3	KOH	2 h	0 °C	83	24
4	KOH	2 h	0 °C	93	12
5	KOH	2 h	0 °C	70	6
6	KOH	2 h	0 °C	84	0
7	KOH	2 h	0 °C	57	4
C3					
3	KOH	2 h	0 °C	84	18
4	KOH	2 h	0 °C	80	20
5	KOH	2 h	0 °C	79	8
6	KOH	2 h	0 °C	75	2
7	KOH	2 h	0 °C	29	8

Table 2.3 | Yield and enantiomeric excess (in %) using catalysts **C2** and **C3** for **3**, **4**, **5**, **6** and **7**

Both catalysts attained moderately good results with sufficient yields yet small enantiomeric excesses. A second possibility for the modification of the organocatalysts was attempted.

C4 and **C5** are catalysts that are highly electron withdrawing due to the fluor containing substituents, **C4** probably even more so.

Regarding the results of **3**, **C4** performed slightly better than **C5**. E.e. of 56 % were observed for both catalysts while the yields differ 10 %.

Product	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			C4		
3	KOH	2 h	0 °C	**78**	**56**
4	KOH	2 h	0 °C	93	38
5	KOH	2 h	0 °C	84	16
6	KOH	2 h	0 °C	89	14
7	KOH	2 h	0 °C	50	14
			C5		
3	KOH	2 h	0 °C	68	56
4	KOH	2 h	0 °C	**93**	**76**
5	KOH	2 h	0 °C	**91**	**42**
6	KOH	2 h	0 °C	**89**	**52**
7	KOH	2 h	0 °C	**80**	**47**

Table 2.4 | Yield and enantiomeric excess (in %) using catalysts **C4** and **C5** for **3**, **4**, **5**, **6** and **7**

The other compounds **4**, **5**, **6** and **7** showed better results with **C5** (Table 2.4). Especially when looking at the e.e. a big impact due to the fine-tuning of the catalysts can be observed. **4** and **6** show differences of 38 %, **7** 33 % and **5** 26 % between **C4** and **C5**. The yield only differs for two compounds **5** and **7** with values of 84 to 91 % and 50 to 80 % respectively.

Before continuing further with the discussion of results one observation has to be stated at this point. Some of the experiments were repeated due to statistical outliers in the development of the results. These outliers showed the importance of the right stirring rate. For if the mixture is not stirred sufficiently, the outcome can be surprisingly low. In case of **7** (with **C5**) it differed from 36 to 80 % yield and 12 to 47 % enantiomeric excess.

For further improvement a stronger base – in this case CsOH – was tested. This was applied to the syntheses with the best catalyst for each compound according to Table 2.4. **C4** was used only for **3** whereas for **4**, **5**, **6** and **7 C5** was applied.

The results using CsOH exceeded the ones with KOH for all compounds. At first, reaction conditions of 0 °C and a reaction time of 2 h were applied using CsOH as the base. When an improvement of the results was observed (especially regarding e.e.), the reaction conditions were changed to −10 °C and 24 h, again with the use of CsOH. Toluene was used for all reactions as the organic phase.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			3		
C1	KOH	2 h	0 °C	62	22
C2	KOH	2 h	0 °C	83	24
C3	KOH	2 h	0 °C	84	18
C4	KOH	2 h	0 °C	78	56
C4	CsOH	2 h	0 °C	83	68
C4	CsOH	24 h	−10 °C	**91**	**70**
C5	KOH	2 h	0 °C	68	56

Table 2.5 | Yield and enantiomeric excess (in %) for **3** under varying reaction conditions

The benzylation of **2** to **3** was performed with poor enantioselectivity using the electron-donating catalysts **C1**, **C2** and **C3**, not exceeding e.e. of 24 %. The fluorinated catalysts **C4** and **C5** on the other hand showed more favourable results of 56 % e.e. and yields of 78 % and 68 % respectively (Table 2.5). Therefore, **C4** was used for the benzylation under new reaction conditions. Even better results could be achieved: after changing the base to CsOH 83 % yield and 68 % e.e. were obtained. At −10 °C, a reaction time of 24 h and again with CsOH yield and e.e. increased to 91 % and 70 % respectively.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			4		
C1	KOH	2 h	0 °C	94	1
C2	KOH	2 h	0 °C	80	12
C3	KOH	2 h	0 °C	80	20
C4	KOH	2 h	0 °C	93	38
C5	KOH	2 h	0 °C	93	76
C5	CsOH	2 h	0 °C	83	76
C5	CsOH	24 h	−10 °C	**83**	**80**

Table 2.6 | Yield and enantiomeric excess (in %) for **4** under varying reaction conditions

Looking at **4** a steady incline of e.e. could be observed for all catalysts. Starting with 1 % for **C1** to 12, 20, 38 and 76 % e.e. for **C2**, **C3**, **C4** and **C5** respectively (Table 2.6). After changing the base to CsOH, the e.e. did again result in 76 % with the same catalyst **C5**. When performing the reaction for 24 h and at lower temperatures of −10 °C an increase of the enantiomeric excess to 80 % could be observed.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			5		
C1	KOH	2 h	0 °C	68	0
C2	KOH	2 h	0 °C	70	6
C3	KOH	2 h	0 °C	79	8
C4	KOH	2 h	0 °C	84	16
C5	KOH	2 h	0 °C	91	42
C5	CsOH	2 h	0 °C	**65**	**48**
C5	CsOH	24 h	−8 °C*	57	48

Table 2.7 | Yield and enantiomeric excess (in %) for **5** under varying reaction conditions
*Due to the hot outside temperatures the cooling bath could be adjusted to only −8 °C

The asymmetric substitution of crotyl to form **5** achieved 48 % e.e. with CsOH and **C5**. A small impact due to the reaction conditions can be observed regarding the yield (Table 2.7). 57 % yield were obtained at −8 °C for 24 h whilst a reaction of 2 h at 0 °C formed 65 % of **5**. The catalysts **C1**, **C2** and **C3** performed very poorly with a maximum of 8 % e.e. and only 16 % e.e. and a yield of 84 % were observed for the electron-withdrawing catalyst **C4**. In contrast, with the second fluorinated catalyst **C5** 42 % e.e. and 91 % yield were gained under the same reaction conditions (KOH, 0 °C, 2 h).

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			6		
C2	KOH	2 h	0 °C	84	0
C3	KOH	2 h	0 °C	75	2
C4	KOH	2 h	0 °C	89	14
C5	KOH	2 h	0 °C	89	52
C5	CsOH	2 h	0 °C	64	60
C5	CsOH	24 h	−8 °C*	**63**	**64**

Table 2.8 | Yield and enantiomeric excess (in %) for **6** under varying reaction conditions
*Due to the hot outside temperatures the cooling bath could be adjusted to only −8 °C

The electron-donating catalysts **C2** and **C3** formed only a racemic mixture of **6**. An increase in e.e. to 14 % could be observed for **C4** (Table 2.8). Much better results were achieved with **C5**:

52 % e.e. and 89 % yield. Continuing under the same reaction conditions of 0 °C, 2 h and the use of the catalyst **C5**, the base was changed from KOH to CsOH. This showed a decline in the yield (64 %) but another incline in e.e. (60 %). For **6** the highest e.e. of 64 % were observed with **C5** at −8 °C and a reaction time of 24 h.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
			7		
C1	KOH	2 h	0 °C	48	2
C2	KOH	2 h	0 °C	57	4
C3	KOH	2 h	0 °C	29	8
C4	KOH	2 h	0 °C	50	14
C5	KOH	2 h	0 °C	80	47
C5	CsOH	2 h	0 °C	72	66
C5	CsOH	24 h	−10 °C	**81**	**70**

Table 2.9 | Yield and enantiomeric excess (in %) for **7** under varying reaction conditions

The formation of the asymmetric quaternary carbon centre of **7** was first attempted with the use of the catalysts **C1**, **C2** and **C3** under the reaction conditions of 0 °C, 2 h and KOH as the base. Not exceeding 8 % e.e., the catalysts **C4** and **C5** were applied next under the same conditions (Table 2.9). This resulted in an increase of e.e. to 14 % and 47 % respectively. Since **C5** performed far better, it was preferably used for further experiments. The switch to CsOH led to increased yield of 72 % and 66 % e.e. A yield of 81 % and e.e. of 70 % could be observed under reaction conditions of −10 °C and 24 h.

By slowing down the reaction at around −10 °C but letting it stir for 24 h better results could be achieved. Yet, the yields and e.e. did not improve further than 9 % and 4 % respectively. This is the reason why no experiments were tried with conditions of e.g. −20 °C and a reaction time of 72 h.

2.4 Optical activity

In order to determine which enantiomer was favoured in the experiments, all five compounds **3**, **4**, **5**, **6** and **7** were tested via polarimeter. Thereupon the compounds with highest value of e.e. were selected for the analysis resulting in all (+) rotations (Table 2.10).

Product	Specific rotation ($[\alpha]_D^{20}$)
3	+22
4	+8
5	+9
6	+22
7	+7

Table 2.10 | Optical rotation for **3**, **4**, **5**, **6**, **7**

Therefore it can be concluded that the favoured enantiomer has an optical rotation of (+) and the same configuration.

When comparing the results of the polarimeter to the NMR spectra that show the diastereomers (due to the shift reagent), it can be concluded that the bigger peak represents the (+) rotating enantiomer. In Figure 2.3 it can be observed that the diastereomeric complex of the (+) enantiomer and the shift reagent is the peak that least shifted.
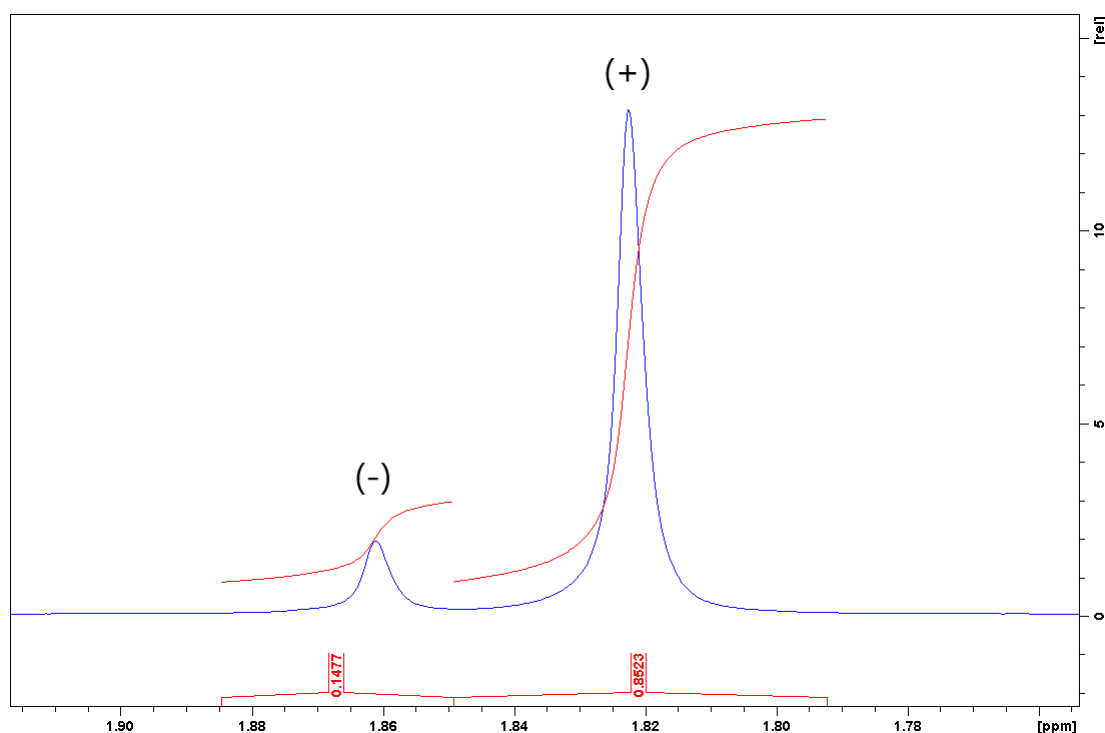
Figure 2.3 | Excerpt of NMR spectra of **3** and shift reagent

If this hypothesis is applied to all other compounds it can be concluded that the least shifted peak always represents the (+) rotating enantiomer. If we take this theory even further it can be argued that the electron withdrawing catalysts (**C4** and **C5**) favor the formation of (+) rotating compounds whereas **C2** and **C3** favour the conformation of the (−) rotating enantiomer in some cases. Most of the time **C1** and **C2** do not exceed 8 % e.e..

Chapter 3
Summary and Outlook

A two step procedure was applied to obtain chiral and highly functionalised asymmetric quaternary carbon centers from α-substituted cyanoacetates and activated bromides. The first section describes the introduction of the ketal group to the substrate *tert*-butyl cyanoacetate **1**. This procedure was performed using NaH to deprotonate the substrate at the α-position.

