Evaluation of Aminoimidate Catalysts for a Michael Reaction

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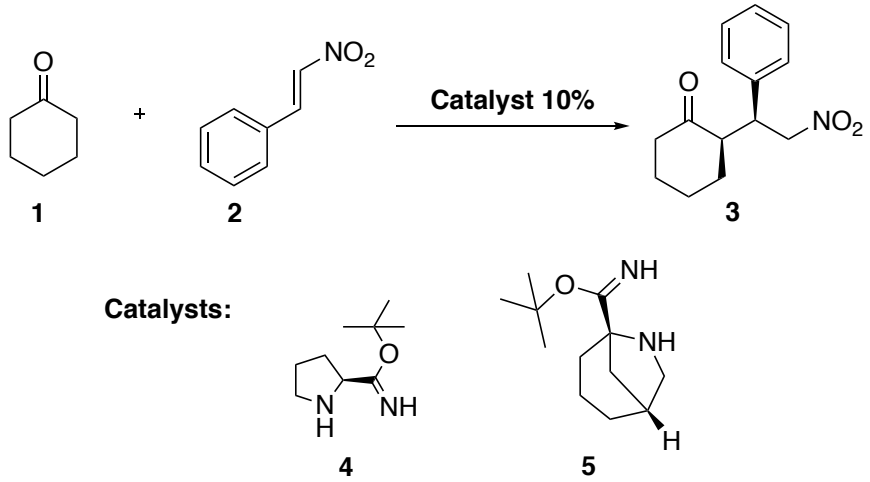
1. Abstract

The basis of this work was previous studies of amino acid derivatives in organocatalysis by the Clarke group. As a result of those studies, a new class of organocatalyst was discovered – aminoimidates, which proved to be good in the aldol reaction. In this work, aminoimidates **4** and **5** were synthesized and investigated as organocatalysts in a Michael reaction (Scheme 1).



Scheme 1. Investigation of a Michael reaction catalyzed by aminoimidates

Catalyst **4** showed good conversions which have been improved by inclusion of a benzoic acid. These conditions were applied to a wide range of substrates. In the reactions catalyzed by *L*-proline imidate **4**, the major diastereomer is the *syn* isomer with enantiomeric excesses of up to 84%. Bicyclic catalyst **5** was unable to catalyze this reaction.

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Thank you to Ukraine and Great Britain!

7. Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text as references.

8. Introduction

8.1. Organocatalysis

The rapid development of all spheres of life in the modern world is connected with the new technologies, that humanity successfully creates and uses. Chemistry is no exception. The manufacture of varnishes, paints, cosmetics, photochemical materials, and pharmaceutical products is becoming more complicated every year. At the same time, organic and inorganic synthesis is becoming more focused on molecules with specified chemical properties.

The process of developing new approaches in chemistry is extremely important because it can generate cheaper methods of synthesis and more efficient use of resources. Every year, a huge number of scientific articles are published to expand our chemicals tools, especially in the areas of chemo-, diastereo- and enantioselectivity. High enantioselectivity is the most difficult to achieve in chemical transformations, and the enantiomeric purity of the compounds is critical, because it affects the properties of the molecules. It should be noted that the great importance of optically active molecules with one or more chiral centers is that they are able to provide exclusive properties, especially in drug discovery. For example, selective binding to selected biological targets.

There are three conceptual tools for creating stereogenic centers in catalysis: biocatalysis (using enzymes), catalysis with complexes of transition metals and organocatalysis (Fig. 1) [1]. All 3 areas are extremely important and complement each other. It is worth mentioning that this year Benjamin List and David MacMillan shared the 2021 Nobel Prize in Chemistry "for the development of asymmetric organocatalysis", which shows the special value of research in this area.

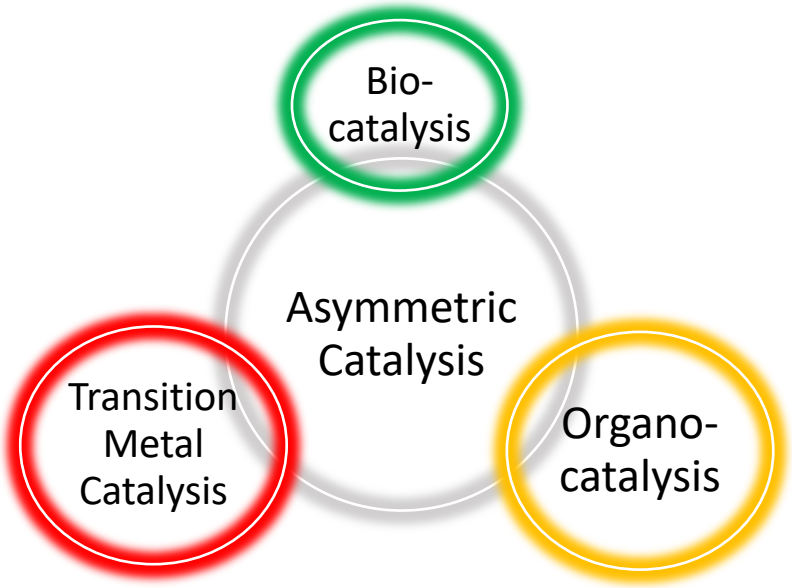
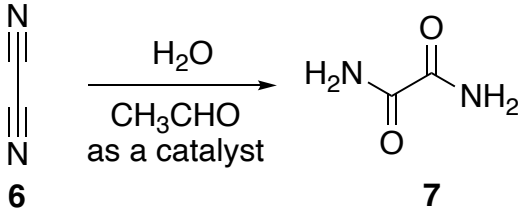


Fig. 1. The three pillars of asymmetric catalysis [1]

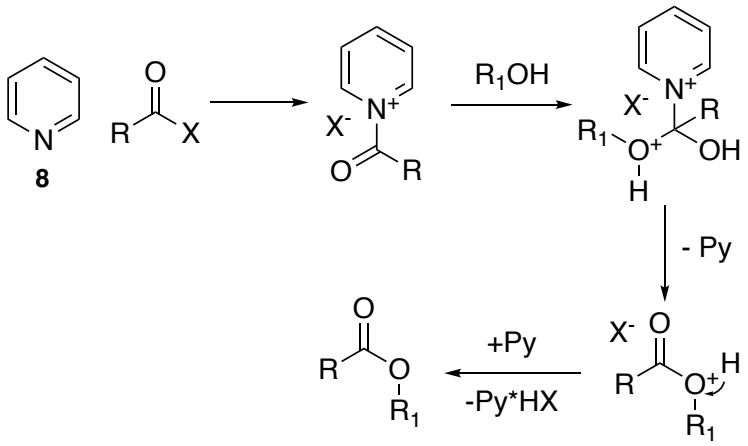
The history of organocatalysis began in 1860 from Justus von Liebig's synthesis of oxamide **7** from dicyan **6** and water, where acetaldehyde was identified as the first discovered pure "organocatalyst" (Scheme 2) [2].



6 **7**

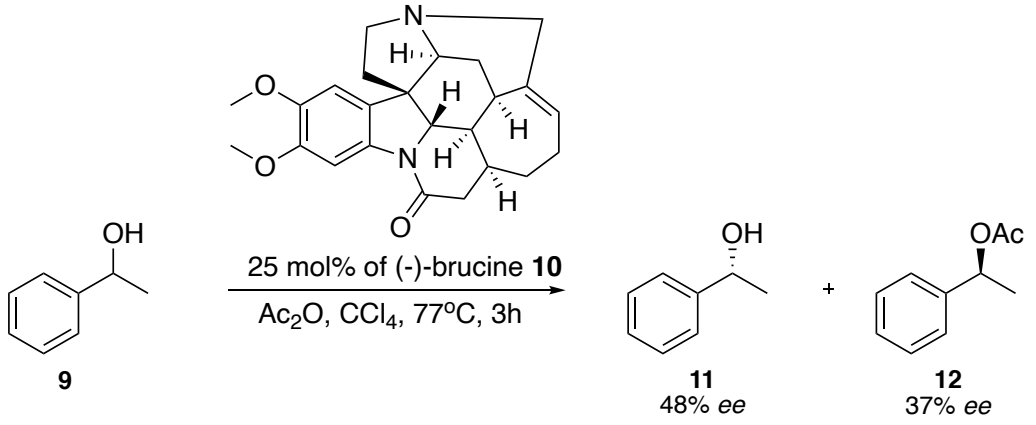
Scheme 2. The first synthesis using organocatalysis

Later, in 1898, A. Einhorn and F. Hollandt published work, where pyridine was used as an auxiliary reagent for the acylation of alcohols and phenols [3]. These were the first “blind” steps in the use of organic molecules as catalysts, because at that time a reasonable explanation of the catalytic role for these molecules did not yet exist. For example, the catalytic role of pyridine has been studied together with the mechanism of the reaction almost 60 years later (Scheme 3) [4].



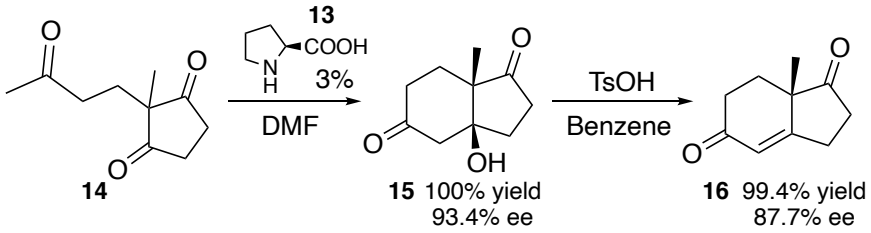
Scheme 3. Pyridine-catalyzed alcohol acylation mechanism

The use of enzymes in catalytic asymmetric reactions has aroused interest in finding small organic molecules that would exhibit similar properties. For example, Vavon and Peignier published work in 1929, where they showed that brucine **10** could be used for the kinetic resolution of racemic secondary alcohols (Scheme 4) [5].



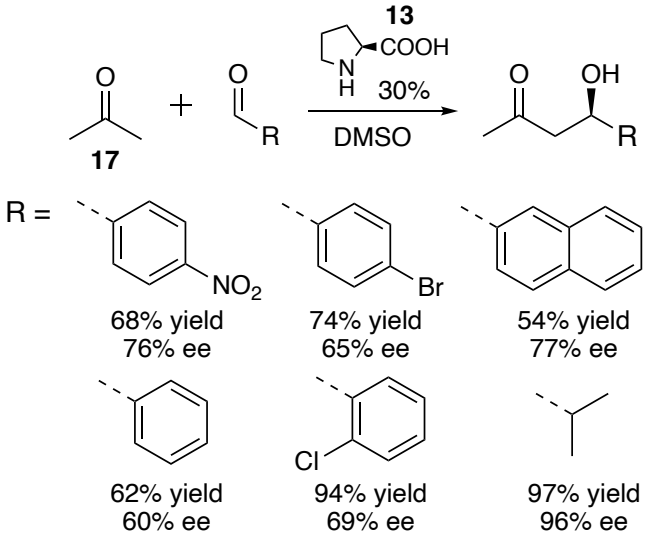
Scheme 4. Brucine as an organocatalyst in the kinetic resolution of racemic secondary alcohols

A breakthrough was the discovery of an asymmetric Robinson annulation using *L*-proline as a catalyst [6]. This intramolecular aldol condensation was called the Hajos-Parrish-Eder-Sauer-Wiechert reaction, and it opened an easy way to synthesize complex optically active natural compounds with excellent enantioselectivity (Scheme 5) [7].



Scheme 5. The Hajos-Parrish-Eder-Sauer-Weichert reaction

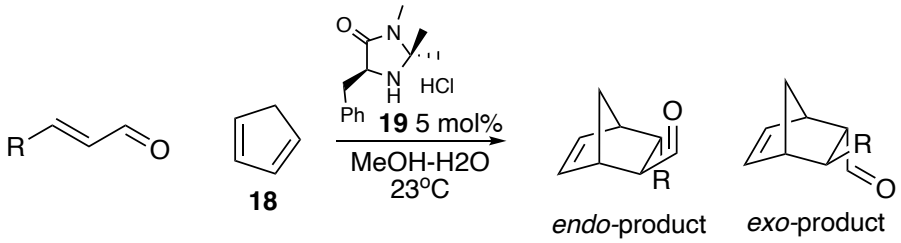
However, the revolutionary work in organocatalysis was the publication by List and Barbas in the early 2000s, which showed that single amino acids can catalyze the aldol condensation of various aldehydes and ketones in good to excellent enantioselectivity (Scheme 6**)** [8].



Scheme 6. Proline-catalyzed direct asymmetric aldol reactions

Contemporaneously, David MacMillan and co-workers published a groundbreaking paper describing an organocatalytic highly selective variant of the Diels-Alder reaction [9]. In this study, the optimal conditions for the reaction were identified and the scope was shown (Table 1).

Table 1. Organocatalyzed Diels-Alder reaction between cyclopentadiene and representative dienophiles



Entry	R	yield	*exo:endo*	*exo ee*	*endo ee*
1	Me	75%	1:1	86%	90%
2	Pr	92%	1:1	86%	90%
3	*i*-Pr	81%	1:1	84%	93%
4	Ph	99%	1.3:1	93%	93%
5	Furyl	89%	1:1	91%	93%

From those two works, a "gold rush" began in organocatalysis, and number of examples were reported, where small organic molecules catalyzed various reactions. The number of the reports rapidly increased (Fig. 2).