The forming of chiral quaternary carbon centres was executed via phase-transfer catalysis with mild reaction conditions of 0 °C, a reaction time of 2 h, 1 mol % of the catalyst and toluene and KOH as the organic and aqueous phases. The application of inert gas argon was dismissed in the course of the thesis. The substitution of functional groups was successfully carried out for racemic mixtures using TBAB. The asymmetric synthesis on the other hand was optimised using modified phase-transfer catalysts of the spiro ammonium salt type. Catalysts substituted with aromatic, electron-donating groups (**C1**, **C2** and **C3**) provided unfavourable results with low enantioselectivity. On the contrary, promising results were achieved using catalysts **C4** and **C5** with electron-withdrawing groups.

The utilisation of CsOH as base improved the enantioselectivity even further with 48 to 76 % e.e. At lower temperatures (−8 to −10 °C) and a longer reaction time of 24 h and CsOH as base, the enantioselectivity with catalysts **C4** and **C5** could be increased to 48 to 80 %.

In summary, the development of optimising the enantioselectivity for **3**, **4**, **5**, **6** and **7** was presented herein. Further improvements can be attempted by testing alternative modifications of the catalyst, by varying organic solvents or altering the reaction conditions like temperature and reaction time.

Procedures of e.g. ring-closing metathesis can be approached using the functionalities of the substituents, for instance via the allyl function.

Chapter 4
Experimental Section

4.1   General information

Glassware and techniques: Inert reactions were performed under argon atmosphere on a Schlenk line and using dried glassware. **Reagents and solvents:** Heptane, dichloromethane (DCM), and ethyl acetate (EtOAc) were distilled, absolute THF from sodium benzophenone ketyl, Et_2O from $LiAlH_4$; acetonitrile, DCM, and triethylamine from CaH_2; All the other chemicals were analytical grade and used without further purification. **Reaction monitoring:** All experiments were monitored by thin layer chromatography (TLC); aluminium sheets coated with silica gel 60 (thickness of 0.2 mm, ALUGRAM$^{©}$ Xtra SIL G/UV$_{254}$). Visualisation was either achieved by UV light or by dipping in a $KMnO_4$ solution. **Chromatography:** Medium Pressure Liquid Chromatography (MPLC) was performed on a Biotage Isolera Flash Purification with self-packed columns, SiO_2, 40-63 μm. **HRMS:** High resolution mass spectroscopy was performed on a Bruker maXis spectrometer using ESI-TOF ionisation/detection. **NMR Spectra:** All NMR spectra were recorded on Bruker Avance III 400, Avance III 600 or Avance III 700 spectrometers. Chemical shifts (δ) are given in ppm and referenced to (residual) solvent peaks [^{1}H: $\delta(CHCl_3)$ = 7.26 ppm; ^{13}C: $\delta(CDCl_3)$ = 77.0 ppm]. Coupling constants (J) were given in Hz. Multiplicity of signals is denoted using the following terms: singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof. Splitting patterns that could not be interpreted or easily visualised are described as multiplet (m). ^{13}C{^{1}H} NMR spectra are recorded in a J-modulated mode; signals are assigned as C, CH, CH_2, and CH_3. **HPLC:** For HPLC determination of chiral products an Agilent 1200 chromatograph equipped with a diode array detector and autosampler was used. **Optical rotation:** Specific rotation ($[\alpha]_D^{20}$) was determined on a Perkin Elmer Polarimeter 241 at 589 nm (sodium D line) in a 100 mm cell.

4.2 Ethyl-2-cyanopropanoate (9)
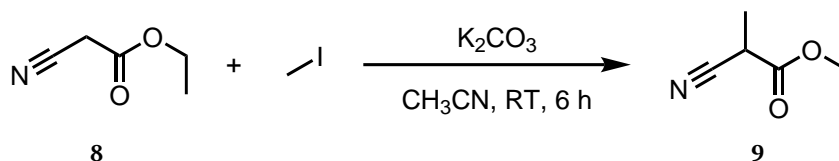
The following reaction followed the procedure of Rao et al.[30] : Cyano ester **8** (5.65 g, 50 mmol) and potassium carbonate (5.18 g, 37.5 mmol) were suspended in acetonitrile (100 mL) and stirred at r.t. for 15 min before methyl iodide (5.33 g, 37.5 mmol) was added dropwise. The mixture was stirred at r.t. for 6 h, filtered over cotton, evaporated and the crude product purified via MPLC (EtOAc (0→15 %)/PE). For detection $KMnO_4$ was used.

Yield: 0.91 g (19 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 4.27 (q, J = 7.1 Hz, 2 H); 3.53 (q, J = 7.4 Hz, 1 H); 1.59 (d, J = 7.4 Hz, 3 H); 1.32 (t, J = 7.2 Hz, 3 H).

4.3 Ethyl 2-cyano-2-methyl-3-phenylpropanoate (16)[33]
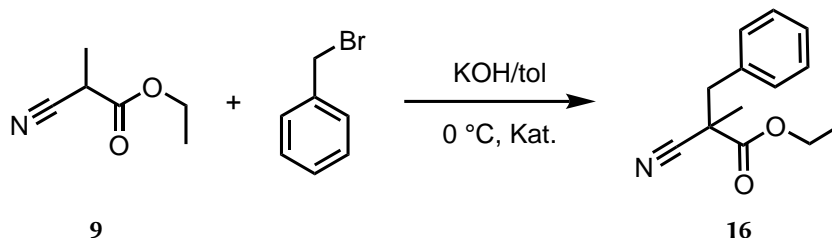
The catalyst TBAB (0.8 mg, 1 mol %) and **16** (31.8 mg, 0.25 mmol) were mixed in toluene (1.5 mL) and KOH (50 %, 0.5 mL) was added. The mixture was degassed and cooled to 0 °C before benzyl bromide (52 mg, 0.3 mmol) was added. After 4 h of stirring at 0 °C, the reaction was diluted with ice water (3 mL) and Et$_2$O (5 mL) and extracted with Et$_2$O (5 × 5 mL). The combined organic layers were washed with sat. NaCl (5 mL) and dried with MgSO$_4$. The product was filtered and the solvents evaporated.

Yield: 34 mg (62 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.30 (m, 5 H); 4.19 (q, J = 7.2 Hz, 2 H); 3.22 (d, J = 13.4 Hz, 1 H); 3.04 (d, J = 13.4 Hz, 1 H); 1.61 (s, 3 H); 1.22 (t, J = 7.1 Hz, 3 H).

4.4 Ethyl 3-(2-bromophenyl)-2-cyano-2-methylpropan-oate (17)
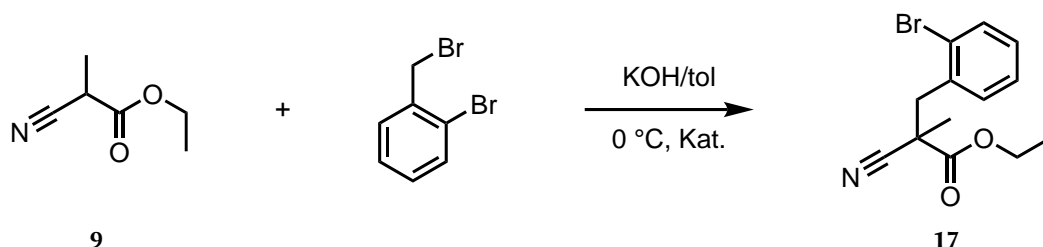
To the catalyst TBAB (0.8 mg, 1 mol %) the substrate **9** (31.8 mg, 0.25 mmol) was added and suspended in toluene (1.5 mL), subsequently KOH (50 %, 0.5 mL). The mixture was degassed and cooled to 0 °C. o-Bromo benzyl bromide (78.9 mg, 0.3 mmol) was dissolved in toluene (0.2 mL) and added to the suspension. The mixture was stirred for 4 h at 0 °C. Afterwards ice water (3 mL) and Et$_2$O (5 mL) were added to the reaction and the organic layer was removed. The aqueous phase was washed with Et$_2$O (5 × 5 mL), the organic phases combined and washed with sat. NaCl (5 mL), dried with MgSO$_4$ and evaporated.

Yield: 33 mg (44 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 7.59 (dd, $J = 8.0, 1.3$ Hz, 1 H); 7.43 (dd, $J = 7.7, 1.7$ Hz, 1 H); 7.31 (td, $J = 7.5, 1.3$ Hz, 1 H); 7.17 (td, $J = 7.9, 1.7$ Hz,1 H); 4.26 (q, $J = 7.1$ Hz, 2 H); 3.4 (s, 2 H); 1.65 (s, 3 H); 1.28 (t, $J = 7.1$ Hz, 3 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 168.9 (C); 134.2 (C); 133.2 (CH); 131.6 (CH); 129.5 (CH); 127.8 (CH); 125.9 (C); 119.7 (C); 63.2 (CH$_2$); 44.8 (C); 41.7 (CH$_2$); 22.9 (CH$_3$); 14.0 (CH$_3$).

HRMS m/z: [M + Na]$^{+}$ Calcd for C$_{13}$H$_{13}$BrNO$_2$Na^{+} 318.0100; Found 318.0109.

HPLC: Chiracel AD-H column, 25 °C, flow rate = 0.5 mL min^{-1}, heptane/2-PrOH 99/1. Retention times: 18.3 min and 20.5 min.

4.5 Ethyl 2-isocyano-3-phenylpropanoate (10)[31]
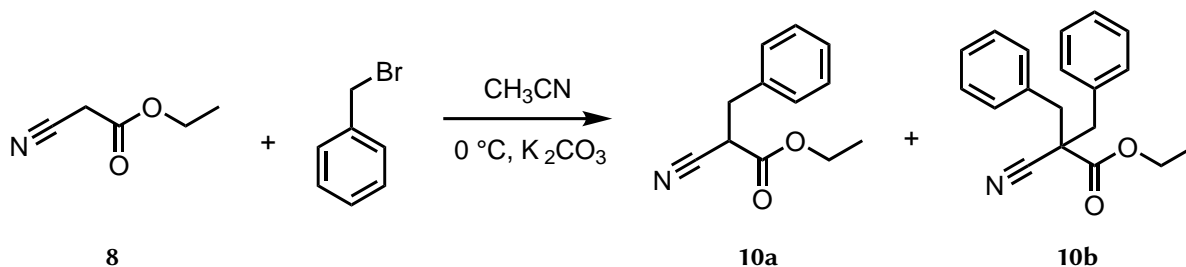
To a solution of ethyl-cyanoacetate **8** (5.7 g, 50.0 mmol) in acetonitrile (100 mL) K_2CO_3 (5.19 g, 37.5 mmol) was added and stirred at r.t. for 15 min before benzyl bromide (6.41 g, 37.5 mmol) was added dropwise. After stirring for 6 h at r.t. the mixture was filtered, evaporated and subjected to MPLC (EtOAc (10→30 %)/PE).
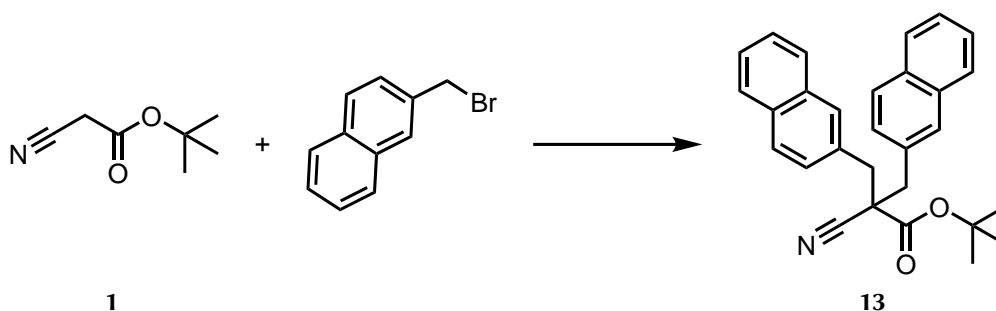
10a

Yield: 1.5 g (20 %)

¹H-NMR (400 MHz, CDCl₃): δ 7.32 (m, 5 H); 4.24 (m, 2 H); 3.71 (dd, J = 8.5, 5.9 Hz, 1 H); 3.28 (dd, J = 5.9, 13.8 Hz, 1 H); 3.19 (dd, J = 8.4, 13.9 Hz, 1 H); 1.27 (t, J = 7.1 Hz, 3 H).

10b[34]

Yield: 2.1 g (38 %)

¹H-NMR (400 MHz, CDCl₃): δ 7.31 (m, 10 H); 4.01 (q, J = 7.2 Hz, 2 H); 3.32 (d, J = 13.5 Hz, 2 H); 3.11 (d, J = 13.5 Hz, 2 H); 0.98 (t, J = 7.2 Hz, 3 H).

4.6 *tert*-Butyl 2-cyano-3-(naphthalen-2-yl)-2-(naphthalen-2-ylmethyl)propanoate (13)

A mixture of the catalyst TBAB (0.8 mg, 1 mol %), the substrate **8** (35.3 mg, 0.25 mmol), toluene (1.5 mL) and KOH (50 %, 0.5 mL) was degassed, stirred and cooled to 0 °C. Then 2-Bromomethyl naphtalene (69.5 mg, 0.3 mmol) was added and stirred for 4 h at 0 °C. For the work-up Et_2O (5 mL) and ice water (3 mL) were added, the organic layer removed and the aqueous phase was washed with Et_2O (5 × 5 mL). After combining the organic extracts, they were washed with sat. NaCl (5 mL), dried with $MgSO_4$ and evaporated.