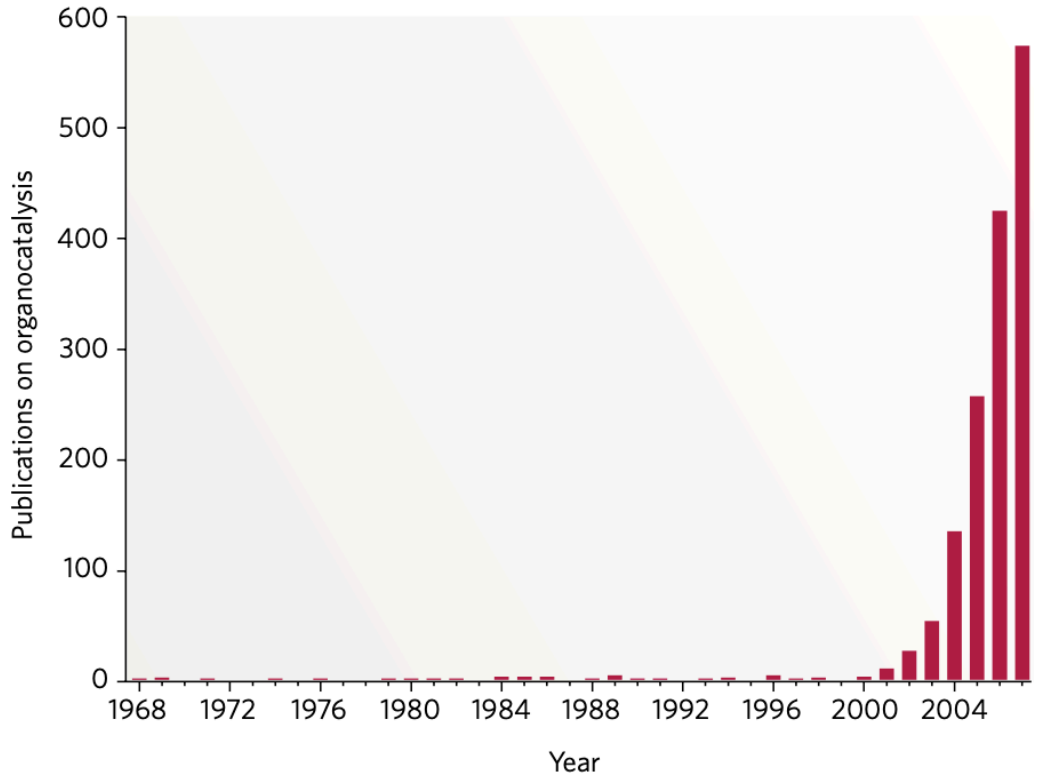


Fig. 2. An explosion of interest to organocatalysis [10]

8.2. Classification of organocatalysts and catalyzed reactions

The accumulation of a large amount of information on organocatalysis allowed the systematic classification of organocatalysts. Today there are 2 popular classifications:

1) Acid-Base Classification

Most organocatalysts can be classified according to the acid-base theories of Lewis and Brønsted. As a result, a general scheme of catalysis can be presented based on this classification (Fig. 3) [11].

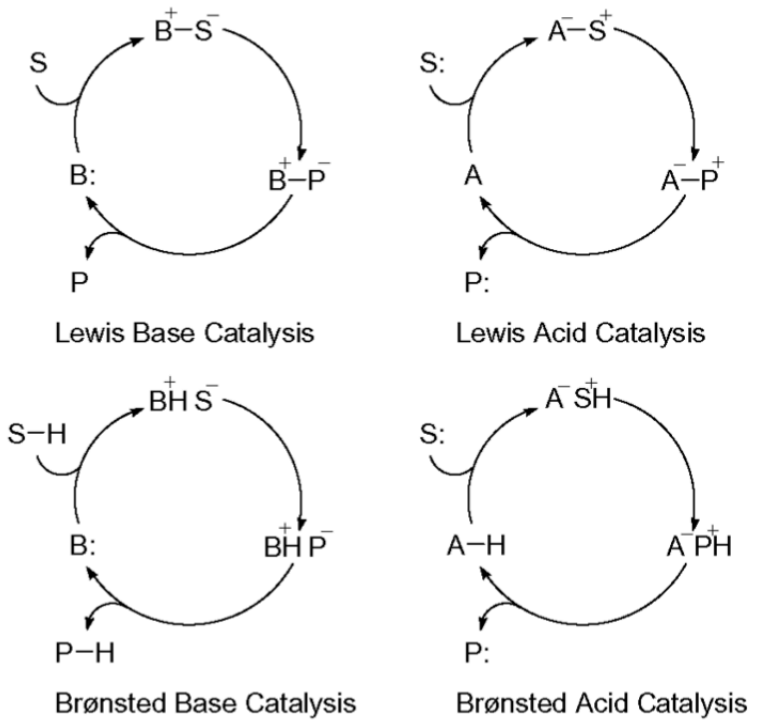


Fig. 3. Organocatalytic cycles based on acid-base classification [11]

A common feature of all catalytic cycles is that an intermediate is first formed between the substrate (S) and the catalyst (A; A-H; B; B-H). The resulting complex will have a chiral center, that will act as a chiral inductor, after which there is a transformation and regeneration of the catalyst. The disadvantage of this model is that it is too simplistic and hence alternative explanations were developed.

2) Classification by mechanism

Much more information can be obtained from this classification, which began to appear in the second half of the 2000s. Since each catalyst forms an intermediate complex with the substrate, together with the study of the mechanisms of reactions, it became clear that many of them operated on the same principle. Today we can identify 2 of the most common types of mechanism for organocatalytic asymmetric reactions:

- *Enamine catalysis*

The most common mechanism in organocatalysis is enamine catalysis. Its main feature is that an intermediate chiral enamine is formed between the chiral catalyst and a carbonyl compound. The key feature of organic molecules that catalyze this mechanism is the presence of an amino group, examples of catalysts in the Figure 4.

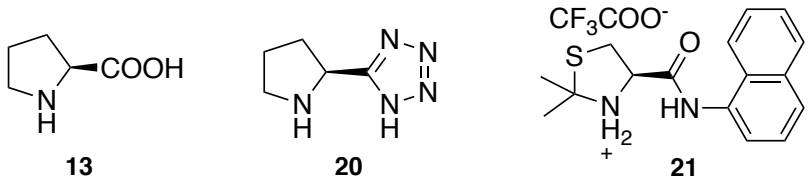
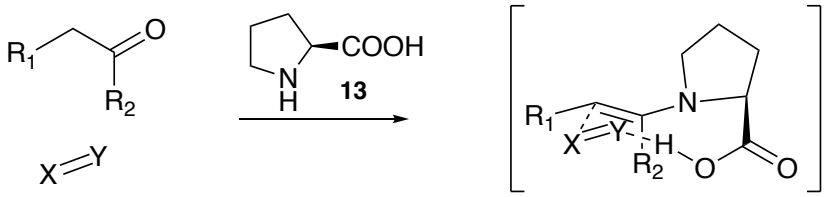


Fig. 4. Examples of molecules that catalyze reactions by the enamine mechanism

The mechanism of enamine catalysis can generally be represented as a six-membered transition state with the enamine hydrogen bonding to the electrophilic group (Scheme 7). In this catalysis, enamine always acts as a nucleophile.

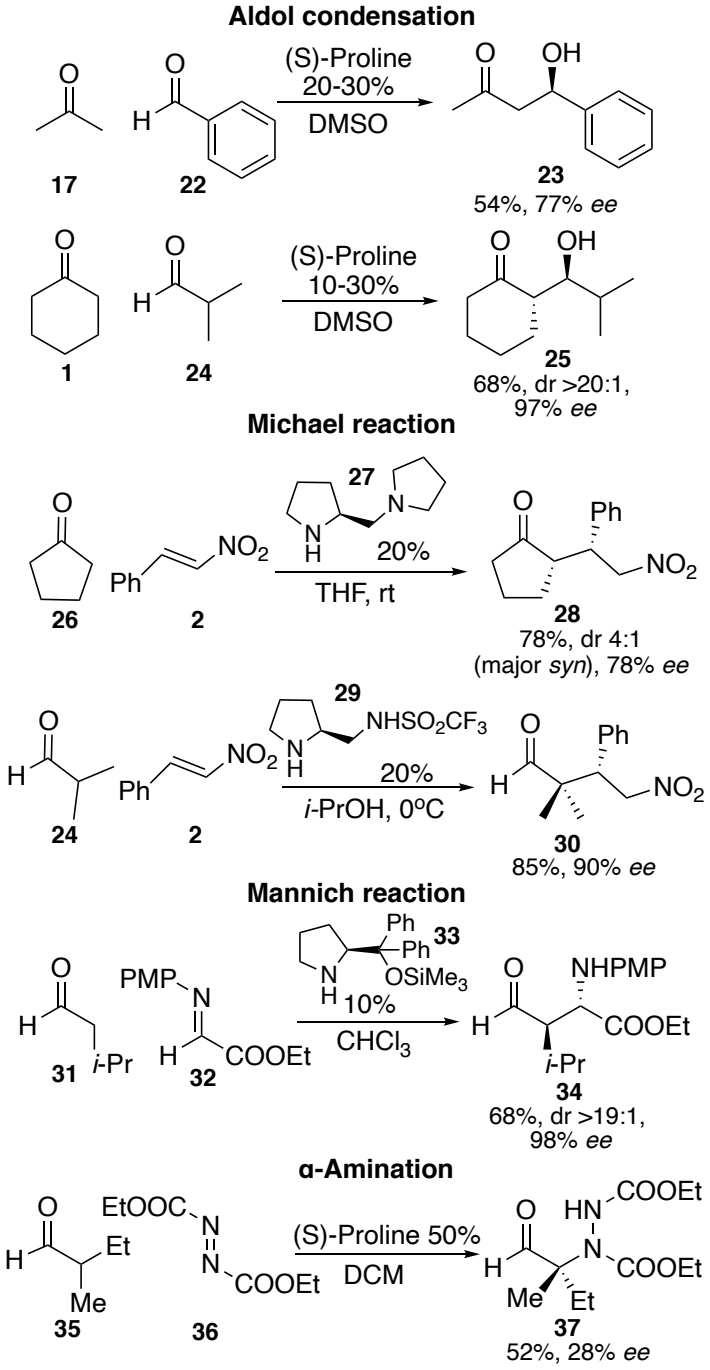


R_1 = any organic chain or ring system
R_2 = alkyl, H
X = C, N, O, S
Y = generic organic atom

Scheme 7. Activation mode of enamine catalysis

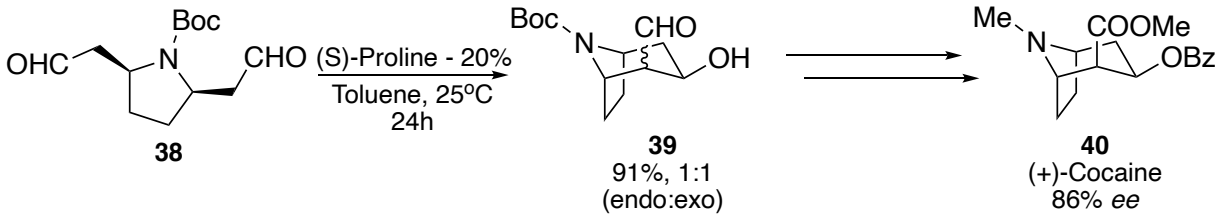
With the development of enamine catalysis, its tools and capabilities have greatly expanded, and today many transformations can be catalyzed by a variety of molecules with excellent yield and selectivity (Scheme 8). Based on the List review

[12], the most popular reactions are aldol condensation, Michael reaction and Mannich reaction. Enamine catalysis is also the main tool for stereoselective α-functionalization of carbonyl compounds such as intermolecular α-alkylation [12], α-amination [12], α-oxygenation [12], α-halogenation [12], α-sulphenylation [12].



Scheme 8. Examples of organocatalytic reactions with enamine mechanism

In addition to one-step transformations, exquisite reactions have also been developed, which also occur due to organocatalysis by the enamine mechanism. These allowed the one pot synthesis of complex optically active compounds including molecules of natural origin (Scheme 9) [12].



Scheme 9. Proline-catalyzed synthesis of the carbon framework for the (+) Cocaine total synthesis

- *Iminium catalysis*

This type of catalysis was first used in 2000 in the MacMillan group [9]. The catalysts are molecules of the same type as for enamine catalysis – amines, which can condense with carbonyl groups to form iminium ions (Fig. 5).

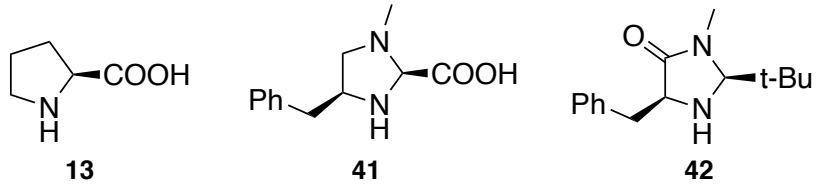
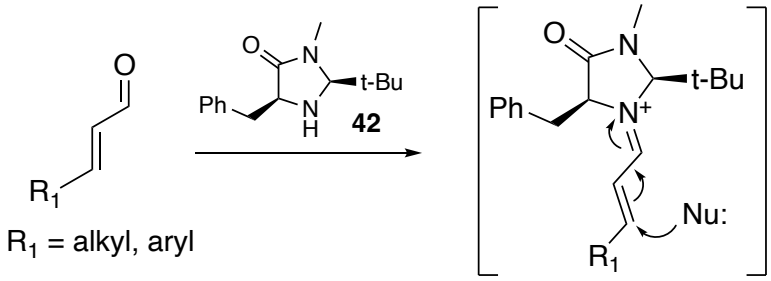


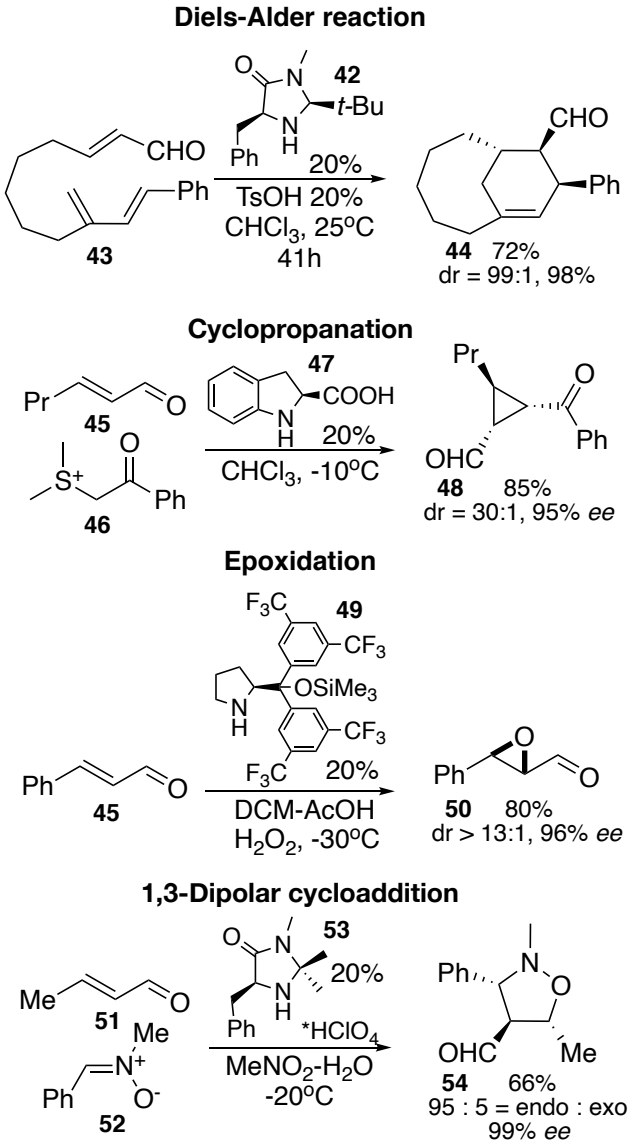
Fig. 5. Examples of molecules that catalyze reactions by the iminium mechanism

The main idea is that when chiral amines react with α,β-unsaturated carbonyls, then an iminium ion is formed, which then undergoes the reaction. Its main difference in comparison with the enamine mechanism is that the carbonyl compounds are not able to form an enamine intermediate due to a lack of enolizable α-protons, so they form iminium ions. This group acts as an acceptor in relation to unsaturated bonds and thus the intermediate acts as an electrophile. The general view of activation mode is shown in Scheme 10.