Yield: 27 mg (26 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.84 (m, 7 H); 7.51 (m, 7 H); 3.54 (d, J = 13.6 Hz, 2 H); 3.29 (d, J = 13.6 Hz, 2 H); 1.15 (s, 9 H).

HRMS m/z: $[M + Na]^+$ Calcd for $C_{29}H_{27}NNaO_2^+$ 444.1940; Found 444.1927; $[2 M + Na]^+$ Calcd for $C_{58}H_{28}Br_2N_2NaO_4^+$ 865.3982; Found 865.3952.

^{13}C-NMR (150 MHz, CDCl$_3$): δ 161.9 (C); 133.5 (C); 133.3 (C); 133.1 (C); 132.9 (C); 132.8 (C); 131.9 (C); 129.4 (CH); 128.7 (CH); 128.3 (CH); 128.2 (CH); 128.1 (CH); 128.0 (CH); 127.9 (CH); 127.8 (CH); 127.7 (CH); 126.9 (CH); 126.5 (CH); 126.3 (CH); 126.2 (CH); 126.1 (CH); 84.5 (C); 43.8 (C); 36.0 (C); 27.9 (CH$_3$); 26.0 (CH$_2$).

4.7 *tert*-Butyl 2-cyano-2-methylacetate (11)[35]
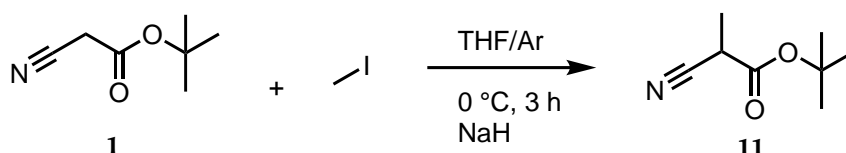
A mixture of NaH (0.79 g, 60 % 19.8 mmol) in THF (20 mL) was degassed and cooled to 0 °C. Cyano acetate **1** (8.73 g, 60.0 mmol) was dissolved in THF (10 mL), degassed and kept under argon atmosphere. The solution was then slowly dropped into the NaH/THF mixture. After 15 min methyl iodide (1.23 mL; 20.0 mmol) was added via syringe and the reaction mixture stirred for 3 h at 0 °C. After quenching the reaction with ice water (30 mL) and Et_2O (100 mL), the aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried with Na_2SO_4 and the solvents evaporated. The crude product was purified via MPLC (EtOAc (0→7 %)/PE) and the product detected via TLC (KMnO$_4$). This synthesis procedure was performed analogue to Zhang et al.[31] (*tert*-Butyl cyanoester was used instead of ethyl cyanoester).

Yield: 1.50 g (14 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.47 (q, J = 7.4 Hz; 1 H); 1.58 (m, 3 H); 1.53 (s, 9 H).

4.8 *tert* Butyl-2-cyano-2-methyl-pent-4-enoate (18)[35]

11   **18**
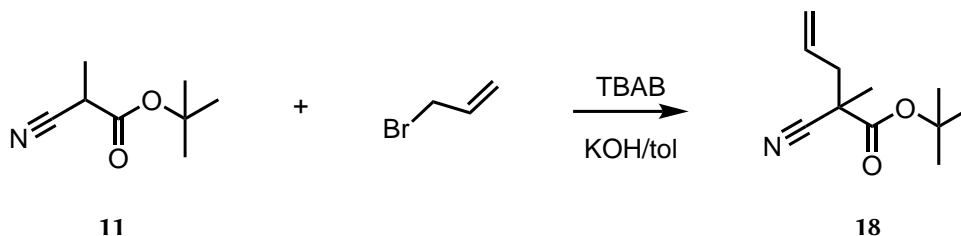
The catalyst TBAB (6.45 mg, 1 mol %) was put into a test tube additional to **11** (310.43 mg, 2 mmol), toluene (13.2 mL) and KOH (50 %, 4 mL). The mixture was degassed, and cooled to 0 °C under Argon while rapidly stirred. Then allyl bromide (2.1 mL, 0.3 mmol) was added and stirred for 2 h. For the work-up Et$_2$O (40 mL) and ice water (30 mL) were added to the reaction and stirred. The aqueous layer was washed with Et$_2$O (3 × 40 mL), the organic phases combined, extracted with sat. NaCl (40 mL) and dried with MgSO$_4$ before evacuation. The product could be synthesised with 99 % purity.

Yield: 25 mg (14 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.78 (m, 1 H); 5.22 (m, 1 H); 5.19 (m, 1 H); 2.60 (ddt, J = 13.8, 7.2, 1.2 Hz, 1 H); 2.43 (ddt, J = 13.8, 7.3, 1.2 Hz, 1 H); 1.50 (s, 3 H); 1.46 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.7 (C); 130.8 (CH); 120.7 (C); 119.9 (CH$_2$); 83.8 (C); 44.2 (CH$_2$); 42.1 (C); 27.7 (CH$_3$); 22.6 (CH$_3$).

HRMS m/z: [M + Na]$^+$ Calcd for C$_{11}$H$_{17}$NNaO$_2$$^+$ 218.1151; Found 218.1155;

[2 M + Na]$^+$ Calcd for C$_{22}$H$_{34}$N$_2$NaO$_4$$^+$ 413.2411; Found 413.2650.

4.9 Attempted reduction of (18) using DIBAL

18
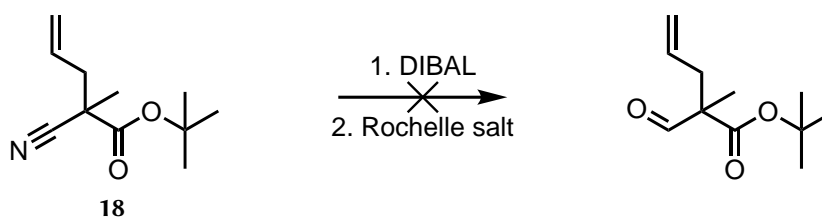
The substrate **18** (46.1 mg, 0.24 mmol) was dissolved in DCM (2 mL), degassed and cooled to −78 °C. DIBAL (1.0 M, 0.65 mL, 0.65 mmol) was added dropwise and the mixture was stirred for 1 h after which a Rochelle salt solution (500.2 mg, 1.77 mmol) and DCM (5 mL) were added as well and the mixture stirred again overnight. An MPLC was performed (EtOAc (10→40 %)/PE). Detection via TLC stained in 4-anisaldehyde. The NMR results showed that the expected product could not be obtained.

4.10   Attempted reduction of (18) using AlH₃

18
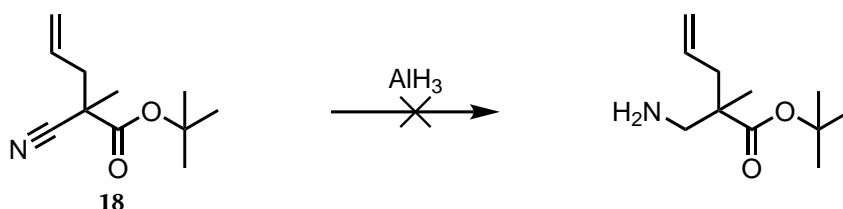
The following procedure was performed according to Widhalm et al.[32]

A suspension of LiAlH₄ (30.0 mg, 0.79 mmol) in abs. Et₂O (2 mL) was cooled to −5 °C and powdered AlCl₃ (33.3 mg, 0.25 mmol) was added to give a milky suspension. After 20 min of rapid stirring a solution of the substrate **18** (46.0 mg, 0.24 mmol) in abs. Et₂O (1 mL) was added dropwise and the mixture was stirred at 0 °C for 30 min. To increase the volume of the organic phase Et₂O (8 mL) was added as well as two pellets of NaOH and water. The mixture was then passed through a short pad of celite (1 cm) and washed with more Et₂O.

4.11   *tert*-Butyl 2-benzyl-2-cyano-3-phenylpropanoate (12)

1   **12a**   **12b**
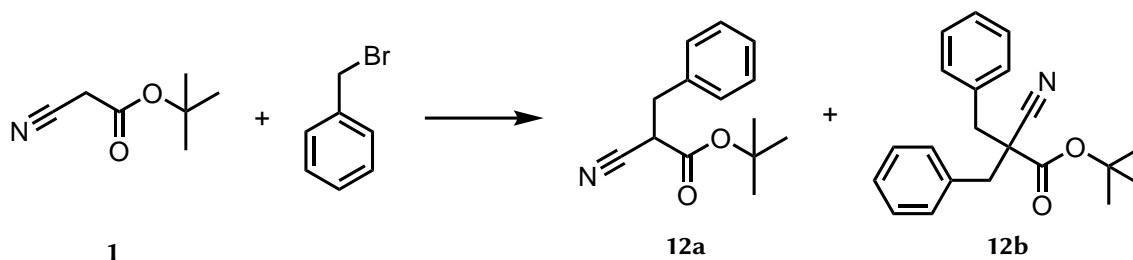
4.11.1 With TBAB/KOH

To introduce a benzyl group, the catalyst TBAB (0.8 mg, 1 mol %) was combined with the substrate **1** (35.3 mg, 0.25 mmol), toluene (1.5 mL) and KOH (50 %, 0.5 mL). The mixture was degassed and cooled to 0 °C under argon before benzyl bromide (54.0 mg, 0.3 mmol) was added. After stirring for 4 h at 0 °C, Et_2O (5 mL) and ice water (3 mL) were used to dilute the reaction. The aqueous phase was extracted with Et_2O (5 × 5 mL), the organic layers combined and washed with sat. NaCl (5 mL), dried over $MgSO_4$ and the solvents evaporated.

12b

Yield: 56 mg (70 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 7.22 (m, 10 H); 3.30 (d, J = 13.7 Hz Hz, 2 H); 3.10 (d, J = 13.5 Hz Hz, 2 H); 1.21 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.1 (C); 134.4 (C); 130.3 (CH); 128.6 (CH); 127.9 (CH); 119.2 (C); 84.3 (C); 53.4 (C); 43.6 (CH$_2$); 27.6 (CH$_3$).

4.11.2 With NaH/THF

To a Schlenk flask with THF (10 mL) the substrate **1** (8.7 g, 0.06 mol) was added and degassed. Another Schlenk with THF (20 mL) was degassed as well and – under Argon atmosphere – NaH (0.79 g, 60 % 0.20 mol) was introduced and cooled to 0 °C. The substrate/THF mixture was slowly dropped into the second flask. After 15 min of continuous stirring the reagent benzyl bromide (3.43 g, 0.02 mol) was added via syringe. The mixture was then stirred for 3 h at 0 °C, quenched with Et_2O (100 mL) and ice water (30 mL) and the aqueous layer separated. It was extracted with Et_2O (2 × 50 mL) and the combined organic phases washed with sat. NaCl (50 mL) and dried with $MgSO_4$. After evaporating the solvents, the crude product was purified via MPLC (EtOAc (0→8 %)/PE).

12a

Yield: 0.47 g (28 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.31 (m, 5 H); 3.63 (dd, J = 8.3, 6.0 Hz 1 H); 3.20 (m, 2 H); 1.44 (s, 9 H).

HRMS m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_2^+$ 344.1321; Found 344.1632.

12b

Yield: 1.31 g (15 %)

4.12   *tert*-Butyl 2-benzyl-2-cyanopent-4-enoate (19)
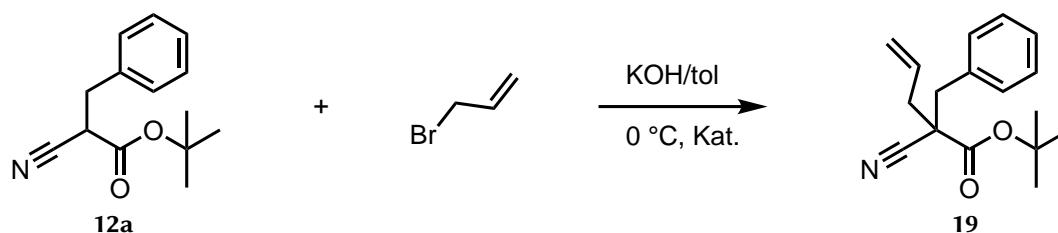
For the phase transfer catalysis reaction the substrate **12a** (58.5 mg, 1 mmol) and TBAB (0.8 mg, 1 mol %) were put into a Schlenk flask with toluene (1.5 mL) and KOH (50 %, 0.5 mL), degassed and cooled to 0 °C. During continuous stirring allyl bromide (37.4 mg, 0.3 mmol) was added to the mixture and stirred for another 2 h at 0 °C. Afterwards Et$_2$O (5 mL) and ice water (3 mL) were added as well and the phases separated. The aqueous layer was washed with Et$_2$O (5 × 5 mL), the combined organic phases extracted with sat. NaCl (5 mL), dried over MgSO$_4$ and the solvents evaporated.

Yield: 8 mg (11 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.24 (m, 5 H); 5.79 (m, 1 H); 5.20 (m, 2 H); 3.09 (d, J = 13.6 Hz, 1 H); 2.96 (d, J = 13.6 Hz, 1 H); 2.64 (m, 1 H); 2.47 (m, 1 H); 1.29 (s, 9 H).

HRMS m/z: [M + Na]$^+$ Calcd for C$_{17}$H$_{21}$NNaO$_2$$^+$ 294.1465; Found 294.1462.

HPLC Chiracel OJ column, 25 °C, flow rate = 1 mL min^{-1}, heptane/2-PrOH 98/2. Retention times: 8.6 min and 13.3 min.

4.13   *tert*-Butyl 2-cyano-3-(1,3-dioxoisoindolin-2-yl)-pro-

panoate (14)

A solution of the substrate **1** (42.4 mg, 0.3 mmol) in DMF (1 mL) was degassed, stirred under Argon and cooled to 0 °C. Then NaH (14.4 mg, 60 %, 0.36 mmol) was added to gain a milky white solution that turned yellow after 10 minute of continuous stirring. The mixture was stirred for 2 h before *N*-(brommethyl)-phthalimid (133.7 mg, 0.45 mmol) was added to the reaction. The stirring was continued for 2 h at 0 °C and overnight at r.t.. To dilute the reaction water (3 mL) and Et_2O (5 mL) were added and extracted in a separating funnel. The organic layer was washed with water (2 × 5 mL), dried with $MgSO_4$ and evaporated. A purification via MPLC was performed (EtOAc (20→40 %)/PE).

Yield: 10 mg (7 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 7.88 (dd, J = 5.6, 3.1 Hz, 4 H); 7.75 (dd, J = 5.5, 3.1 Hz, 4 H); 4.32 (dd, J = 18.1, 14.4 Hz, 4 H); 1.50 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.4 (C); 164.2 (C); 134.5 (CH); 131.6 (C); 123.8 (CH); 115.7 (C); 86.0 (C); 51.3 (C); 41.1 (CH$_2$); 27.6 (CH$_3$).

HRMS m/z: $[M + Na]^+$ Calcd for $C_{25}H_{21}N_3NaO_6^+$ 482.1323; Found 482.1313

$[2M + Na]^+$ Calcd for $C_{50}H_{42}N_6NaO_{12}^+$ 941.2753; Found 941.2751.

4.14 4-(*tert*-Butyl) 1,7-diethyl (1E,6E)-4-cyanohepta-1,6-diene-1,4,7-tricarboxylate (15)

To a Schlenk tube equipped with a magnetic stirrer the substrate **1** (45.7 mg, 0.32 mmol) and DMF (1 mL) were added. The solution was then degassed and cooled to 0 °C under argon when NaH (15.0 mg, 60 %, 0.37 mmol) was added as well. The mixture continued to stir for 2 h at 0 °C and overnight at r.t.. The reaction was quenched with Et_2O (5 mL) and ice water (3 mL) and extracted. The organic layer was washed with water (2 × 5 mL) and dried over $MgSO_4$. A

yellow oil was sustained and purified via MPLC (EtOAc (10→30 %)/PE). The required product (mono-substituted crotonate) could not be achieved.
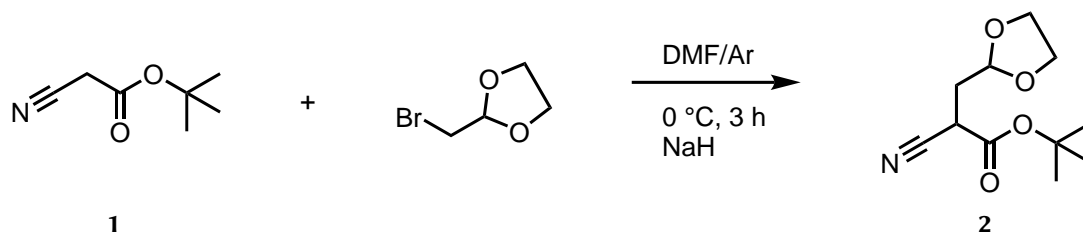
Yield: 34 mg (42 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 6.85 (m, 1 H); 5.98 (m, 1 H); 4.19 (q, J = 7.1 Hz, 2 H); 2.70 (m, 2 H); 1.48 (s, 9 H); 1.28 (t, J = 7.1 Hz).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 165.7 (C); 165.3 (C); 139.0 (CH$_2$); 127.0 (CH$_2$); 117.7 (C); 85.4 (C); 60.7 (v); 48.3 (C); 38.9 (v); 27.8 (CH$_3$); 14.2 (CH$_3$).

HRMS m/z: [M + Na]$^+$ Calcd for C$_{19}$H$_{27}$NNaO$_6$$^+$ 388.4158; Found 388.1736
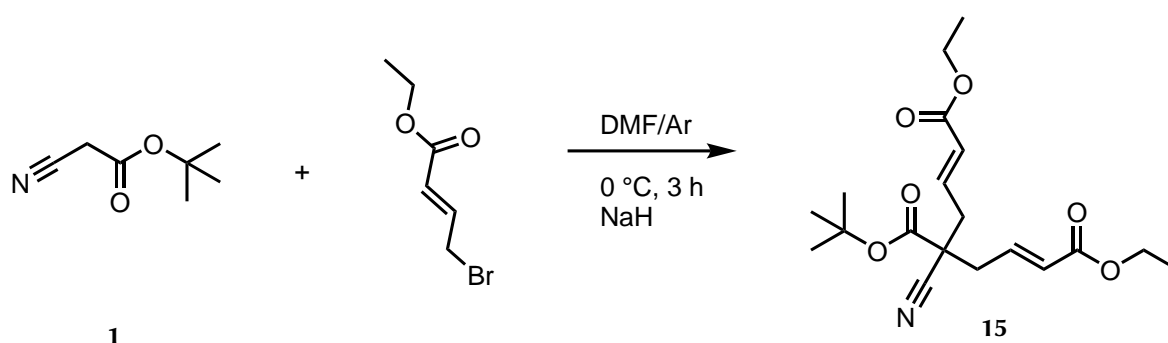
[2 M + Na]$^+$ Calcd for C$_{38}$H$_{54}$N$_2$NaO$_{12}$$^+$ 753.3567; Found 753.3567.

4.15 *tert*-Butyl 2-cyano-3-(1,3-dioxolan-2-yl)-propan-oate (2)

The substrate **1** (1.84 g, 0.013 mol) was dissolved in DMF (40 mL) and the solution degassed and cooled to 0 °C under argon. During rapid stirring NaH (0.62 g, 60 %, 0.016 mol) was added and the mixture continued to stir for 2 h at 0 °C before 2-(bromomethyl)-1,3-dioxolane (75.2 mg, 0.450 mol) was slowly dropped into the mixture. It was stirred for another 1 h at 0 °C and overnight at r.t.. Et$_2$O and water were added until the NaH was neutralised and the two phases separated. The organic phase was washed with water (2 × 25 mL), dried with MgSO$_4$ and evaporated to obtain a yellow oil. The product was purified via MPLC (EtOAc (20→40 %)/PE).

Yield: 48 mg (16 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 5.09 (dd, J = 4.3, 3.7 Hz, 1 H); 3.95 (m, 4 H); 3.59 (m, 1 H); 2.30 (m, 2 H); 1.50 (s, 9 H).

4.16 *tert*-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2-cyano-3-phenylpropanoate (3)

The catalyst TBAB (0.8 mg, 1 mol %) and the substrate **2** (56.8 mg, 0.25 mmol) were combined in a Schlenk flask with toluene (1.5 mL) and KOH (50 %, 0.5 mL). The mixture was degassed, cooled to 0 °C and rapidly stirred when benzyl bromide (52.9 mg, 0.3 mmol) was added to the reaction which was left stirring for another 2 h at 0 °C. The reaction was quenched with Et_2O (5 mL) and ice water (54.0 mg). The aqueous phase was extracted with Et_2O (5 × 5 mL), the organic phases combined, washed with sat. NaCl (5 mL) and dried with $MgSO_4$. A purification MPLC was performed (EtOAc (0→15 %)/PE).

Yield: 46 mg (59 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.31 (m, 5 H); 5.19 (q, J = 3.1 Hz, 1 H); 3.98 (m, 2 H); 3.87 (m, 2 H); 3.14 (d, J = 13.4 Hz, 1 H); 3.06 (d, J = 13.4 Hz, 1 H); 2.38 (dd, J = 14.2, 6.4 Hz, 1 H); 2.14 (dd, J = 14.1, 3.2 Hz, 1 H); 1.36 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.1 (C); 134.0 (C); 130.5 (CH); 128.6 (CH); 128.0 (CH); 118.8 (C); 101.5 (CH); 84.0 (C); 65.3 (CH$_2$); 64.9 (CH$_2$); 47.8 (C); 43.9 (CH$_2$); 40.5 (CH$_2$); 27.7 (CH$_3$).

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{23}NNaO_4^+$ 340.1519; Found 340.1514; $[2 M + Na]^+$ Calcd for $C_{36}H_{46}N_2NaO_8^+$ 657.3146; Found 657.3119.

Asymmetric synthesis

The procedure was performed in the same manner as seen above. Varying factors are described respectively in the table below.
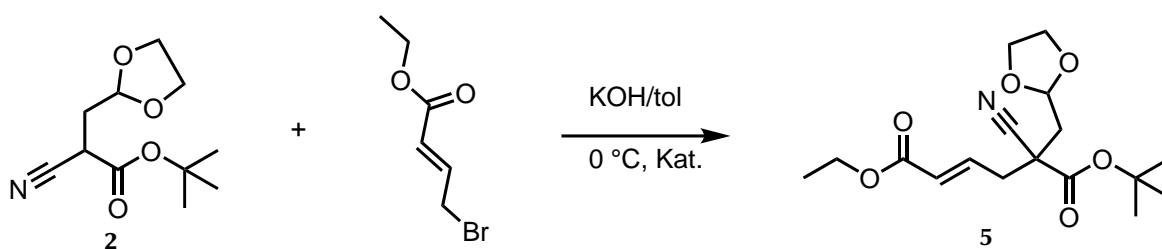
The optical activity of the obtained product under reaction conditions of −10 °C for 24 h was measured:

$[\alpha]_D^{20}$ +22 (c 0.1 , DCM).

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C1	KOH	2 h	0 °C	62	22
C2	KOH	2 h	0 °C	83	24
C3	KOH	2 h	0 °C	84	18
C4	CsOH	2 h	0 °C	83	68
C4	CsOH	24 h	−10 °C	91	70
C4	KOH	2 h	0 °C	78	56
C5	KOH	2 h	0 °C	68	56

Table 4.1 | Yield and enantiomeric excess (in %) using different reaction conditions for **3**

4.17 *tert*-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2-cyano-pent-4-enoate (4)

Toluene (1.5 mL) and KOH (50 %, 0.5 mL) were added to a mixture of the catalyst TBAB (0.8 mg, 1 mol %) and the substrate **2** (56.8 mg, 0.25 mmol). The now yellow solution was degassed, cooled to 0 °C and stirred rapidly before allyl bromide (37 mg, 0.3 mmol) was added as well. After 2 h of stirring at 0 °C Et$_2$O (5 mL) and ice water (3 mL) were used to quench the reaction. The aqueous layer was extracted with Et$_2$O (5 × 5 mL) and the combined organic phases washed with sat. NaCl (5 mL) and dried over MgSO$_4$.

Yield: 64 mg (94 %)

^{1}H-NMR (700 MHz, CDCl$_3$): δ 5.84 (m, 1 H); 5.26 (m, 1 H); 5.23 (m, 1 H); 5.17 (dd, J = 5.9, 3.5 Hz, 1 H); 3.98 (m, 2 H); 3.86 (m, 2 H); 2.62 (m, 1 H); 2.52 (m, 1 H); 2.29 (dd, J = 14.2, 5.9 Hz 1 H); 2.11 (dd, J = 14.2, 3.4 Hz 1 H); 1.49 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.0 (C); 130.4 (CH); 121.0 (CH$_2$); 118.5 (C); 101.3 (CH); 83.9(C); 65.2(CH$_2$); 64.8(CH$_2$); 46.0 (C); 42.3 (CH$_2$); 39.6 (CH$_2$); 27.8 (CH$_3$).

HRMS m/z: [M + Na]$^+$ Calcd for C$_{14}$H$_{21}$NNaO$_4{}^+$ 290.1363; Found 290.1374

[2 M + Na]$^+$ Calcd for C$_{28}$H$_{42}$N$_2$NaO$_8{}^+$ 557.2833; Found 557.2838.

Asymmetric synthesis

The procedure was performed in the same manner as seen above. Varying factors are described respectively in the table below.
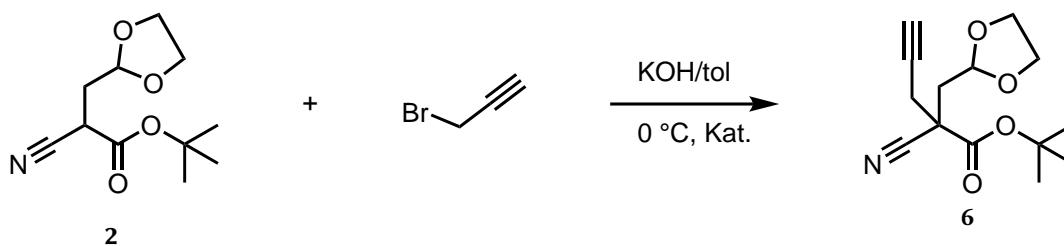
Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C1	KOH	2 h	0 °C	94	1
C2	KOH	2 h	0 °C	93	12
C3	KOH	2 h	0 °C	80	20
C4	KOH	2 h	0 °C	93	38
C5	KOH	2 h	0 °C	93	76
C5	CsOH	2 h	0 °C	83	76
C5	CsOH	24 h	−10 °C	83	80

Table 4.2 | Yield and enantiomeric excess (in %) using different reaction conditions for **4**

The optical activity of the obtained product under reaction conditions of −10 °C for 24 h was measured:

$[\alpha]_{\mathrm{D}}^{20}$ +8 (c 0.1 , DCM).