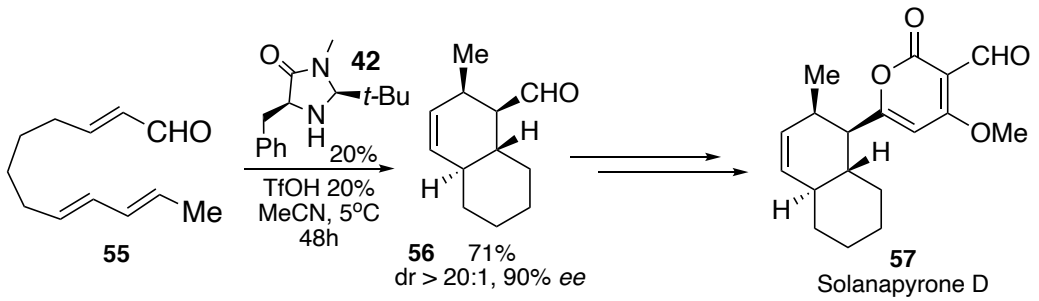
Scheme 10. Activation mode of iminium catalysis

Iminium organocatalysis has found wide application in organic synthesis and has become an important tool for asymmetric reactions such us Diels-Alder reaction [13], 1,3-dipolar cycloaddition [13], cyclopropanation [13], epoxidation [13], and many others (Scheme 11).



Scheme 11. Examples of organocatalytic reactions with iminium mechanism

The development of organocatalysis with an iminium mechanism has also led to the creation of powerful tools for organic synthesis and is used in highly selective syntheses of natural compounds. For instance, the synthesis of an optically active bicyclic core of Solanapyrone D has been successfully achieved by the intramolecular Diels-Alder reaction. Catalyst **42** forms an iminium intermediate with the α,β-unsaturated carbonyl group of molecule **55**, after which it reacts with the diene moiety at the other end of the molecule (Scheme 12) [13].



Scheme 12. Organocatalytic asymmetric synthesis of Solanapyrone D

8.3. Amino acids derivatives in organocatalysis

At the beginning of the search for organic molecules that could have catalytic properties, substances of natural origin were widely studied. This is primarily due to their cheapness and easy availability. As a result, natural amines, in particular alkaloids, and amino acids were used in the first systematic studies [14]. As was mentioned earlier, the "gold rush" in organocatalysis began with the work of List [8] for asymmetric aldol reactions, where the catalyst was *L*-proline. Although these were only the first steps in a study of organocatalysis, the yield and enantiomeric excesses of the reactions were good, but it still left room for further research. This was the impetus for many works. The main idea of all these studies was to investigate the influence of the structure of the molecule on its catalytic properties. As a result, the library of organic substances that can be a catalyst has expanded enormously. A wide variety of different types of substances were formed. Very good results were shown by amino acids (including with primary amino group) [15], peptides [16] and other various derivatives, where the framework of catalyst or main functional groups were improved.

One of the first works on the systematic study of the structures of amino acids, such as proline, was published by the Barbas group for asymmetric aldol addition reaction of acetone and 4-nitrobenzaldehyde in DMSO (Fig. 6) [17].

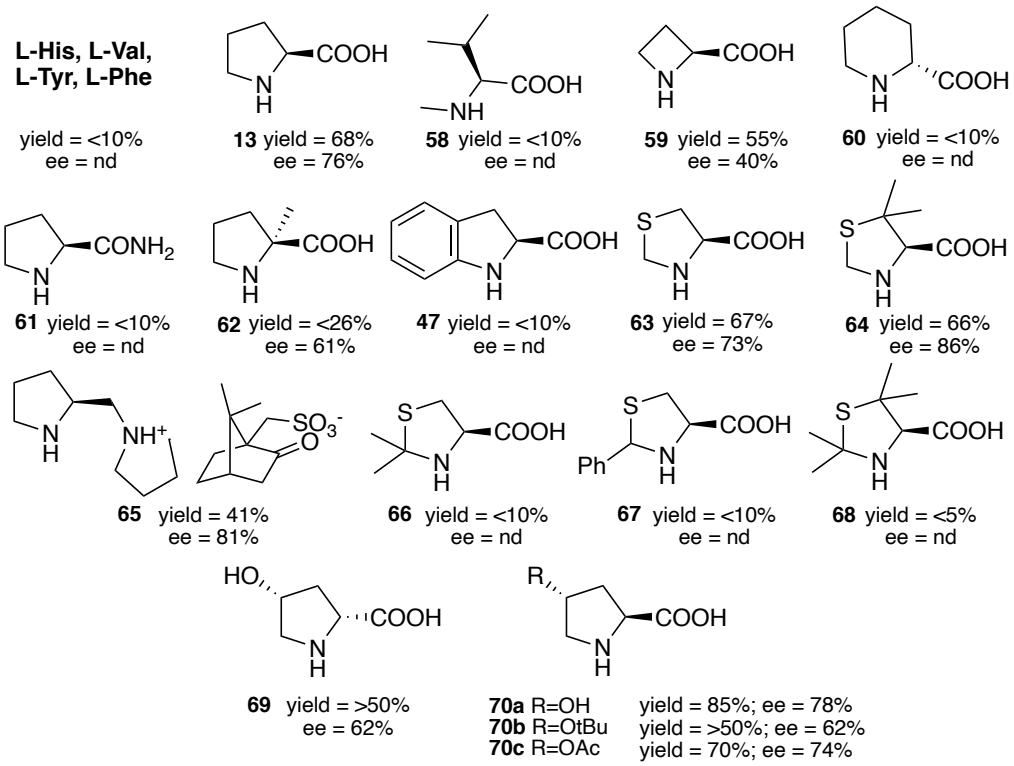


Fig. 6. Catalytic characteristics of amino acids with various structure for aldol reaction of acetone and 4-nitrobenzaldehyde

Compounds with 5-membered rings showed the best results. Particularly good results were obtained with 4-hydroxyproline **70a** and its derivatives at the hydroxy group **70b**, **70c**. High enantioselectivity were seen for compounds **63** and **64**. Their common feature is an increase in the size of the catalyst framework, which increases the selectivity. It can be noted that an increase in sterics may lose catalyst activity as for compounds **66**, **67** and **68**, which are derivatives **63**, however derivative **64** showed an increase of enantiomeric excess.

In addition, the derivatives **61** and **65** of proline, which were obtained by converting a functional carboxyl group, were investigated. Amide **61** had almost no catalytic activity, but the salt of diamine derivative **65** showed one of the best results [17].

Derivatives of the carboxyl group were also studied. For example, investigating the catalytic activity of amides for aldol condensation had some success [18]. As a result, the Gong group found the optimal conditions and structures of proline amides for the studied reaction. The best result was for amides, which have additional stereocenters, that play a key role in increasing stereoselectivity up to 99% as for compound **74 (**Fig. 7) [19].

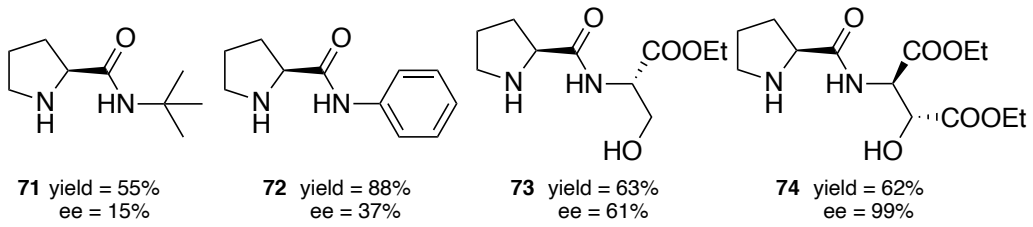


Fig. 7. Catalytic characteristics of *L*-proline amides for aldol reaction of acetone and 4-nitrobenzaldehyde

The use of various proline derivatives was also investigated in the asymmetric Michael reaction of cyclohexanone with trans-β-nitrostyrene (Fig. 8) [20].

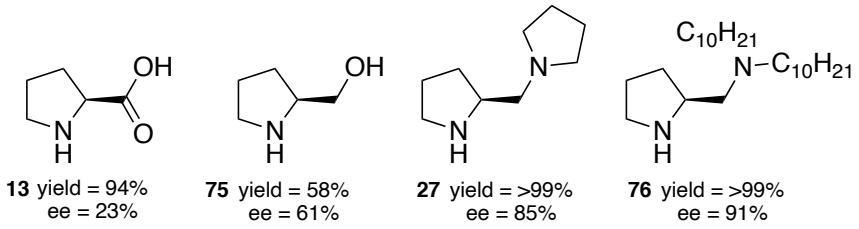


Fig. 8. Catalytic characteristics of *L*-proline derivatives for the asymmetric Michael reaction of cyclohexanone with trans-*β*-nitrostyrene

As a result, reaction conditions were found and excellent stereoselectivity was shown for diamines **27** and **76**, however, simple reduction of acid **13** to alcohol **75** gave also good increase of *ee*.

Considering the role of α-substituents in the pyrrolidine core, we can distinguish two fundamentally different effects on the catalytic process (Fig. 9) [21]. In the formation of the catalytic complex, the substituent can perform:

- the stabilizing role of the transition state through the formation of H-bonds. This function is characteristic of substituents having F, O, N or OH, NH groups, which can form H-bonds
- the role of just a large substitute with a steric directing role, shielding one of the sides of the transition state from attack.

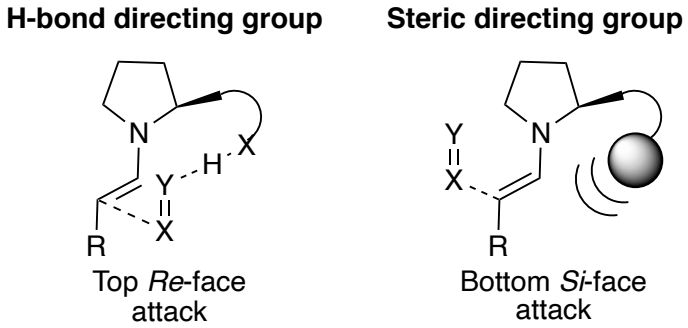


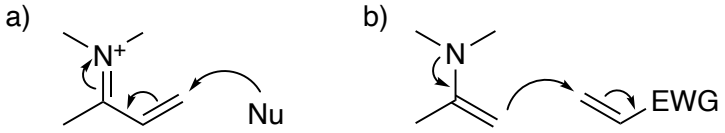
Fig. 9. H-bond vs steric shielding in directing process [21]

The great interest in the 2000s and the rapid development of organocatalysis gave a huge amount of knowledge that helped chemists solve scientific problems. Despite years of research in this field, new classes of catalysts, their derivatives and their application are still published, which expands the synthetic possibilities and deepens the fundamental understanding of science.

8.4. Michael reaction and organocatalysis

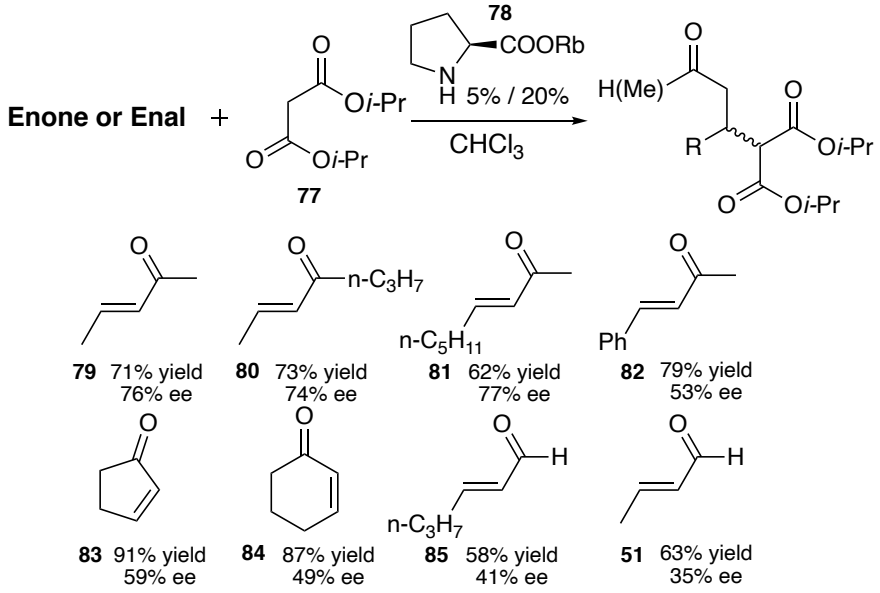
The Michael reaction is an important method for creating C-C bonds by addition of nucleophiles to α,β-unsaturated compounds with an electron withdrawing group. In general, organocatalyzed Michael reactions can be divided into two conceptually

different branches according to the reaction mechanism: a) iminium mechanism, b) enamine mechanism (Scheme 13) [22].



Scheme 13. Iminium and enamine mechanisms of a Michael reaction [22]

One of the first works to show an asymmetric version of the Michael reaction was published in 1993 by Yamaguchi and co-workers. The addition reaction occurred for diisopropyl malonate to prochiral acceptors catalyzed by the rubidium salt of *L*-proline **78** (Scheme 14) [23].

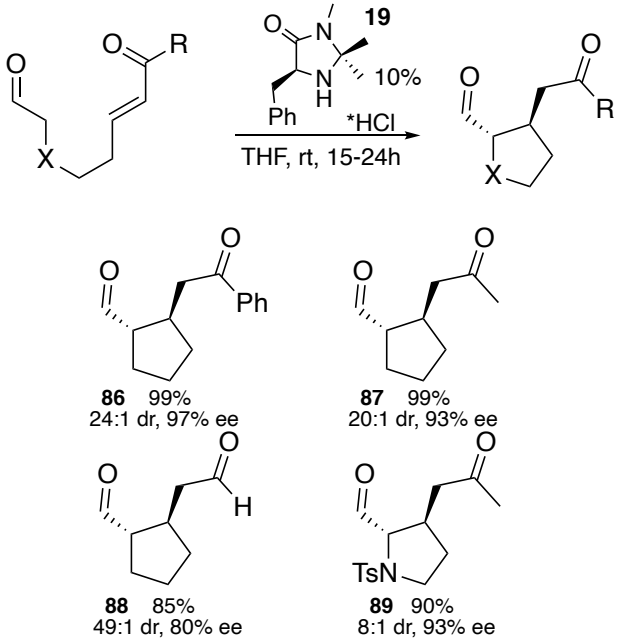


Scheme 14. Michael reaction catalyzed by the rubidium salt of *L*-proline

All products were *S*-isomers except for cyclic enones. The general amount of catalyst was 5%; 20% of rubidium salt was used for less active substrates **80** and **82**. These conditions gave excellent yields of up to 91%, and the enantiomeric excess was up to 77%, but this still left the potential for improvement. As a result, after this

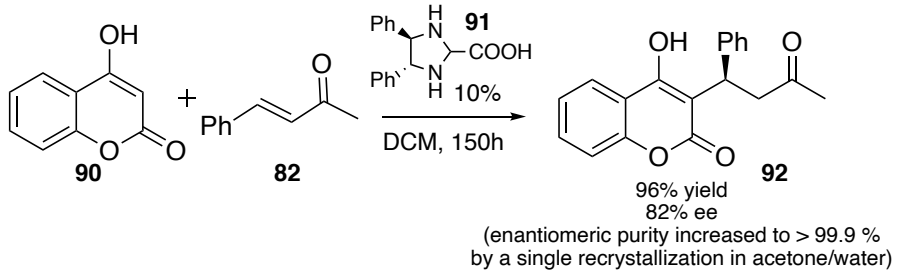
work, subsequent studies have expanded the application of the reaction and initiated the search for new catalysts that could give better results. [24].

The development of these approaches has given excellent results in the synthesis of optically active derivatives and precursors of natural compounds [25], exclusive building blocks [26] and other molecules that are difficult to synthesize alternatively (Scheme 15).



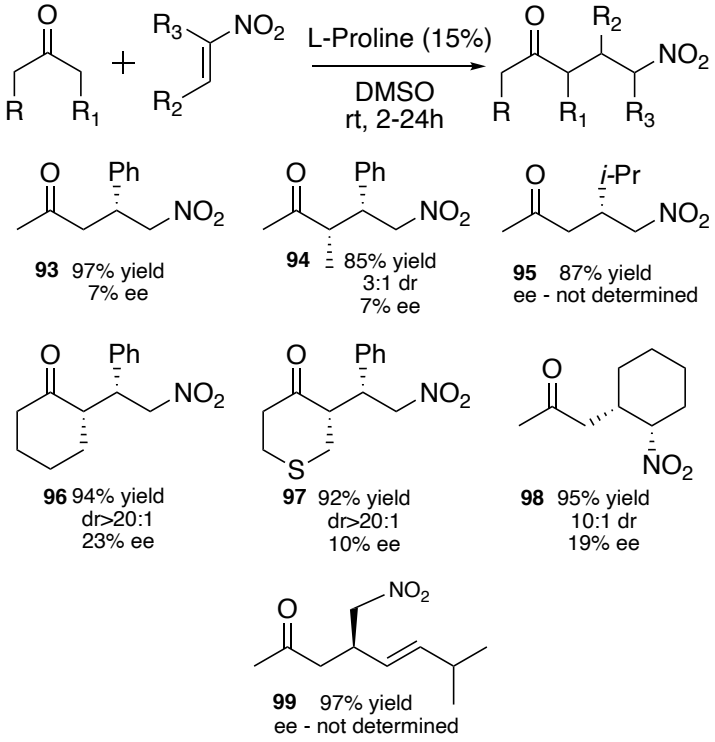
Scheme 15. Advanced asymmetric intramolecular Michael reaction [26]

A good example is the enantioselective one-step synthesis of *Warfarin* **92** (Scheme 16) [27], it is a medication used as an anticoagulant (blood thinner).



Scheme 16. The enantioselective one-step synthesis of *Warfarin*

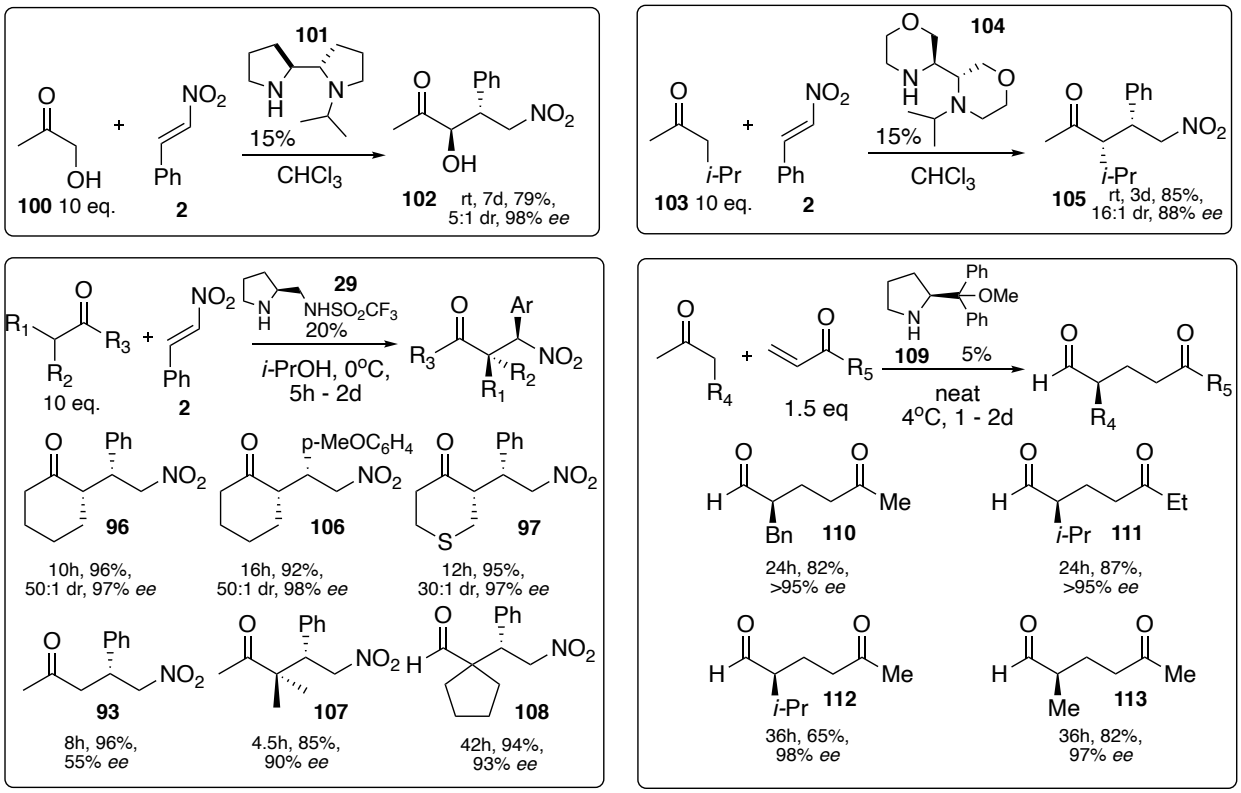
The first example of an organocatalytic Michael reaction with an enamine mechanism was shown by List and co-workers (Scheme 17) [22]. The basis for this work was Stork's original enamine research [28] and asymmetric variants [29]. The reaction was performed in DMSO with 15% *L*-proline as a catalyst. In all cases the yield and diastereoselectivity was excellent. The use of E-isomer of alkenes gave the *syn*-isomer as a major product, in cases where the product has 2 chiral centers. At the same time, the enantiomeric excess for the major enantiomer was very low in all cases with a best result of 23%. Like the publication of List and Barbas [8], which investigated the organocatalytic aldol reaction, this work aroused a lot of interest due to its synthetic possibilities with the study of new organocatalysts for this reaction.



Scheme 17. The first example of a Michael organocatalytic reaction with the enamine mechanism

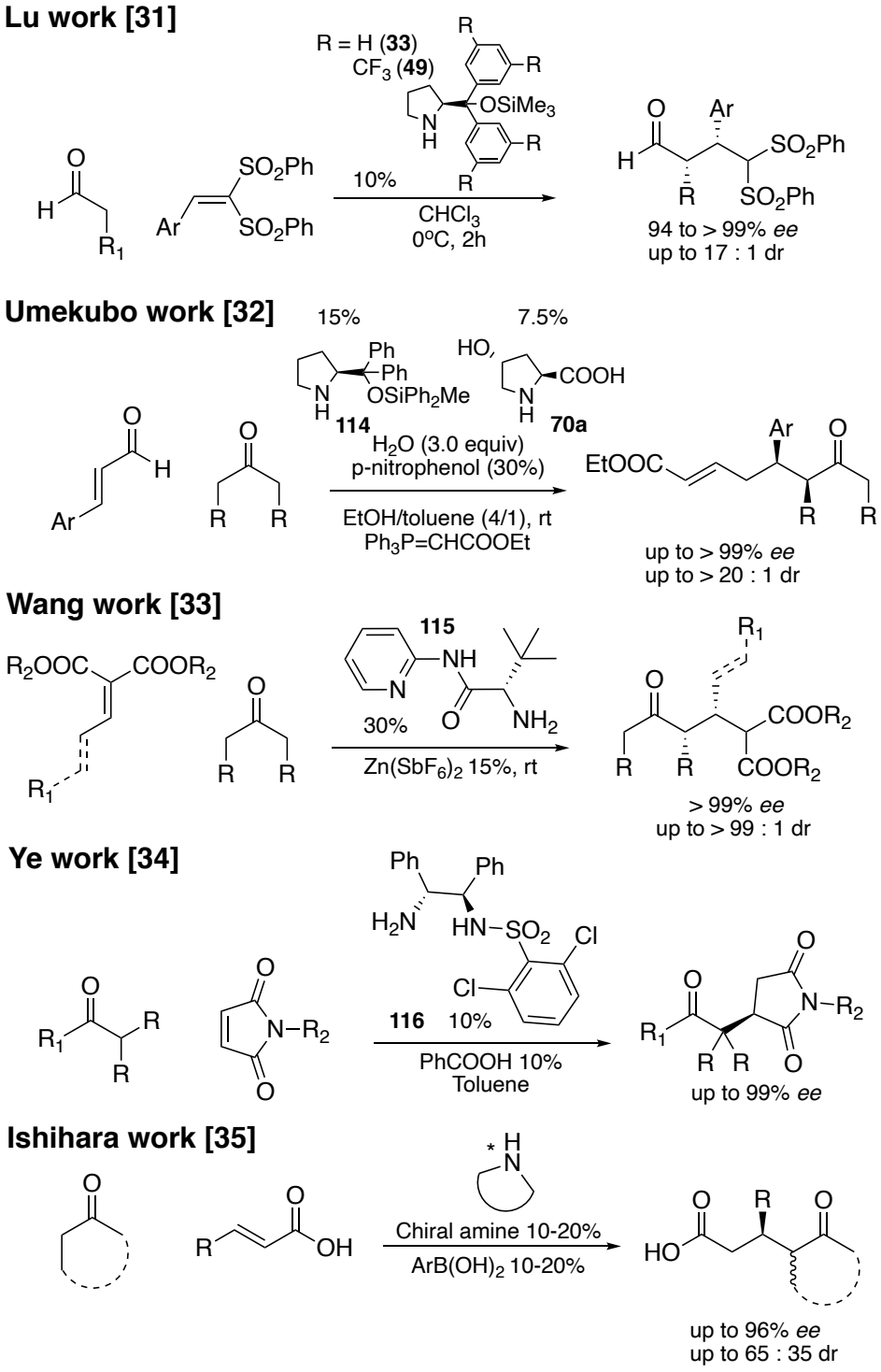
Further research yielded good results. Today, there are many examples of organocatalysts with excellent yields, diastereo- and enantioselectivities for a wide

scope of substrates (Scheme 18). Aliphatic and cyclic aldehydes and ketones can be used as nucleophiles, which form with a catalyst a chiral enamine intermediate, that plays a key role in the asymmetric addition. Different alkenes with conjugated electron withdrawing groups can be used in the electrophilic molecule, however, nitro and keto groups are the most popular [30].



Scheme 18. Advances in the application of a Michael reaction

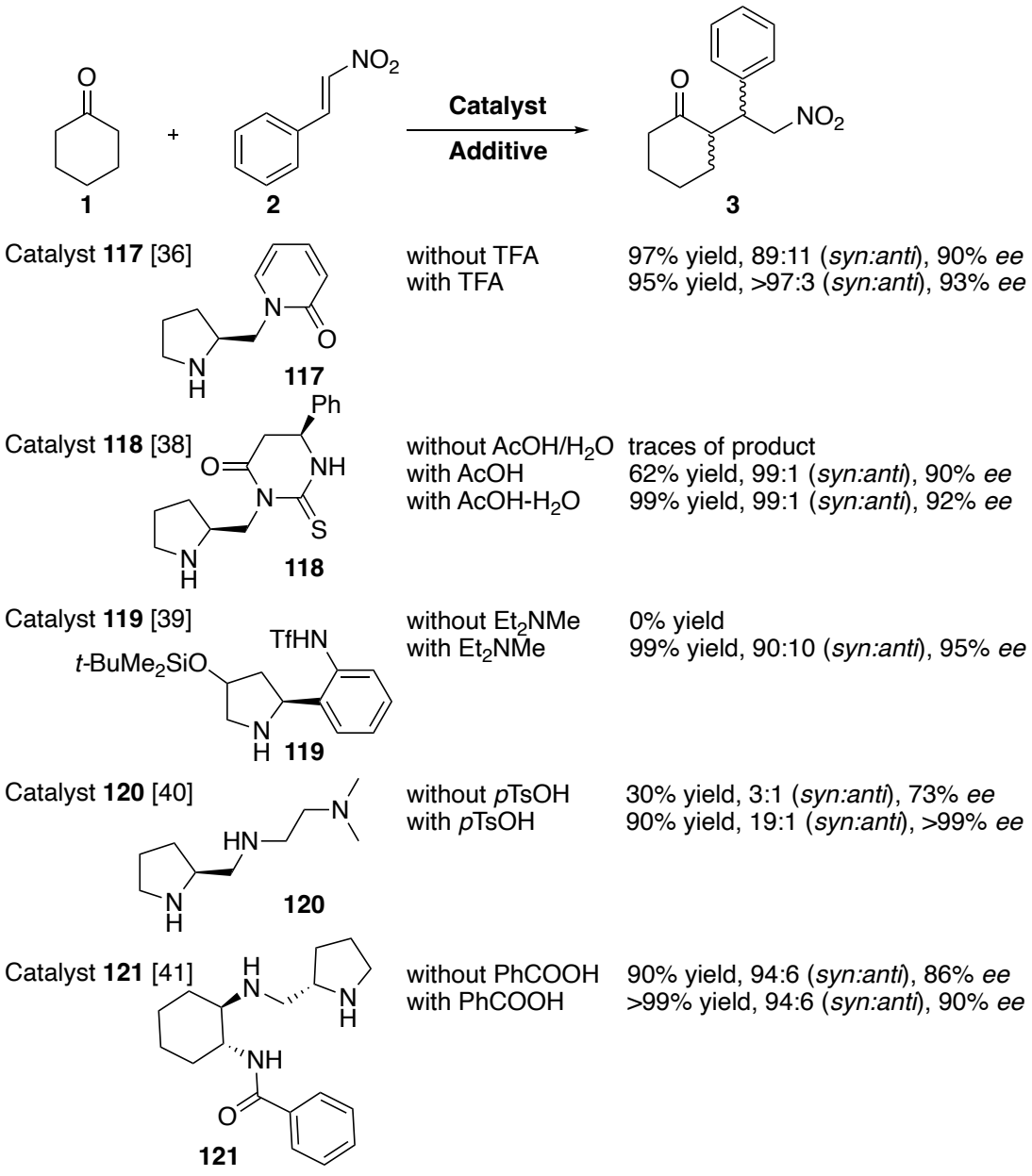
There are also examples, where α,β-unsaturated sulfones [31], aldehydes [32], esters [33], imides [34], acids [35] were used as electrophiles (Scheme 19), but reactions with these substrates are much less common.