4.18   (6-*tert*-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)-methyl)-5-cyanohex-2-enedioate (5)

A Schlenk tube with TBAB (0.8 mg, 1 mol %) and **2** (56.8 mg, 0.25 mmol) in toluene (1.5 mL) and KOH (50 %, 0.5 mL) was degassed and stirred under Argon. After cooling the mixture to 0 °C the reagent ethyl 4-bromocrotonate (76.8 mg, 0.3 mmol) was added and continued to stir for 2 h. The now red solution was quenched with Et_2O (5 mL) and ice water (3 mL). After extracting the aqueous phase with more Et_2O (5 × 5 mL), the organic phases were combined and washed with sat. NaCl and dried over magnesium sulfate. An MPLC was performed (EtOAc (30→50 %)/PE).

Yield: 45 mg (53 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 6.87 (m, 1 H); 5.97 (dt, J = 15.5, 1.3 Hz 1 H); 5.16 (dd, J = 5.6, 3.4 Hz, 1 H); 4.19 (q, J = 7.1 Hz, 2 H); 3.98 (m, 2 H); 3.86 (m, 2 H); 2.71 (m, 2 H); 2.31 (dd, J = 14.2, 5.7 Hz, 1 H); 2.12 (dd, J = 14.2, 3.5 Hz, 1 H); 1.49 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 166.5 (C); 165.5 (C); 139.5 (CH); 126.9 (CH); 118.1 (C); 101.2 (CH); 84.6 (C); 65.4 (CH$_2$); 64.9 (CH$_2$); 60.7 (CH$_2$); 45.6 (C); 40.3 (CH$_2$); 39.8 (CH$_2$); 27.8 (CH$_3$); 14.3 (CH$_3$).

HRMS m/z: $[M + Na]^+$ Calcd for C$_{14}$H$_{25}$NNaO$_6{}^+$ 362.1574; Found 362.1567

$[2\,M + Na]^+$ Calcd for C$_{31}$H$_{50}$N$_2$NaO$_{12}{}^+$ 701.3256; Found 701.3219.

Asymmetric synthesis

The procedure was performed in the same manner as seen above. Varying factors are described respectively in the table below.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C1	KOH	2 h	0 °C	68	0
C2	KOH	2 h	0 °C	70	6
C3	KOH	2 h	0 °C	79	8
C4	KOH	2 h	0 °C	84	16
C5	KOH	2 h	0 °C	91	42
C5	CsOH	2 h	0 °C	65	48
C5	CsOH	24 h	−8 °C	57	48

Table 4.3 | Yield and enantiomeric excess (in %) using different reaction conditions for **5**

The optical activity of the obtained product under reaction conditions of −10 °C for 24 h was measured:

$[\alpha]_D^{20}$ +9 (c 0.1, DCM).

4.19 *tert*-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyano-pent-4-ynoate (6)

After mixing the substrate **2** (56.8 mg, 0.25 mmol) with toluene (1.5 mL) and KOH (50 %, 0.5 mL), the catalyst TBAB (0.8 mg, 1 mol %) was added. The mixture was degassed and cooled to 0 °C when 2-brompropin (44.2 mg, 0.3 mmol) was added as well. The reaction was rapidly stirred for 4 h at 0 °C. Ethyl ether (5 mL) and ice water (3 mL) were poured into the mixture and the organic layer separated. The aqueous layer was washed with DCM (5 × 5 mL) and the organic extracts combined and shaken out with sat. NaCl (5 mL).

Yield: 64 mg (95 %)

^{1}H-NMR (600 MHz, CDCl$_3$): δ 5.16 (dd, J = 5.4, 3.8 Hz, 1 H); 3.99 (m, 2 H); 3.87 (m, 2 H); 2.83 (dd, J = 16.6, 2.6 Hz, 1 H); 2.76 (dd, J = 16.6, 2.6 Hz, 1 H); 2.33 (dd, J = 14.3, 5.3 Hz, 1 H); 2.26 (dd, J = 14.3, 3.9 Hz, 1 H); 2.21 (t, J = 2.6 Hz, 1 H); 1.52 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 166.2 (C); 118.0 (C); 101.3 (CH); 84.6 (C); 73.3 (C); 65.3 (CH$_2$); 64.9 (CH$_2$); 45.8 (C); 39.0 (CH$_2$); 28.0 (CH$_2$); 27.8 (CH$_3$).

HRMS m/z: [M + Na]$^+$ Calcd for C$_{14}$H$_{19}$NNaO$_4$$^+$ 288.1206; Found 288.1211

[2 M + Na]$^+$ Calcd for C$_{28}$H$_{38}$NNaO$_4$$^+$ 553.2520; Found 553.2514.

Asymmetric synthesis

The procedure was performed in the same manner as seen above. Varying factors are described respectively in the table below.

The optical activity of the obtained product under reaction conditions of −10 °C for 24 h was measured:

$[\alpha]_D^{20}$ +22 (c 0.1 , DCM).

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C2	KOH	2 h	0 °C	84	0
C3	KOH	2 h	0 °C	75	2
C4	KOH	2 h	0 °C	89	14
C5	KOH	2 h	0 °C	89	42
C5	CsOH	2 h	0 °C	64	60
C5	CsOH	24 h	−8 °C	63	64

Table 4.4 | Yield and enantiomeric excess (in %) using different reaction conditions for **6**

4.20   *tert*-Butyl (E)-2-((1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate (7)
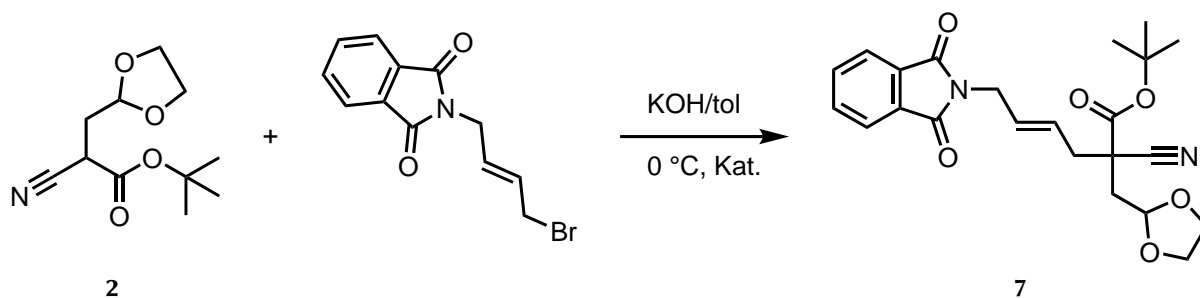
The substrate **2** (56.8 mg, 0.25 mmol) and TBAB (0.8 mg, 1 mol %) were mixed in toluene (1.5 mL) and KOH (50 %, 0.5 mL). The mixture was degassed and cooled to 0 °C. During continuous stirring (E)-2-(4-bromobut-2-en-1-yl)isoindoline-1,3-dione (111.6 mg, 0.3 mmol) was added and the mixture stirred for 4 h at 0 °C to gain a milky solution. After adding Et_2O (5 mL) and ice water (3 mL) the aqueous layer was washed with DCM (5 × 5 mL) and the organic extracts were combined and washed with sat. NaCl and dried over $MgSO_4$. An MPLC was performed (EtOAc (10→50 %)/PE).

Yield: 57 mg (53 %)

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.83 (m, 2 H); 7.70 (m, 2 H); 5.73 (m, 2 H); 5.12 (dd, J = 5.9, 3.4 Hz, 1 H); 4.26 (m, 2 H); 3.94 (m, 2 H); 3.83 (m, 2 H); 2.58 (m, 1 H); 2.48 (m, 1 H); 2.24 (dd, J = 14.2, 5.9 Hz, 1 H); 2.05 (dd, J = 4.2, 3.4 Hz, 1 H); 1.45 (s, 9 H).

^{13}C-NMR (150 MHz, CDCl$_3$): δ 167.8 (C); 166.8 (C); 134.0 (CH); 132.1 (C); 129.9 (CH); 126.1 (CH); 123.3 (CH); 118.3 (C); 101.3 (CH); 84.0 (C); 65.2 (CH$_2$); 64.7 (CH$_2$); 46.0 (C); 40.7 (CH$_2$); 39.6 (CH$_2$); 39.9 (CH$_2$); 27.7 (CH$_3$).

HRMS m/z: $[M + Na]^+$ Calcd for $C_{23}H_{26}NNa_2O^+$ 449.1683; Found 449.1687

$[2M + Na]^+$ Calcd for $C_{46}H_{52}NNa_4O^+$ 874.3474; Found 875.3477.

Asymmetric synthesis

The procedure was performed in the same manner as seen above. Varying factors are described respectively in the table below.

Catalyst	Base	Reaction time	Temperature	Yield (%)	e.e. (%)
C1	KOH	2 h	0 °C	48	2
C2	KOH	2 h	0 °C	57	4
C3	KOH	2 h	0 °C	29	8
C4	KOH	2 h	0 °C	50	14
C5	KOH	2 h	0 °C	80	47
C5	CsOH	2 h	0 °C	72	66
C5	CsOH	24 h	−10 °C	81	70

Table 4.5 | Yield and enantiomeric excess (in %) using different reaction conditions for **7**

The optical activity of the obtained product under reaction conditions of −10 °C for 24 h was measured:

$[\alpha]_D^{20}$ +7 (*c* 0.1 , DCM).

Chapter 5
References and Notes

[1] G. C. Barrett, D. T. Elmore, *Amino Acids and Peptides*, Cambridge University Press, **1998**.

[2] S. S. Schiffman, K. Sennewald, J. Gagnon, *Physiology & Behavior* **1981**, *27*, 51–59.

[3] Y.-P. Xue, C.-H. Cao, Y.-G. Zheng, *Chemical Society Reviews* **2018**, *47*, 1516–1561.

[4] E. A. Bell, A. A. Watson, R. J. Nash, *Natural Product Communications* **2008**, *3*.

[5] G. Wu, *Advances in Nutrition* **2010**, *1*, 31–37.

[6] H.-J. Gais, H. Hemmerle, *Chemie in unserer Zeit* **1990**, *24*, 239–248.

[7] F. Fülöp in *Bioactive Natural Products (Part C)*, Elsevier, **2000**, pp. 273–306.

[8] C. Nájera, J. M. Sansano, *Chemical Reviews* **2007**, *107*, 4584–4671.

[9] A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley, **2005**.

[10] *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), John Wiley & Sons, Inc., **2000**.

[11] S. C. Stinson, *Chemical & Engineering News* **2001**, *79*, 79–97.

[12] H. Kawai, N. Shibata, *The Chemical Record* **2014**, *14*, 1024–1040.

[13] S. Shirakawa, S. A. Moteki, K. Maruoka in *Modern Tools for the Synthesis of Complex Bioactive Molecules*, John Wiley & Sons, Inc., **2012**, pp. 213–242.

[14] E. Reyes, U. Uria, J. L. Vicario, L. Carrillo in *Organic Reactions*, *Vol. 90*, American Cancer Society, **2016**, pp. 1–898.

[15] U. H. Dolling, P. Davis, E. J. J. Grabowski, *Journal of the American Chemical Society* **1984**, *106*, 446–447.

[16] M. J. O'Donnell, W. D. Bennett, S. Wu, *Journal of the American Chemical Society* **1989**, *111*, 2353–2355.

[17] B. Lygo, P. G. Wainwright, *Tetrahedron Letters* **1997**, *38*, 8595–8598.

[18] E. J. Corey, F. Xu, M. C. Noe, *Journal of the American Chemical Society* **1997**, *119*, 12414–12415.

[19] S.-s. Jew, M.-S. Yoo, B.-S. Jeong, I. Y. Park, H.-g. Park, *Organic Letters* **2002**, *4*, 4245–4248.

[20] R. Chinchilla, P. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281.

[21] K. Maruoka, *Organic Process Research & Development* **2008**, *12*, 679–697.

[22] E. Corey, M. C. Noe, F. Xu, *Tetrahedron Letters* **1998**, *39*, 5347–5350.

[23] S. Arai, R. Tsuji, A. Nishida, *Tetrahedron Letters* **2002**, *43*, 9535–9537.

[24] T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Letters* **2002**, *43*, 9539–9543.

[25] T. Ooi, M. Kameda, J.-i. Fujii, K. Maruoka, *Organic Letters* **2004**, *6*, 2397–2399.

[26] S. Kusumoto, S. Imaoka, Y. Kambayashi, T. Shiba, *Tetrahedron Letters* **1982**, *23*, 2961–2964.

[27] A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angewandte Chemie International Edition* **2005**, *44*, 4564–4567.