Scheme 19. Michael reactions with less common EWGs

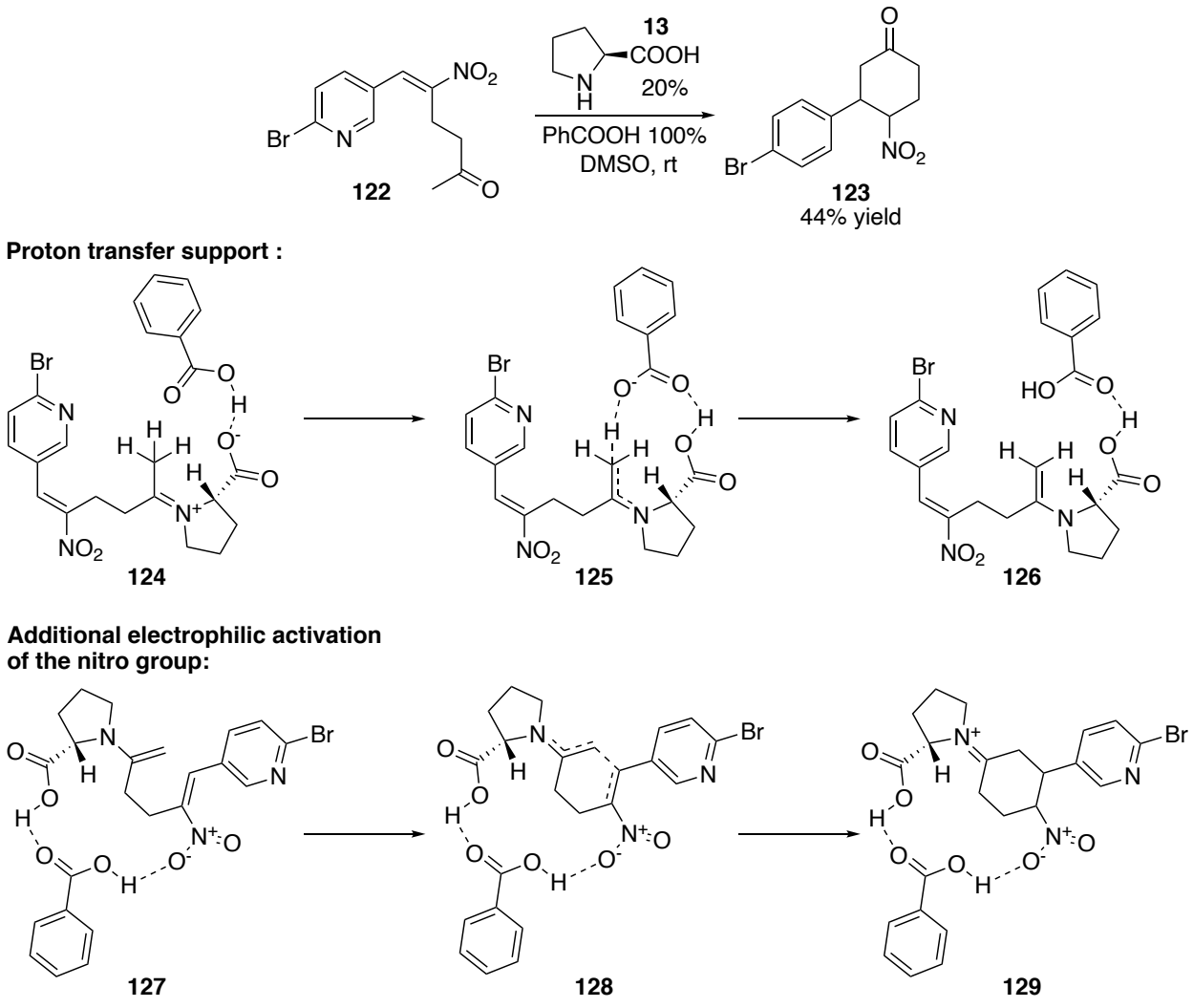
In the study of new organocatalysts, the strategy to improve the structure of the catalyst gave positive results in increasing conversion, enantioselectivity and

diastereoselectivity, but it also was found that different additives can increase selectivities and conversions for them. There are a lot of examples of the additives with various natures (Scheme 20), in particular: TFA [36], acetic acid [37], water [38], triethylamine and N,N-diethylmethylamine [39], TsOH [40] and others, but the most popular additive is benzoic acid [41] or its derivatives like 4-nitrobenzoic acid [42].



Scheme 20. Michael reactions with different additives

The role of benzoic acid as an additive in the Michael reaction has been investigated and described in several works, including using DFT calculations [43][44]. During the study, energy models of transition states for the Michael reaction were studied with and without benzoic acid. The results showed that the acid significantly reduces the energy barrier at the stage of enamine formation, which occurs before the addition process. This is due to assisting proton transfer by the carboxyl group. Calculations have also shown that benzoic acid reduces the energy barrier for conjugated addition. The reason is that the acid additionally activates the nitro group due to the formation of H-bonds with it in the transition complex (Scheme 21).

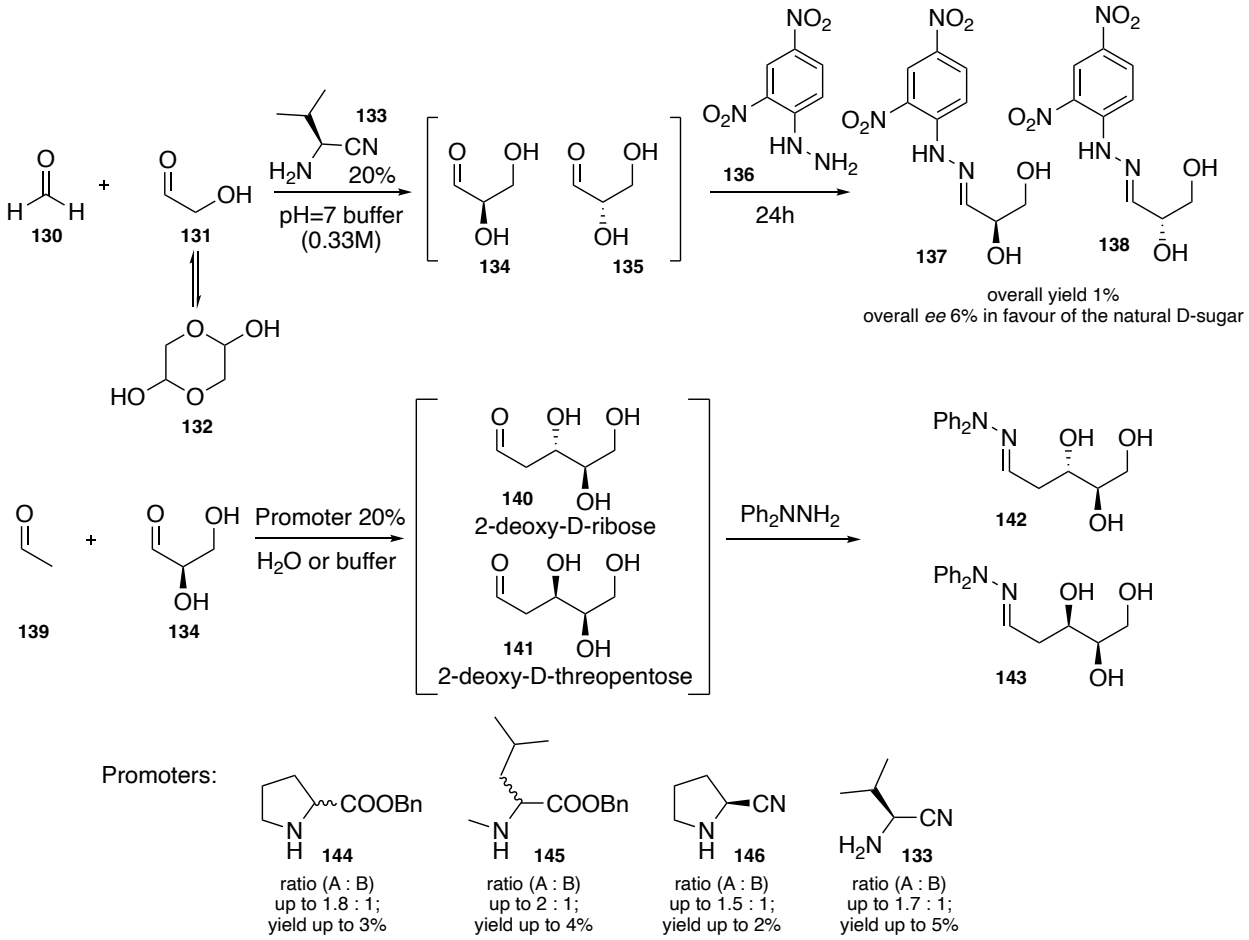


Scheme 21. The role of benzoic acid as an additive in a Michael reaction [44]

Benzoic acid participates in the processes for the formation of transition complexes in undissociated form, which explains its greater success in many cases compared to stronger acids, which dissociate more easily. Other benzoic acid derivatives act by the same mechanism, but the ability to reduce energy barriers depends on the steric and electronic effects in the aromatic nucleus of the acid.

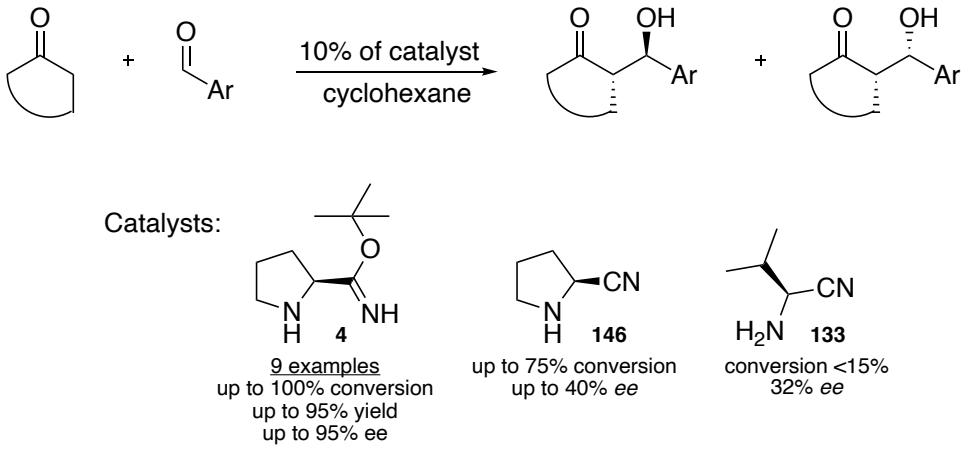
8.5. Aim of the project

The roots of this study began with one of the most interesting and fascinating studies on the origins of life. Chemists have long studied the possibility of the formation of biomolecules under plausible prebiotic conditions. Particular attention is paid to such molecules as amino acids, peptides, carbohydrates, nucleic acids, and RNA. Clarke and co-workers began to actively explore this topic, in particular the synthesis of carbohydrates. In 2017, they published studies that showed that esters and nitriles of the simplest natural amino acids are catalysts for the condensation reaction in an aqueous medium with the formation of natural sugars (Scheme 22) [45]. It was shown for the first time that aminonitriles are excellent promoters and therefore they were further studied for organocatalytic properties.



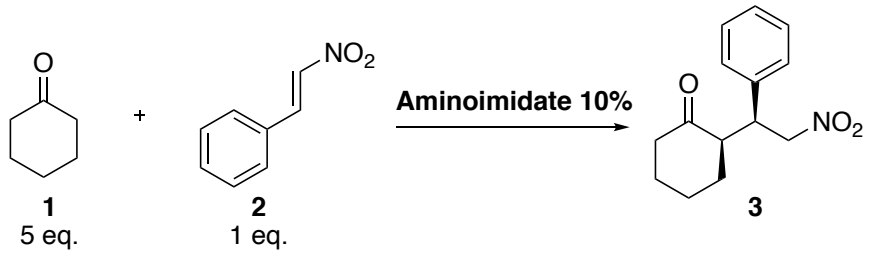
Scheme 22. Esters and nitriles of the amino acids as promoters for formation of sugars

A continuation of that work was the study of nitriles of valine and proline on the catalytic activity for a general aldol condensation reaction in organic solvents [46][47]. During the removal of the Boc protection from *L*-proline nitrile, in addition to proline nitrile product, an additional product was formed, which was *L*-proline *t*-butylimidate. It was decided to test its catalytic activity, so a method for obtaining this compound in high yield was developed. As a result of these studies, the imidate showed better results as catalysts in the aldol reaction than the nitriles (Scheme 23). This was the first example of the discovery and use of a new class of organocatalysts – aminoimidates.



Scheme 23. Catalytic activity of nitriles and imidate for aldol reaction

The aim of this study is to evaluate the catalytic activity of aminoimidates and expand their scope in organocatalysis on the example of the Michael reaction. Cyclohexanone (5 eq.) and trans-*β*-nitrostyrene (1 eq.) along with catalyst (0.1 eq.) were chosen as the starting point because reactions under similar conditions have been examined in the past (Scheme 24).

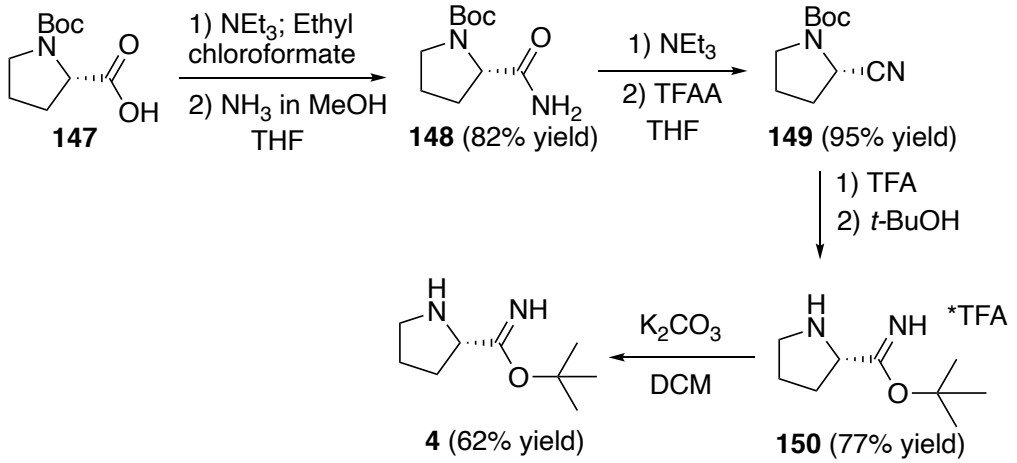


Scheme 24. Basic conditions for a studied Michael reaction

9. Results and discussion

9.1. Synthesis of *t*-butyl *L*-proline imidate

The study began with the synthesis the catalyst. For initial screening *t*-butyl *L*-proline imidate was chosen. This was synthesized according to the previously described procedures (Scheme 25) [46].



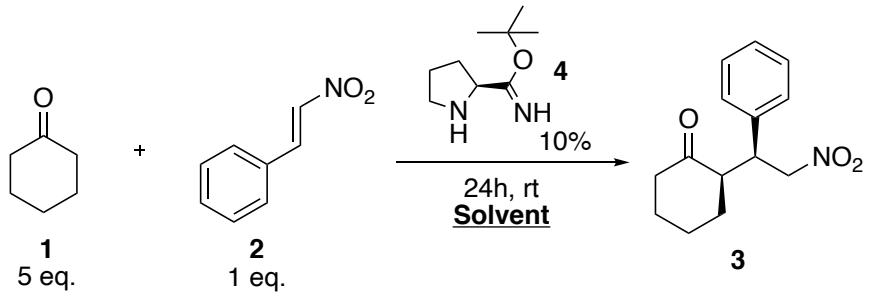
Scheme 25. Synthesis of *t*-butyl *L*-proline imidate

Boc-protected *L*-proline **147** was treated with Et_3N and ethyl chloroformate to form the mixed anhydride which was then quenched with methanolic ammonia solution. Product **148** was isolated with a yield of 82%. Amide **148** was converted to the Boc-protected *L*-proline nitrile **149** in 95% yield by dehydration in the presence of TFAA. After chromatographic purification the product, was submitted to the reaction to form *t*-butyl imidate. The imidate forming reaction was carried out in trifluoroacetic acid, where the amine Boc protecting group was first removed, and then 2 equivalents of *t*-butyl alcohol were added to form the imidate **150**. Direct transformation of the amide **148** to the salt **150** was not carried out. The salt obtained after trituration was converted into the free base **4** with potassium carbonate. Yields for imidate formation and conversion to the free base were 77% and 62% respectively. The final product **4** was purified by column chromatography before use

as a catalyst in Michael reactions. For the aminoimidate salt **150**, the optical rotation of the compound was measured, compared to the literature values ($[\alpha]_D^{20}$ –44.36 (c=1.0 mg/mL, DCM); lit. [46] $[\alpha]_D^{25}$ –47.23 (c=1.0 mg/mL, DCM)) and we confirmed the absence of racemization.

9.2. Solvent screening

The next important step was to study the conditions of the Michael reaction. The general scheme of the reaction was explained in the introductory section (chapter 8.5). Study of optimal conditions began with screening solvents for the reaction – looking to optimize enantio- and diastereoselectivity of the reaction. The reaction was carried out under the same conditions (Scheme 26) for all thirteen solvents shown in the Table 2.



Scheme 26. Basic conditions for a solvent screening

All relevant information is shown in Table 2.

Table 2. Screening of solvents for a Michael reaction

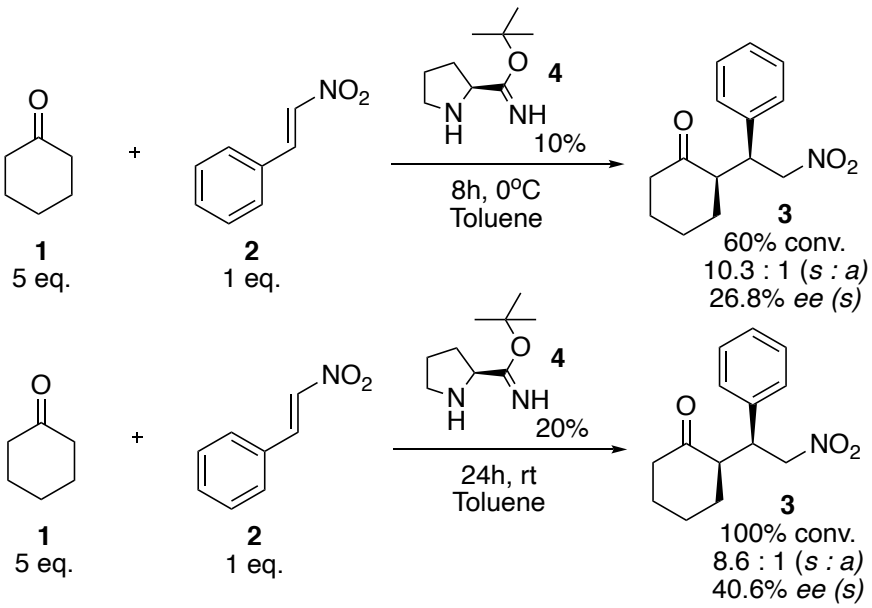
Entry	Solvent	Conv. 24h[a]	Conv. 48h[a]	*syn* : *anti*[b]	*ee* (*syn*)[c]
1	DMF	14%	17%	1: traces	-[d]
2	DMSO	0%	0%	-	-
3	Dioxane	63%	91%	7.1:1	28.8%
4	MeCN	92%	-	8:1	7.4%[e]
5	THF	99%	-	7.9:1	18.8%
6	Cyclohexane	100%	-	10.7:1	38.6%
7	EtOAc	100%	-	9:1	21.6%
8	DCM	100%	-	12.6:1	20.6%
9	Diethyl carbonate	88%	-	5.6:1	27.8%
10	**Toluene**	**100%**	**-**	**9.7:1**	**42.8%**
11	MeOH	11%	14%	6.6:1	-[d]
12	MeOH : IPA = 1:1	6%	7%	6:1	-[d]
13	EtOH : IPA = 1:1	14%	17%	5.8:1	-[d]

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] not determined; [e] other enantiomer

A variety of solvents were chosen including protic, aprotic, polar, and non-polar. After a complete analysis of the data, it can be concluded that highly polar aprotic and protic solvents had the worst results: DMF (entry 1) – 17% conversion, DMSO (entry 2) – no conversion, MeOH (entry 11) – 14% conversion, MeOH : IPA = 1:1 (entry 12) – 7% conversion, EtOH : IPA = 1:1 (entry 13) – 17% conversion. Another seven solvents: MeCN (entry 4), THF (entry 5), cyclohexane (entry 6), ethyl acetate (entry 7), DCM (entry 8), diethyl carbonate (entry 9) and toluene (entry 10) had a

conversion more than 80% at 24h and dioxane (entry 3) – at 48h. It should also be noted that in all cases there was good *syn* to *anti* (determined by known ^{1}H NMR data [48a]) selectivity from 5.6:1 for diethyl carbonate (entry 9) to 12.6:1 for DCM (entry 8). At the same time, the enantioselectivity was disappointing. Polar solvents showed poor enantioselectivity, the best result was for diethyl carbonate (entry 9) – 28%. Cyclohexane (entry 6) and toluene (entry 10) showed better results – 39% *ee* and 43% *ee* respectively. Therefore, non-polar hydrocarbons such as toluene and cyclohexane are the best solvents for this reaction, as they give good conversion and higher enantioselectivity compared to polar solvents. A similar situation was found with the study of our aminoimidate catalyst **5** in the aldol reaction [46]. Non-polar solvents may promote enamine formation that could explain why they are better, however, as was mentioned before, polar solvents also had excellent conversion in some catalyst systems. The reason for the better enantiomeric excesses in non-polar solvents may be that non-polar solvents cannot form hydrogen bonds with the intermediate enamine, and at the same time polar solvents can form them, which may impair the enantioselectivity. Toluene was chosen as the best solvent for the reaction, because the reagents were more soluble in it compared to cyclohexane.

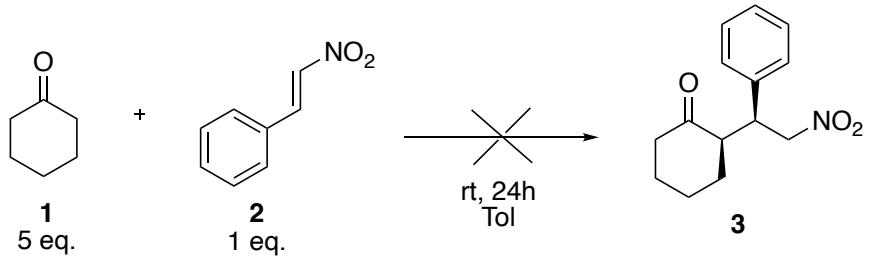
To determine the best conditions for the selected solvent, two additional experiments were carried out (Scheme 27). The first experiment was to study the effect of an increase in the amount of catalyst on the reaction characteristics, and the second one was to examine the effect of decreasing the temperature. The aim was to evaluate the possibility of increasing diastereo- and enantioselectivity for the chosen solvent.



Scheme 27. Additional study of a Michael reaction for the selected solvent

The decrease in temperature did not improve the reaction. After 8 hours at 0°C, we obtained a conversion of 60%, and a decrease in enantioselectivity from 42.8% to 26.8%. At the same time, there was a slight increase in diastereoselectivity from 9.7 : 1 to 10.3 : 1 – *syn* : *anti*. Increasing the amount of catalyst to 20%, we found essentially no different in the results compared to the reaction with 10% of the catalyst (Table 2, entry 10). Only a slight decrease in diastereo- (from 9.7 : 1 to 8.6 : 1 – *syn* : *anti*) and enantioselectivity (from 42.8% to 40.6%) was noted. Therefore, the reaction is best carried out in toluene for 24 hours at room temperature with 10% of catalyst. Studies with reduced catalyst loads have not been performed.

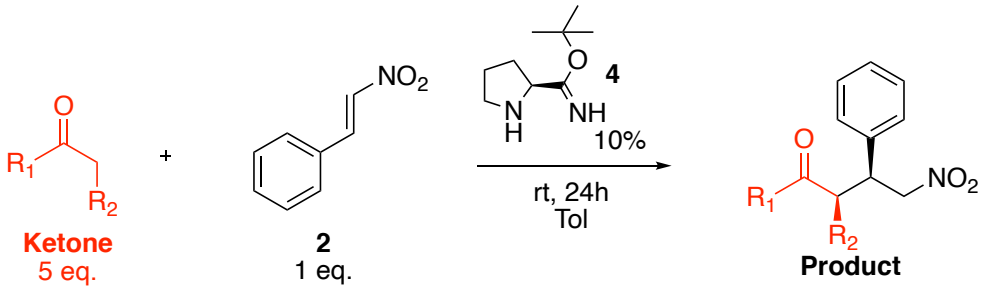
A reaction run in the absence of catalyst showed that the reaction did not proceed, and no product was formed in the absence of catalyst (Scheme 28).



Scheme 28. Model Michael reaction without catalyst

9.3. Initial ketone screening

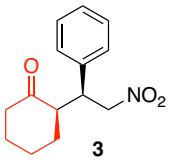
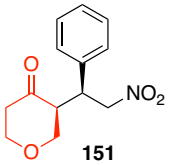
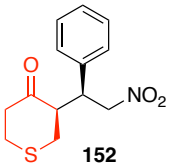
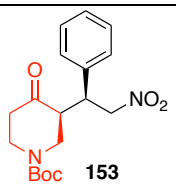
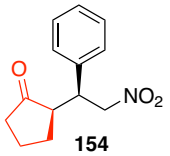
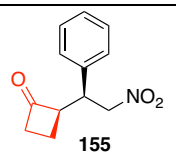
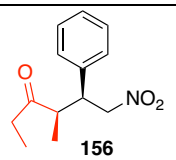
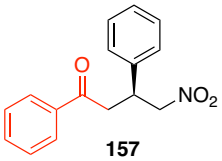
The next step was to conduct a primary screening of ketones to assess the scope of the reaction (Scheme 29).



Scheme 29. Conditions for a primary screening of ketones

All reactions were performed under the optimal conditions in toluene at room temperature for 24 hours. The results are shown in Table 3.

Table 3. Initial ketone screening

Entry	Product	Conv. 24h[a]	*syn* : *anti* [b]	*ee* (*syn*)[c]	Yield
1[d]	 **3**	100%	9.7 : 1	42.8%	62%
2	 **151**	100%	5.8 : 1	25.8%	88%
3	 **152**	30%	10.0 : 0[e]	32.2%	25%
4	 **153**	0%	-	-	-
5	 **154**	6%	-[f]	-[f]	-[f]
6	 **155**	40%	3.9 : 1	46.3% (*syn*) 15.8% (*anti*)	27%
7	 **156**	0%	-	-	-
8	 **157**	0%	-	-	-

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] experimental data are taken from Table 2 (entry 10); [e] *anti* not detected; [f] not determined

Two ketones, cyclohexanone (entry 1) and tetrahydropyran-4-one (entry 2), had full conversion. Tetrahydrothiopyran-4-one (entry 3), cyclopentanone (entry 5) and cyclobutanone (entry 6) showed some conversion of 30%, 6% and 40% respectively. However, there was no conversion for the reaction with aliphatic ketones (entry 7 and 8) and N-Boc-piperidin-4-one (entry 4). In general, there is a trend that with 6-membered ring ketones the conversions were better (exception for N-Boc-piperidin-4-one – entry 4). Simultaneously, when the size of the ring is reduced to 5 and 4 members, the conversion decreases (entry 5 and 6). This feature of reactivity may be explained by the fact that in 6-membered ketones there is better overlap of the C-H σ orbital with the C=O π* orbital, which is required for enolization (Fig. 10).