[28] T. Ooi, M. Kameda, K. Maruoka, *Journal of the American Chemical Society* **2003**, *125*, 5139–5151.

[29] T. Hashimoto, K. Maruoka, *Tetrahedron Letters* **2003**, *44*, 3313–3316.

[30] M. N. Rao, M. Haridas, M. K. Gangwar, P. Rajakannu, A. C. Kalita, P. Ghosh, *European Journal of Inorganic Chemistry* **2015**, *2015*, 1604–1615.

[31] X. Zhang, X. Jia, L. Fang, N. Liu, J. Wang, X. Fan, *Organic Letters* **2011**, *13*, 5024–5027.

[32] M. Widhalm, U. Nettekoven, K. Mereiter, *Tetrahedron: Asymmetry* **1999**, *10*, 4369–4391.

[33] K. Nagata, D. Sano, Y. Shimizu, M. Miyazaki, T. Kanemitsu, T. Itoh, *Tetrahedron: Asymmetry* **2009**, *20*, 2530–2536.

[34] H.-J. Li, R. Guillot, V. Gandon, *The Journal of Organic Chemistry* **2010**, *75*, 8435–8449.

[35] B. M. Trost, J. R. Miller, C. M. Hoffman, *Journal of the American Chemical Society* **2011**, *133*, 8165–8167.

Appendix A
NMR spectra

tert-Butyl 2-cyano-3-(1,3-dioxoisoindolin-2yl)-propan-oate (14)

^{1}H-NMR

^{13}C-NMR

6Dec1118 91 1 "C:\NMR bebe"
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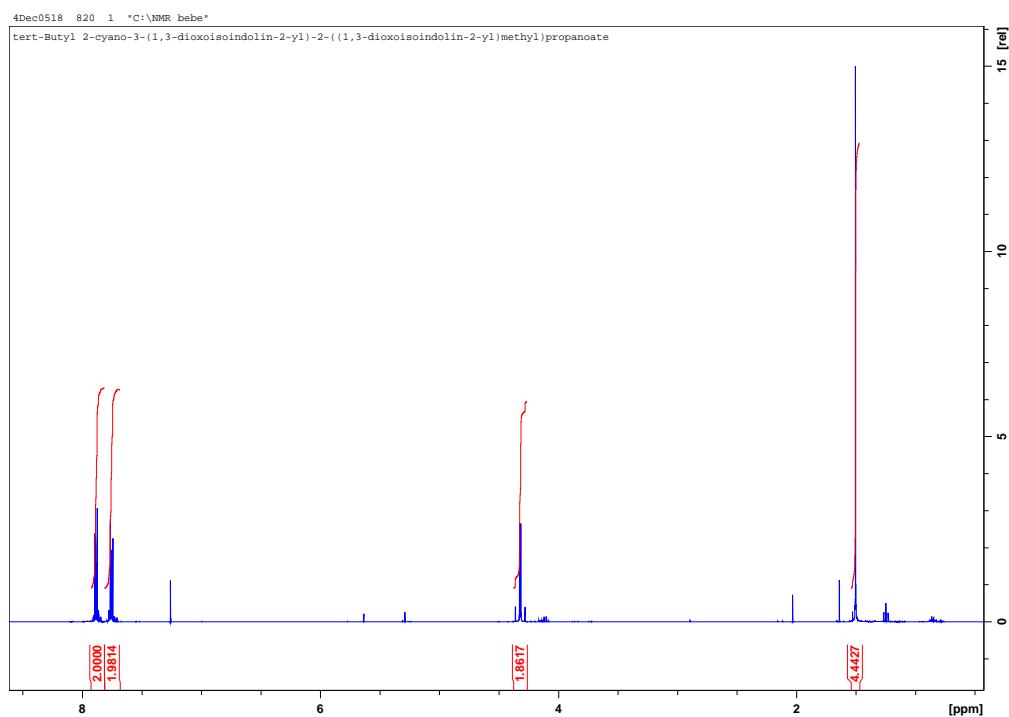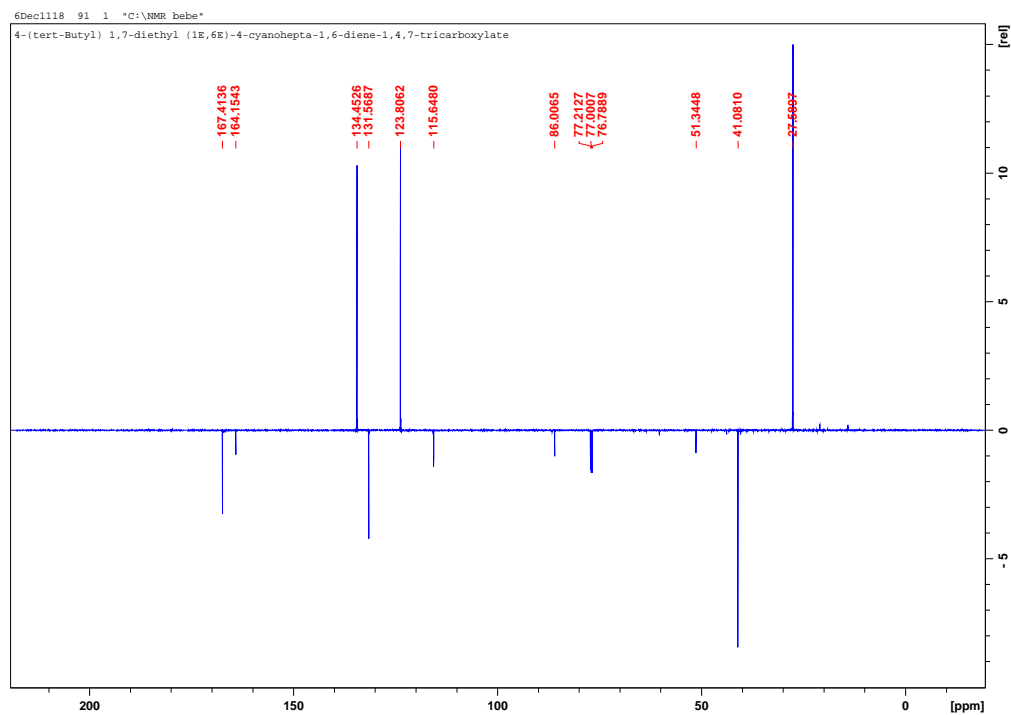
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¹H-NMR

^{13}C-NMR
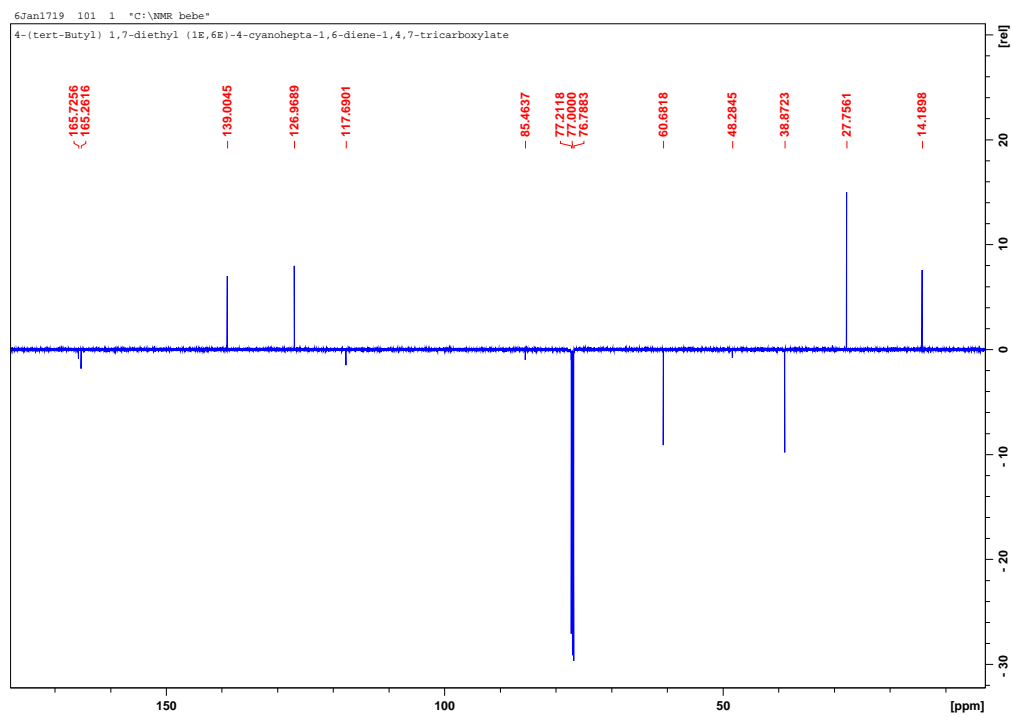
6Jan1719 101 1 "C:\NMR bebe"

4-(tert-Butyl) 1,7-diethyl (1E,6E)-4-cyanohepta-1,6-diene-1,4,7-tricarboxylate

COSY-NMR

6Jan1719 102 1 "C:\NMR bebe"

4-(tert-Butyl) 1,7-diethyl (1E,6E)-4-cyanohepta-1,6-diene-1,4,7-tricarboxylate

HSQC-NMR

6Jan1719 103 1 "C:\NMR bebe"

4-(tert-Butyl) 1,7-diethyl (1E,6E)-4-cyanohepta-1,6-diene-1,4,7-tricarboxylate

HMBC-NMR

6Jan1719 104 1 "C:\NMR bebe"

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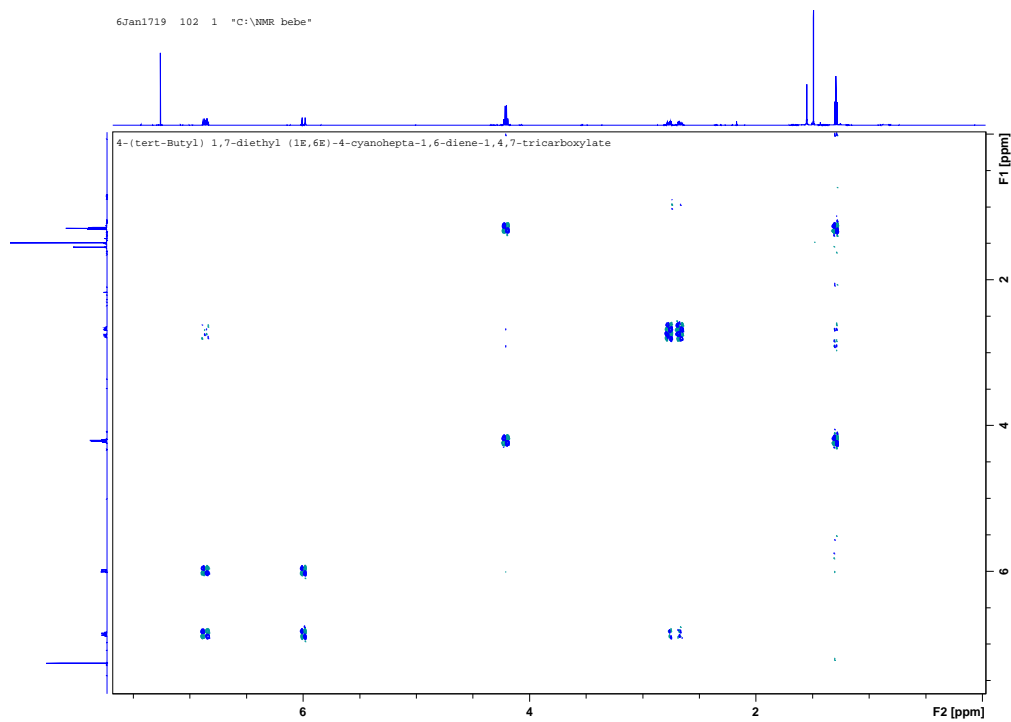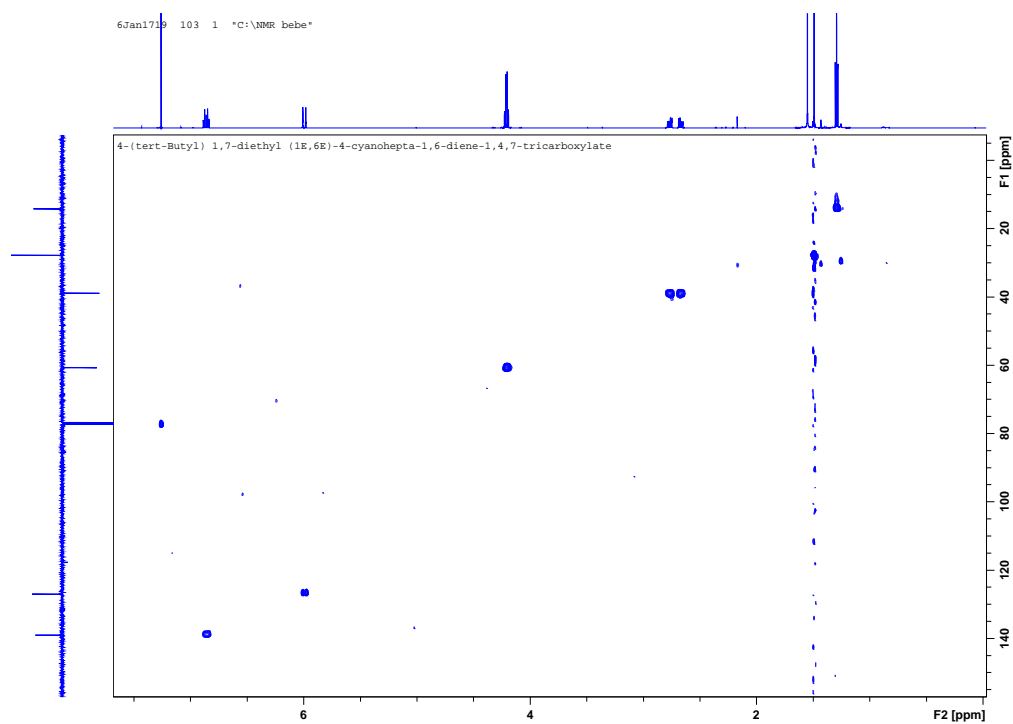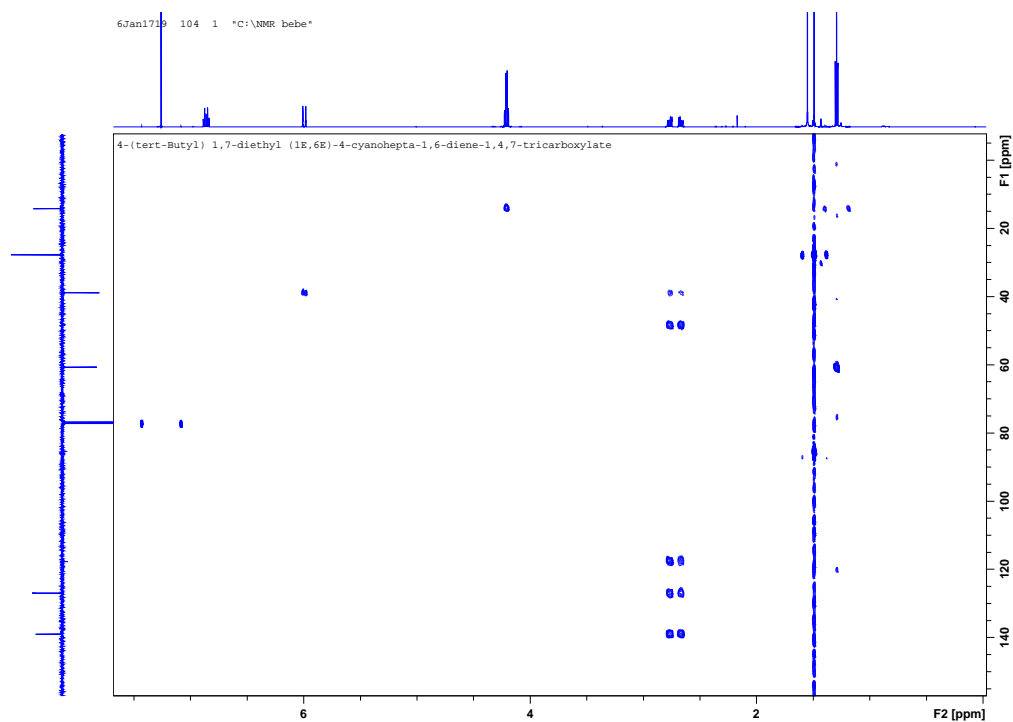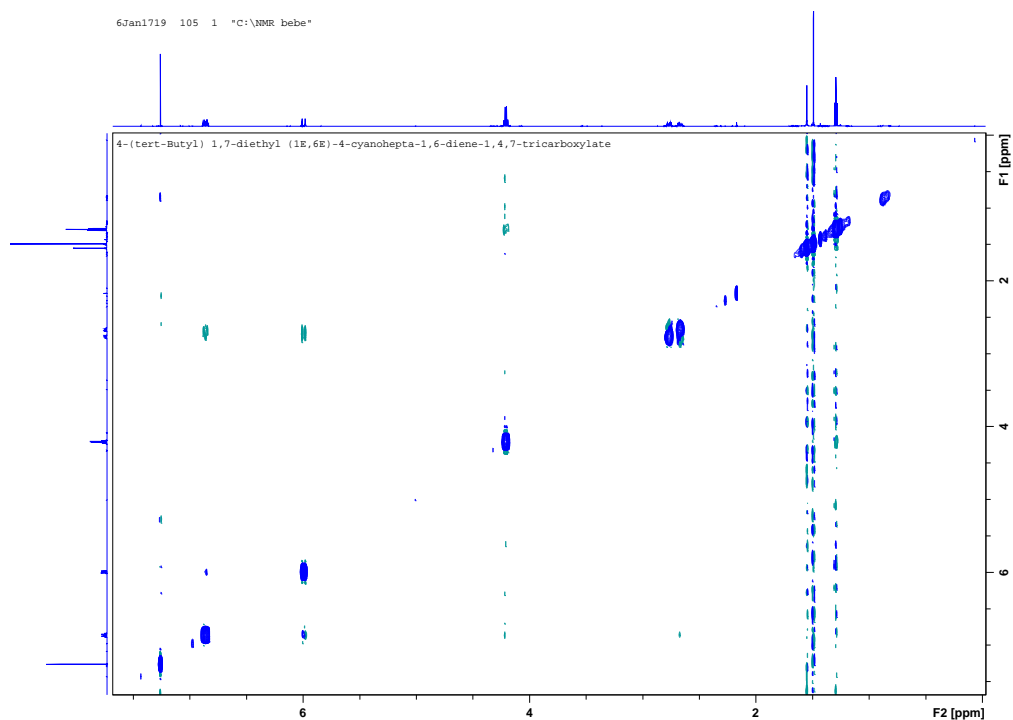
NOESY-NMR

tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2-cyano-3-phenyl-propanoate (3)

¹H-NMR

^{13}C-NMR

6Jun1419 151 1 "C:\NMR bebe"

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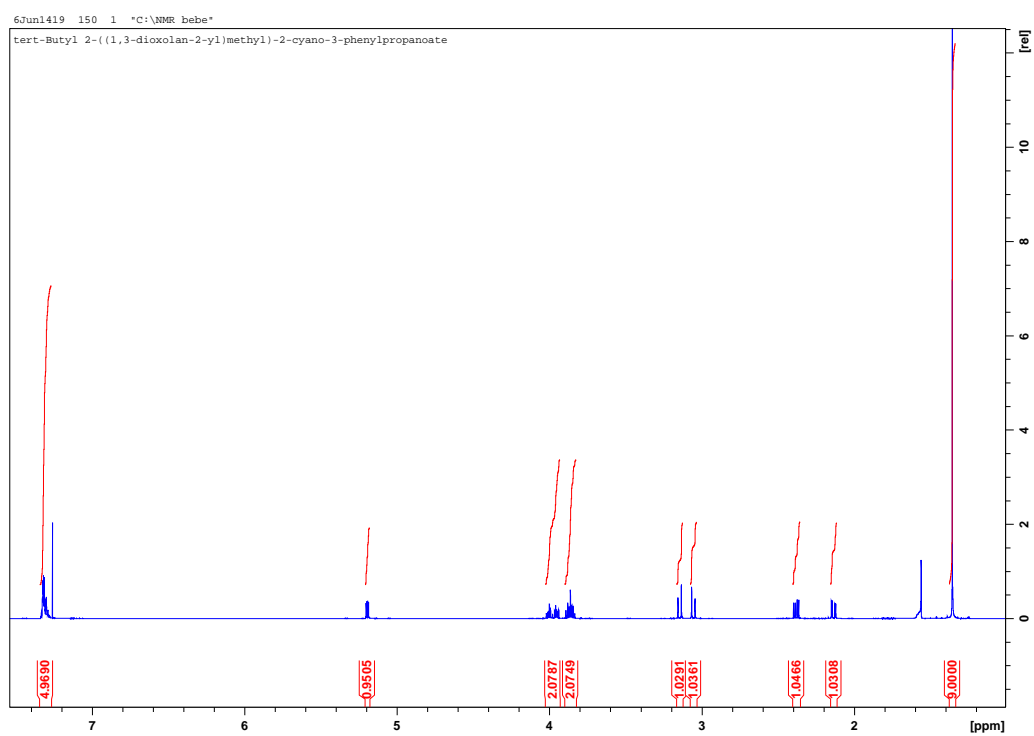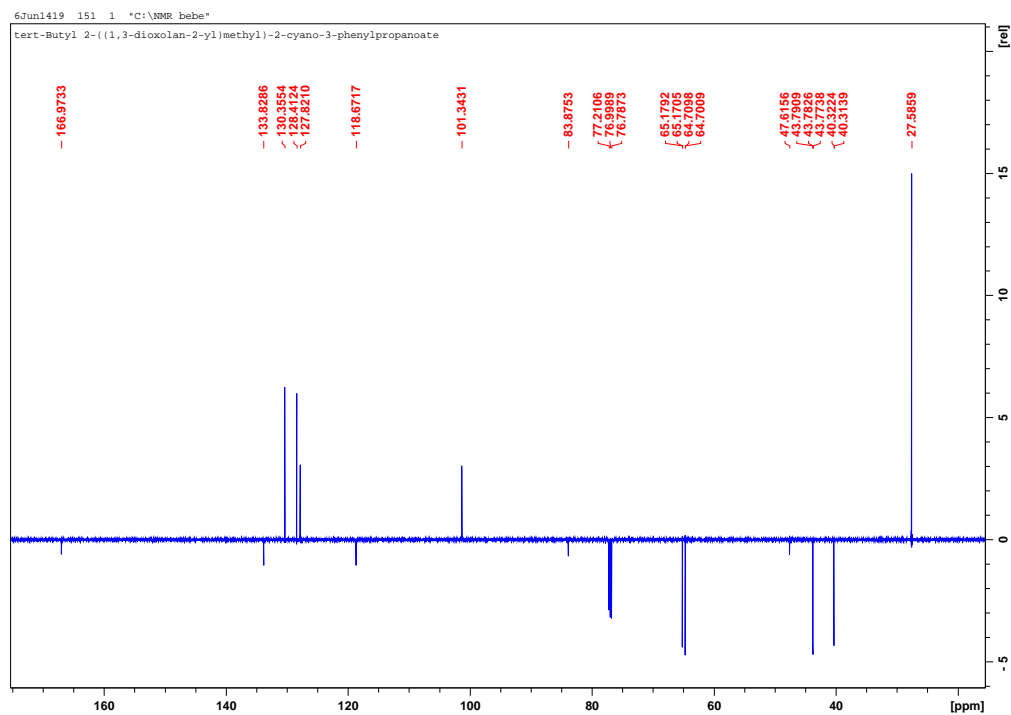
tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-enoate (4)

^{1}H-NMR

^{13}C-NMR

6Jan1719 91 1 "C:\NMR bebe"

tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2cyanopent-4-enoate

COSY-NMR

6Jan1719 92 1 "C:\NMR bebe"

tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2cyanopent-4-enoate

HSQC-NMR

6Jan1719 93 1 "C:\NMR bebe"

tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2cyanopent-4-enoate

HMBC-NMR

6Jan1719 94 1 "C:\NMR bebe"