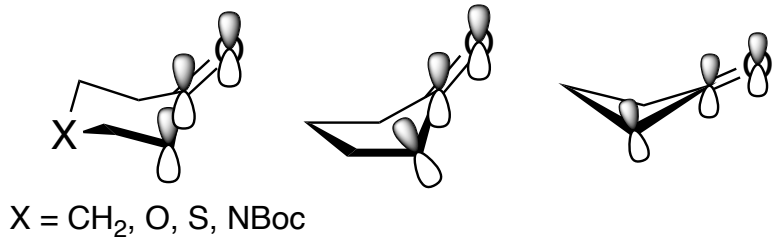


Fig. 10. Conformation of cycles and relative position of orbitals with respect to the π-orbitals of the carbonyl group

However, it should be noted that diastereoselectivity in all cases, where it could be determined, remained quite high from 3.9 : 1 as *syn* : *anti* for cyclobutanone product **155** (entry 6) to 10.0 : 0 for the tetrahydrothiopyran-4-one **152** (entry 3) product. The major *syn* diastereomer was determined and confirmed by comparison with previously described ^{1}H NMR spectra (entry 1 – [48b], entry 2 – [48b], entry 3 – [48b], entry 6 – [49],). The level of enantioselectivity seen are disappointing. Among our studied ketones, the best results were for cyclohexanone (entry 1) and cyclobutanone (entry 6) products, 42.8% *ee* (*syn*) and 46.3% *ee* (*syn*), respectively.

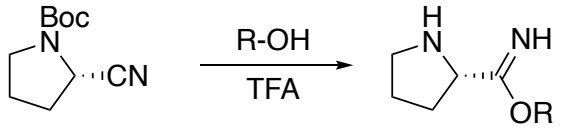
For products **151** (entry 2) and **152** (entry 3), the enantiomeric excess is only 25.8% and 32.2%, respectively. These results show the need to improve the reaction conditions, the catalyst, or both to obtain good conversion for a wider range of substances and to increase enantioselectivity.

9.4. Studies to increase the conversion and the enantioselectivity by exploring catalyst design

Changing catalyst structure was investigated to see if conversion and enantioselectivity could be improved. One of the easiest changes to be made was replacement of *t*-Bu group with another alcohol. Unfortunately, all attempts to synthesize any new imidates with *L*-proline core were unsuccessful. Conditions and reaction products are shown in Tables 4-6.

It was decided not to use the basic methods of obtaining imidates due to the possibility that amino acid derivatives could be easily racemized. Firstly, TFA was chosen as the proton source for imidate formation and for Boc-deprotection. All data obtained are listed in Table 4.

Table 4. Attempts to synthesize imidate with TFA



149

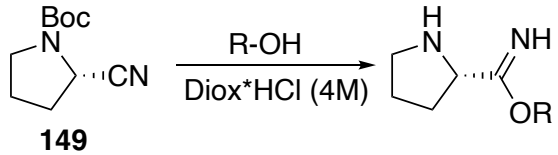
Entry	Conditions	Starting material	Aminonitrile	Ester	*t*-BuOH Imidate
1	MeOH / TFA	-	45%	-	55%
2	BnOH / TFA	23%	77%	traces	traces
3	Ph_2MeC-OH / TFA	-	35%	-	65%
4	MeOH / TFA-DCM	13%	87%	traces	traces

Products determined by ^1H NMR and MS from crude reaction mixture

The procedure for obtaining the *t*-butyl imidate in TFA has been described previously (Scheme 25, transformation 3 to 4), so it would be logical to try and replace *t*-butyl alcohol with other alcohols, as was attempted for methanol (entry 1), benzyl alcohol (entry 2) and 1,1-diphenylethyl alcohol (entry 3). However, for each alcohol, target imidates were not obtained. In all cases, the main product was the aminonitrile salt, and in entry 1 and 3, the product was the *t*-butyl imidate. Traces of a side-imidate and proline benzyl ester were also identified when trying to obtain the benzyl imidate (entry 2). For methanol, the solution was diluted with DCM (entry 4) which reduced the formation of *t*-butyl imidate as a competing product, but the target methyl imidate still was not obtained.

The main problem was the lack of imidate formation from the nitrile group. It was decided to change the proton source and use HCl. Reactions were performed in 4N dioxane solution of HCl (relevant information in Table 5) and in 2N diethyl ether solution of HCl (relevant information in Table 6).

Table 5. Attempts to synthesize imidates with Diox∗HCl (4N)



149

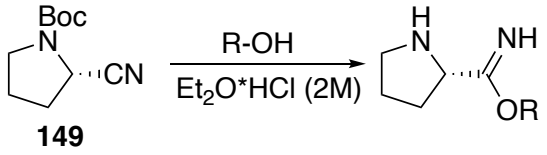
Entry	Conditions	Starting material	Proline hydrochloride	Ester	*t*-BuOH Imidate
1	MeOH / Diox∗HCl	-	14%	86%	-
2	BnOH / Diox∗HCl	-	main product[a]	traces	-
3	Ph_2MeC-OH / Diox∗HCl	-	main product[a]	-	-

Products determined by ^{1}H NMR and MS from crude reaction mixture; [a] percentage cannot be clearly defined

To have a direct comparison with previous attempts, experiments were conducted for the same alcohols (Table 5): methanol (entry 1), benzyl alcohol (entry 2) and 1,1-

diphenylethyl alcohol (entry 3). In all experiments, target imidates were not obtained, and the main by-product was proline hydrochloride due to hydrolysis of the nitrile group. In the case of methanol (entry 1) and benzyl alcohol (entry 2), the corresponding esters were additionally formed.

Table 6. Attempts to synthesize imidates with Et_2O*HCl (2N)



149

Entry	Conditions	Starting material	Proline hydrochloride	Ester	*t*-BuOH Imidate
1	MeOH / Et_2O*HCl	-	48%	52%	-
2	BnOH / Et_2O*HCl	-	main product[a]	-	-
3	PhOH / Et_2O*HCl	-	main product[a]	-	-

Products determined by ^1H NMR and MS from crude reaction mixture; [a] percentage cannot be clearly defined

A similar situation occurred for experiments with methanol (entry 1), benzyl alcohol (entry 2) and phenol (entry 3) in diethyl ether (Table 6). The main problem was complete hydrolysis of the nitrile group, which occurred together with the removal of Boc group. Therefore, we obtained proline hydrochloride in all cases, and the methyl ester of proline was an additional product for the reaction with methanol (entry 1).

After a series of failures, it was decided to try to synthesize *t*-butyl imidate, but to change the carbon framework of the catalyst. A target catalyst **5** with bicyclic structure was chosen imidate (Fig. 11).

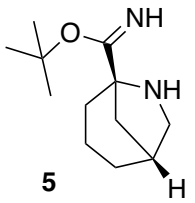
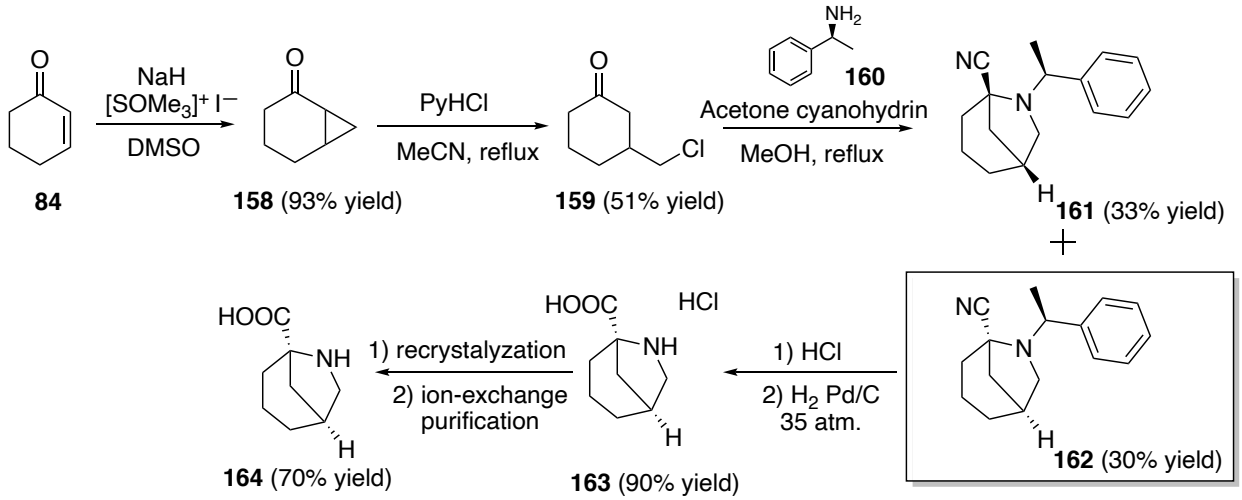


Fig. 11. Target structure of the bicyclic catalyst **5**

This framework structure was chosen, because it showed excellent potential for increasing enantioselectivity in the α-benzylation reaction of aldehydes compared to proline or other simpler carbon structures [50]. Amino acid **164** was synthesized according to Scheme 30.

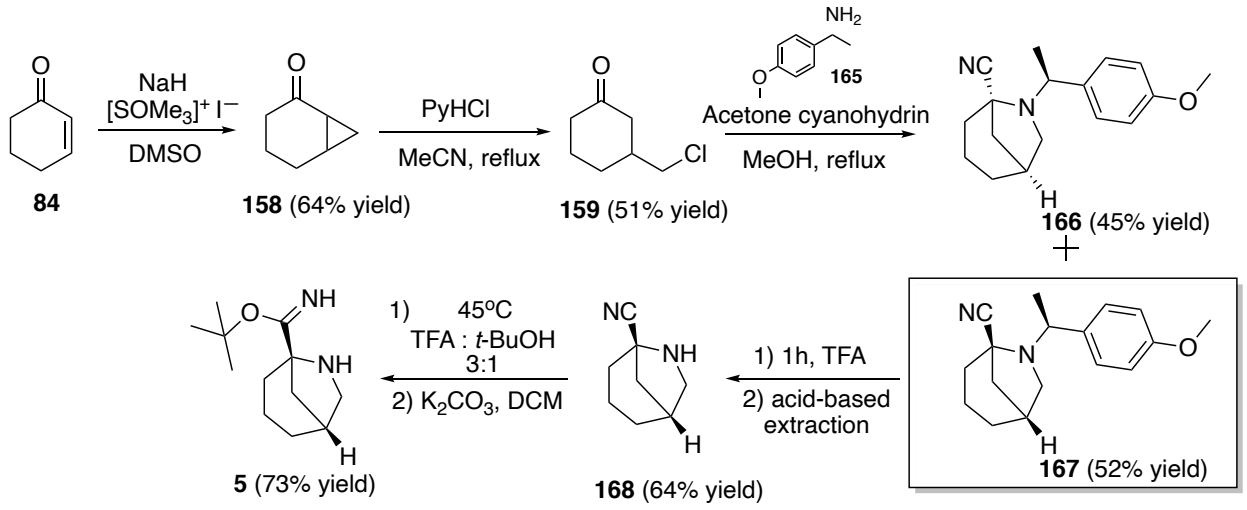


Scheme 30. Synthesis of bicyclic amino acid **164** for catalyst use

2-Cyclohexen-1-one **84** was subjected to cyclopropanation with 1.1 equivalents of trimethylsulfoxonium iodide and sodium hydride in DMSO. Compound **158** was isolated in a 93% yield. Then for the regioselective opening of the cyclopropane ring was used pyridine hydrochloride in refluxing acetonitrile. As a result of the reaction, **159** was obtained in a 51% yield, and was used along with α-methylbenzylamine **160** and acetone cyanohydrin in the cyclization reaction. The obtained diastereomers were separated by flash chromatography to give **161** in a 33% yield of and **162** in a

30% yield. The next transformations were performed with compound **162**. The nitrile group was hydrolyzed to acid in concentrated refluxing HCl, and, after work-up, the obtained solid was dissolved in methanol and hydrogenated (35 atm). Salt **163** was obtained in a 90% yield after two transformations. Free base form **164** was prepared after recrystallization and ion-exchange purification with a 70% yield.

Since our goal was to obtain an aminoimidate formed from the corresponding nitrile, it was decided to change protection type of the amino group and, as result, amine. α-Methylbenzylamine **160** was used for the formation of benzyl-type protecting group, which was removed by hydrogen under high pressure. These conditions are not tolerant to the nitrile group, which is absolutely needed for transformation to the imidate, so it was decided to use α-methyl *p*-methoxybenzylamine **165**. It is a derivative of PMB-protecting group and can be removed with trifluoroacetic acid like the Boc-protection of proline nitrile **149** in Scheme 31.



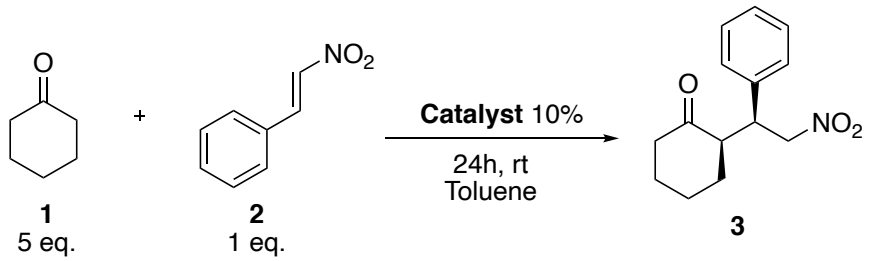
Scheme 31. Synthesis of the bicyclic catalyst **5**

The synthesis of target molecule **5** was carried out according to Scheme 31, which is based on the route described in Scheme 30. Cyclopropanation of commercially available alkene **84** was performed in DMSO, where ylide was pre-generated by the

reaction between trimethylsulfoxonium iodide and sodium hydride. To increase the conversion of the reaction, we used 2 equivalents of sulfonium salt and base. Compound **158** was obtained in a 64% yield and was used for the next transformation. Regioselective opening of the cyclopropane ring was performed by pyridine hydrochloride in refluxing acetonitrile. As a result, after isolation and chromatographic purification, alkyl chloride **159** was obtained in 51% yield. For the key cyclization step, we used α-methyl p-methoxybenzylamine **165**. Compound **159, 165** and acetone cyanohydrin was heated in methanol under reflux. After completion of the reaction, diastereomers **166** and **167** were separated by flash chromatography with yields of 45% and 52%, respectively. We now faced the problem of the formation of imidate **5**. Attempts to deprotect the amino group and to form the key compound **5** *in situ*, as it was for the transformation of **149** to **150** (Scheme 25), failed. The main problem was the formation of aminonitrile **168** as the major product and the decomposition of the products over time. It was decided to separate the stages of the amine deprotection and imidate formation. The deprotection of the amino group of **167** took place in 1 hour in trifluoroacetic acid, with the formation of the corresponding trifluoracetic salt. Purification and preparation of the free base form was performed by acid-base extraction (K_2CO_3 as a base), and aminonitrile **168** was isolated in 64% yield. The optimal conditions for obtaining the target aminoimidate **5** were a solution of TFA/*t*-BuOH 3/1 at 45°C, because at a lower temperature or less alcohol the conversion of nitrile was not complete. Pure compound **5** was isolated as the free base with a yield of 73%, after treating with K_2CO_3 in DCM, and it was used without further purification. The configuration of compound **5** was determined by optical rotation for the nitrile-derived acid hydrochloride based on the information in the literature [51].