tert-Butyl 2-((1,3-dioxolan-2-yl)methyl)-2cyanopent-4-enoate
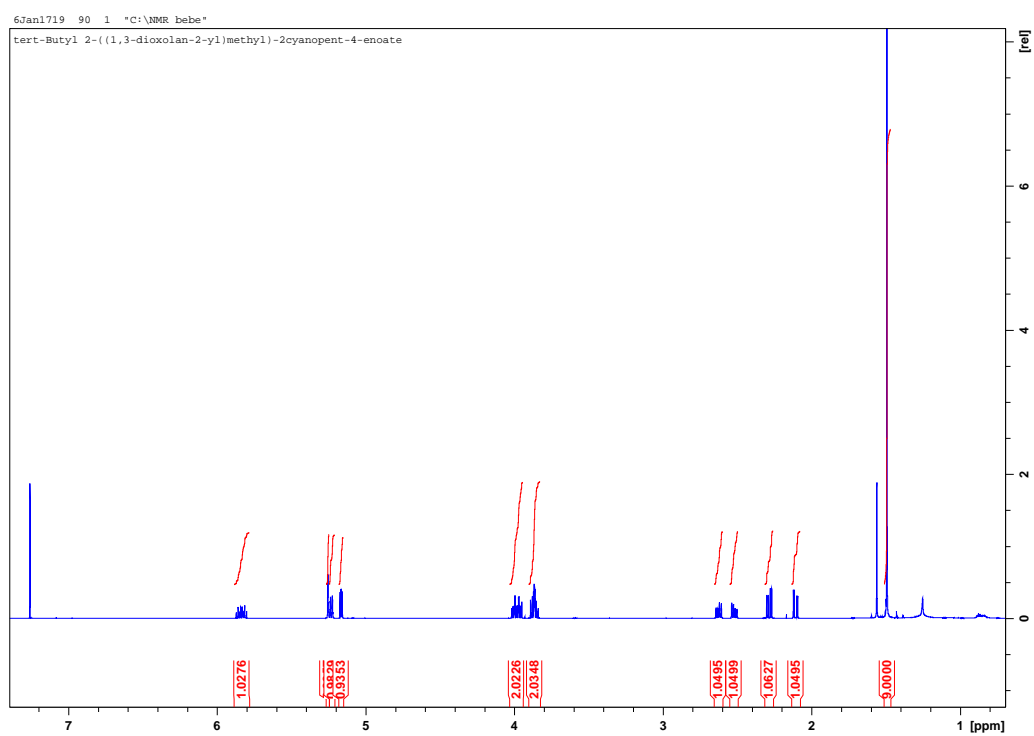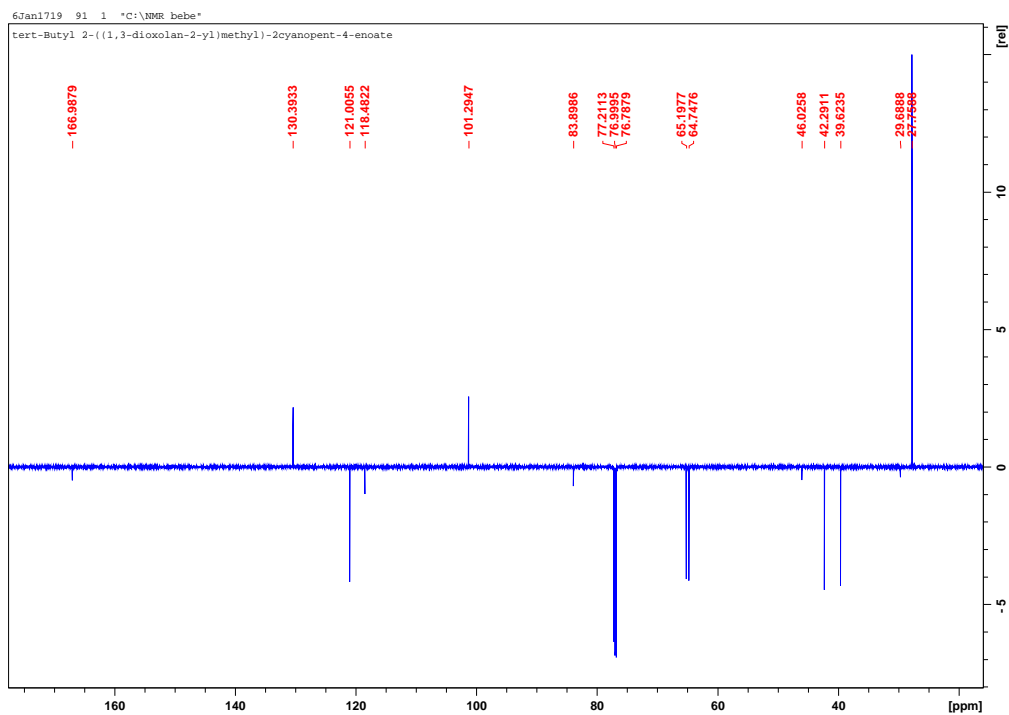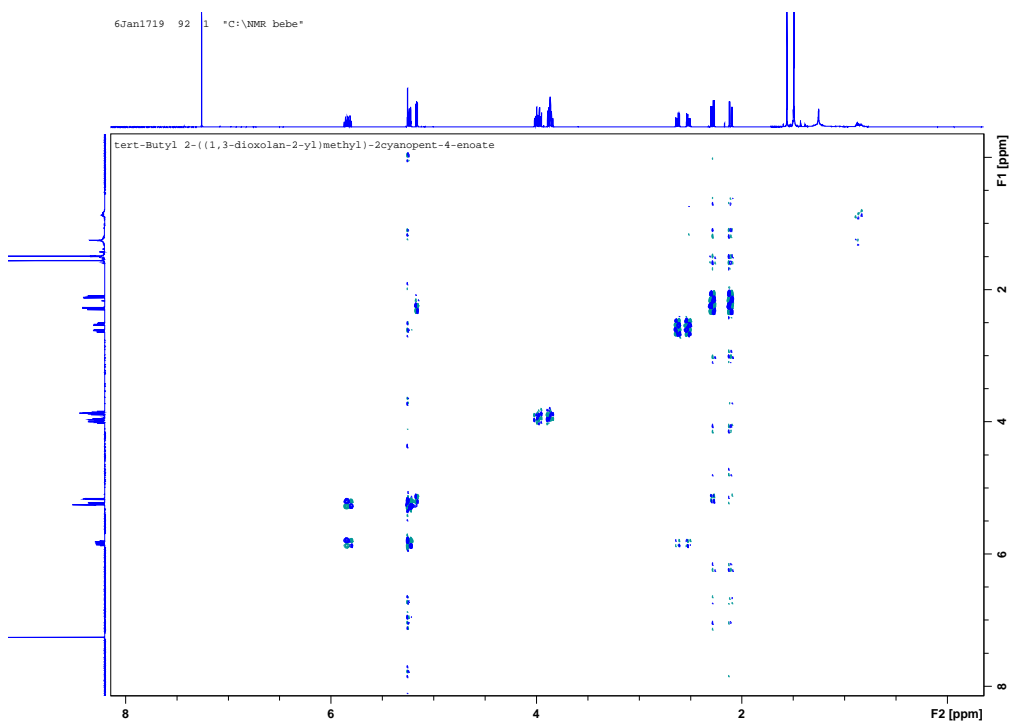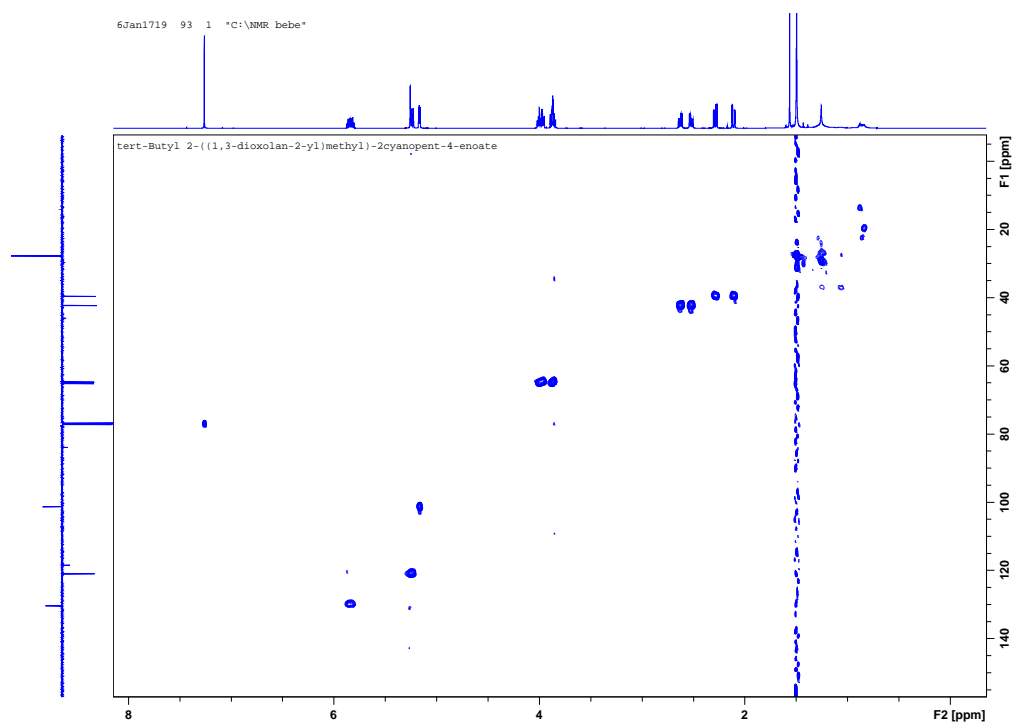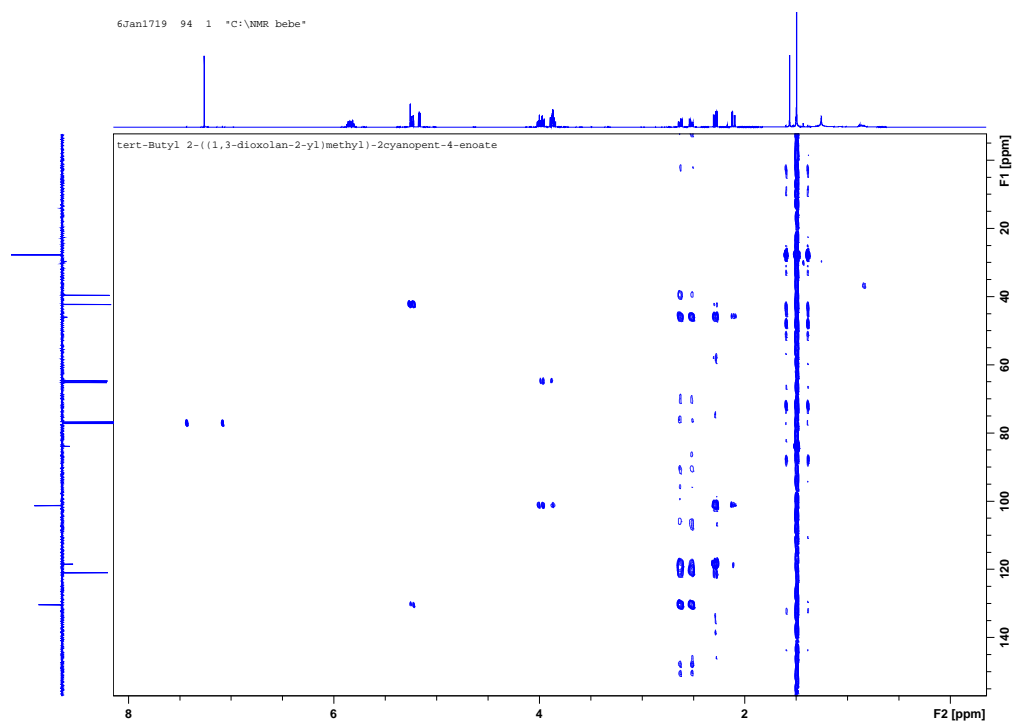
NOESY-NMR

(6-*tert*-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)methyl)-5-cyanohex-2-enedioate (5)

¹H-NMR

^{13}C-NMR

6Jan1719 111 1 "C:\NMR bebe"

(6-tert-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)methyl)-5-cyanohex-2-enedioate

COSY-NMR

6Jan1719 112 1 "C:\NMR bebe"

(6-tert-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)methyl)-5-cyanohex-2-enedioate

HSQC-NMR

(6-tert-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)methyl)-5-cyanohex-2-enedioate

HMBC-NMR

(6-tert-Butyl) 1-ethyl (E)-5-((1,3-dioxolan-2-yl)methyl)-5-cyanohex-2-enedioate

NOESY-NMR

tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-yn-oate (6)

¹H-NMR

6Feb2519 130 1 "C:\NMR bebe"
tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-ynoate

^{13}C-NMR

6Feb2519 131 1 "C:\NMR bebe"

tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-ynoate

COSY-NMR

6Feb2519 132 1 "C:\NMR bebe"

tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-ynoate

HSQC-NMR

6Feb2519 133 1 "C:\NMR bebe"

tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-ynoate

HMBC-NMR

6Feb2519 134 1 "C:\NMR bebe"

tert-Butyl (2-(1,3-dioxolan-2-yl)methyl)-2-cyanopent-4-ynoate

tert-Butyl (E)-2-(1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate (7)

¹H-NMR

^{13}C-NMR

6Jan0919 41 1 "C:\NMR bebe"

tert-Butyl (E)-2-(1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate

COSY-NMR

6Jan0919 42 1 "C:\NMR bebe"

tert-Butyl (E)-2-(1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate

HSQC-NMR

6Jan0919   43   1   "C:\NMR bebe"

tert-Butyl (E)-2-(1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate

HMBC-NMR

6Jan0919   44   1   "C:\NMR bebe"

tert-Butyl (E)-2-(1,3-dioxolan-2-yl)methyl)-2-cyano-6-(1,3-dioxoisoindolin-2-yl)hex-4-enoate

Appendix B
Display Elements

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Abstract

The asymmetric substitution of cyanoacetates to form highly functionalised quaternary carbon centres was performed under phase-transfer catalytic conditions. Varying reaction conditions and modified *N*-spiro ammonium salt type catalysts were used to optimise reactivity and enantioselectivity, up to 91 % and 80 % e.e., respectively, were observed. All new compounds hold a β-amino acid function and were first substituted at the α-position with an acetal group. The fourth substituents are of benzylic, allylic or alkyne nature or include ester or phthalimid moieties.

Zusammenfassung

Asymmetrische Substitution von Cyanoacetat wurde unter phasentransfer-katalytischen Bedingungen zur Bildung von hochfunktionalisierten quaternären Kohlenstoffzentren durchgeführt. Variierende Reaktionsbedingungen und modifizierte *N*-Spiroammoniumsalz-Katalysatoren wurden verwendet um Reaktivität und Enantioselektivität zu verbessern, bis zu 91 % beziehungsweise 80 % konnten erreicht werden. Alle neuen Verbindungen besitzen eine β-Aminosäure-Funktion und wurden zuerst am α-Kohlenstoff mit einem Acetal substituiert. Die vierten Substituenten verfügen über benzylische, allylische oder alkine Funktionen beziehungsweise über Ester- oder Phthalimid-Einheiten.