The Michael reaction was performed according to Table 7 to compare directly with the results from *t*-butyl *L*-proline imidate **4**.

Table 7. Comparison of proline based and bicyclic catalysts



1 5 eq. **2** 1 eq. **3**

Entry	Catalyst	Conv. 24h[a]	Conv. 48h[a]	*syn* : *anti* [b]	*ee* (*syn*) [c]
1[d]	Proline imidate **4**	100% (rt)	-	9.7:1	42.8%
2	Bicyclic imidate **5**	Traces (rt)	24% (75°C)	2.5:1	-[e]

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] experimental data are taken from Table 2 (entry 10); [e] not determined

Unfortunately, the bicyclic structure of catalyst **5** led to a loss of activity (entry 2). After 24 hours, the conversion of the reaction was close to zero, which compared unfavorably to the full conversion seen for the proline catalyst (entry 1). The reason for the loss of conversion may be a more complex spatial structure of the catalyst **5**. An attempt to increase the conversion, by raising the temperature to 75°C, did not lead to a much better result, and gave a low conversion of 24%. Additionally there was a large decrease in diastereoselectivity (from 9.7 : 1 to 2.5 : 1 as *syn* to *anti*) of the products formed along with the formation of unidentified by-products. Therefore, we looked to other strategies to increase conversion and enantioselectivity.

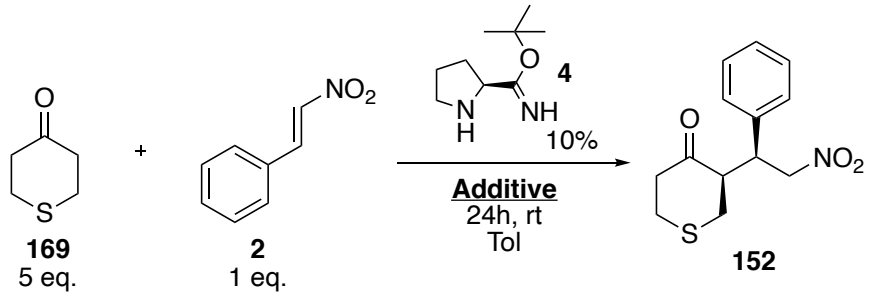
9.5. Studies to increase conversion and enantioselectivity by additives

The next strategy was to study the role of additives in the reaction. The reaction between trans-*β*-nitrostyrene **2** and tetrahydrothiopyran-4-one **169** was chosen as a model reaction for subsequent studies, because, according to the results that were

shown in the chapter 9.2, the change in enantioselectivity, but also the change in conversion can be monitored.

Additives selected were those that had previously been reported as effective in organocatalytic reactions: water [38][52], Lewis acid – Lanthanum (III) trifluoromethanesulfonate [53], organic acids – TFA [36] and benzoic acid [41], and organic base – triethylamine [39][54]. In all cases, it was decided to use 1.5 equivalents of the additive, with the exception for Lanthanum (III) trifluoromethanesulfonate, which was used in an amount of 0.15 equivalents. This is due to the high molar mass of the compound, the use of 1.5 equivalents would require a reaction with a big amount of toluene-insoluble salt, which would make stirring inefficient. All relevant data are listed in Table 8.

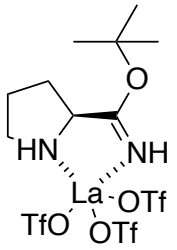
Table 8. Study of additives for a Michael reaction



Entry	Additive – eq.	Conversion [a]	*syn* : *anti* [b]	*ee (syn)* [c]
1[d]	No additive	30%	10.0 : 0[e]	32.2%
2	H_2O – 1,5eq	11%	-[f]	-[f]
3	$La(OTf)_3$ – 0.15eq	0%	-	-
4	TFA – 1,5eq	0%	-	-
5	**PhCOOH – 1,5eq**	**49%**	**8.6:1**	**80.2%**
6	NEt_3 – 1,5eq	10%	-[f]	-[f]

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] experimental data are taken from Table 3 (entry 3); [e] *anti* not detected [f] not determined.

Entry 1 corresponds to the experiment performed for the initial ketone screening and was described in chapter 9.3. This is the basic result used for comparison. For the water experiment (entry 2), the conversion was reduced to 11%. The explanation may be that water promotes the hydrolysis of enamine (which is critically needed for Michael reaction) and shifts the equilibrium reaction to the starting materials. Addition of Lanthanum (III) trifluoromethanesulfonate (entry 3) completely inhibited the reaction, no product was formed. This may be explained by the formation of chelate **170** between the catalyst **4** and Lewis acid (Fig. 12), which prevents the formation of enamine.



170

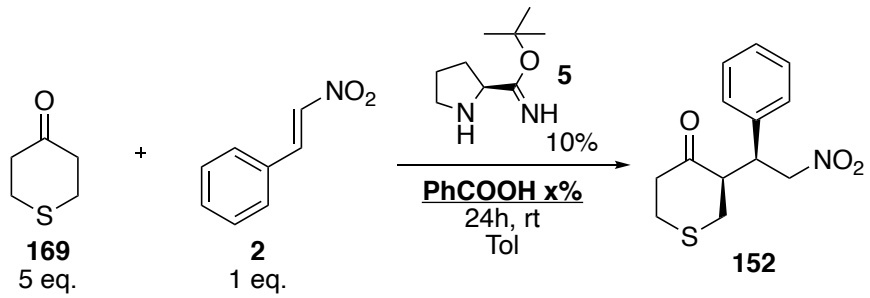
Fig. 12. Predicted chelate of catalyst **4** with Lanthanum (III) triflate

Addition of TFA (entry 4) also completely inhibited the reaction. This may be due to formation of the TFA salt **150** from the free base catalyst **4**, which is unable to form the enamine. Triethylamine (entry 6) also showed disappointing result and suppressed the conversion to the 10%. However, benzoic acid showed generally positive results: an increase in the conversion from 30% to 49% and a significant increase in enantioselectivity from 32.2% to 80.2%. The diastereoselectivity of the reaction also remained high – 8.6 to 1 as *syn* to *anti*. As was explained in chapter 8.4, this key role of benzoic acid is to assist with proton transfer at the stage of enamine formation and additional activation of the nitro group as an acceptor during nucleophilic addition. The increase in the activity of the catalyst with this acid also

can be explained by the fact that the optimal pH for the formation of enamine is 4-6. Therefore, a weaker benzoic acid medium will be more favorable for the reaction, than a TFA or NEt_3 medium.

Encouraged by these results, a study of benzoic acid as an additive was investigated further. It was decided to determine the optimal amount of benzoic acid and to investigate the effect of this on conversion, diastereo- and enantioselectivity. Experiments using 0.1 (entry 1), 0.5 (entry 2), and 1.0 (entry 4) equivalents of benzoic acid were performed. Comparison of the obtained data is shown in Table 9. Other benzoic acid derivatives have not been evaluated.

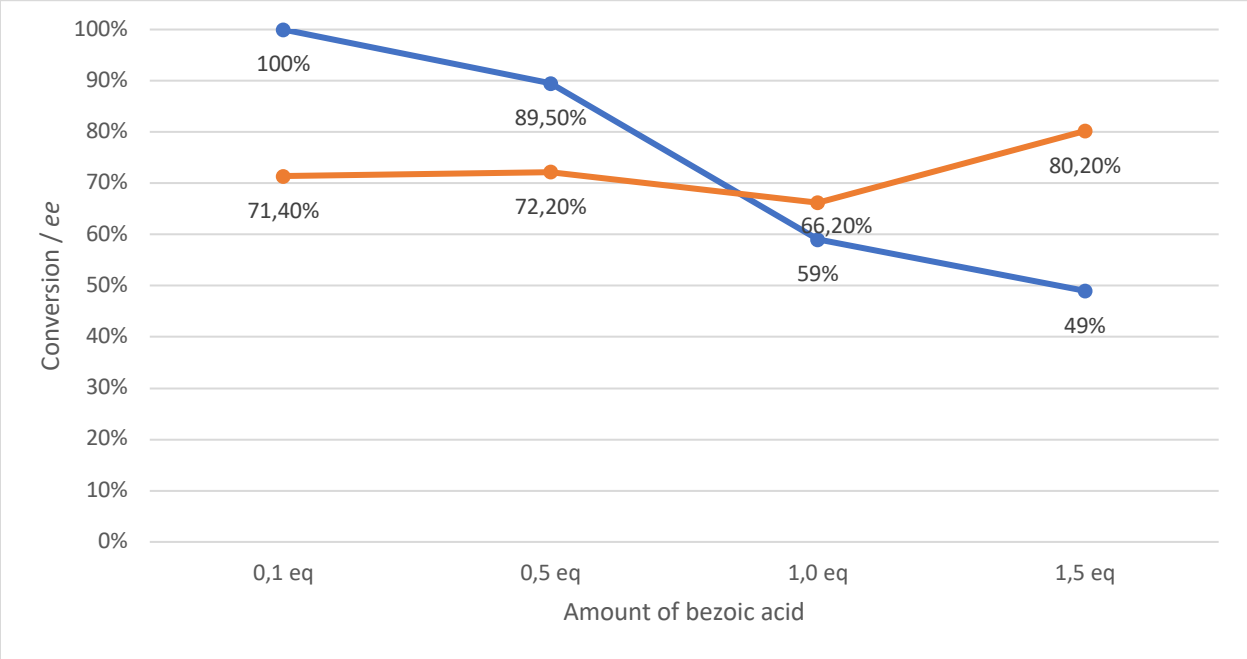
Table 9. Study of the optimal amount of benzoic acid



Entry	PhCOOH eq	Conversion [a]	*syn* : *anti* [b]	*ee (syn)* [c]
1	**0.1 eq**	**100%**	**7.9:1**	**71.4%**
2	0.5 eq	89.5%	7.5:1	72.2%
3	1.0 eq	59%	6.0:1	66.2%
4[d]	1.5eq	49%	8.6:1	80.2%

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] Experimental data are taken from Table 8 (entry 5)

The data obtained from these reactions were very encouraging. Experiments with different amounts of benzoic acid allowed us to track two the most important trends (Fig. 13).



Blue line – conversion; orange line – *ee*

Fig. 13. Graph of the dependence of conversion and enantioselectivity on the amount of benzoic acid

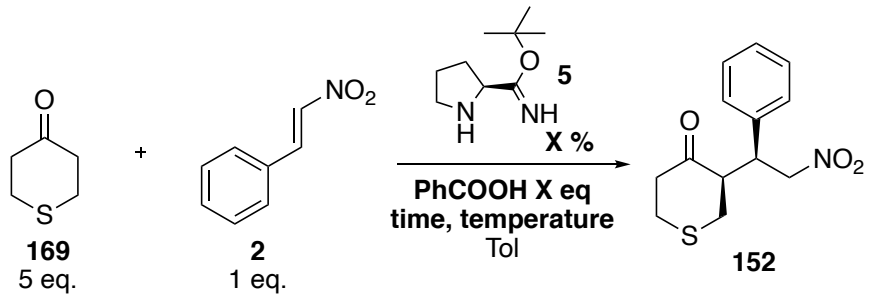
The increase in the amount of benzoic acid showed a trend to decrease the conversion of the reaction from full conversion for 0.1 equivalent (entry 1) to 49% for 1.5 equivalents (entry 4). This can be explained by the fact that with increasing acid concentration, the pH of the medium decreases and, at the same time, there is greater protonation of the catalyst, which makes it less able to form enamine. Changing the amount of the BzOH from the 0.1 to 0.5 and 1.0 equivalents almost did not affect the enantiomeric excess – 71.4% (entry 1), 72.2% (entry 2), 66.2% (entry 3). At the same time, an increase of the acid from 1.0 equivalent (entry 3) to 1.5 (entry 4) showed us a positive trend for enantiomeric excess – increasing from 66.2% to 80.2%, although, the conversion dropped. The change in the amount of acid did not significantly affect the ratio of *syn* to *anti* isomers: minimum was 6.0 :

1 – 85% *syn* (1.0 equivalent, entry 3) and maximum was 8.6 : 1 – 89% *syn* (1.5 equivalent, entry 4).

To get a more complete picture of the reaction with benzoic acid as an additive, it was decided to conduct additional experiments (Table 10):

- Reaction with 0.1 equivalent of benzoic acid and without aminoimidate **4** – to confirm key role of the catalyst.
- Reaction with 1.5 equivalents of benzoic acid for 48 hours – to increase the conversion for the best enantioselectivity conditions.
- Reaction with 0.1 equivalent of benzoic acid at 0°C – to increase the enantioselectivity for the best conversion conditions.

Table 10. Additional study of benzoic acid as an additive



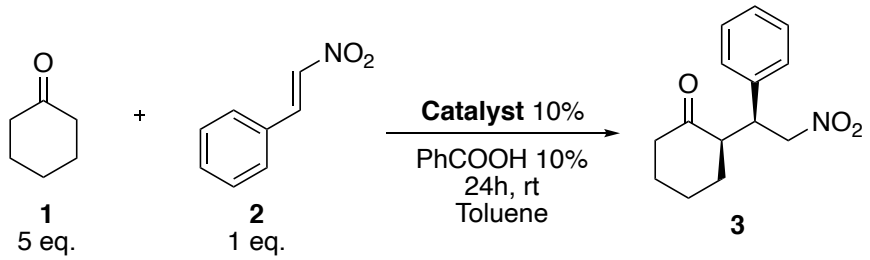
Entry	Conditions	Conv. [a]	*syn* : *anti* [b]	*ee* (*syn*) [c]
1	No catalyst, 0.1 eq of benzoic acid, 24h at rt	0%	-	-
2	10% of catalyst, 1.5eq. of benzoic acid, 48h at rt	50%	9.3 : 1	72.9%
3	10% of catalyst, 0.1eq. of benzoic acid, 8h at 0°C	35%	8.1 : 1	61.8%

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC

It was unsurprisingly the lack of product in the reaction without a catalyst (entry 1), which confirmed only the supporting role of benzoic acid. In the experiment with 1.5 equivalents of the additive (entry 2), the results were dissatisfying, because increasing the reaction time from 24 to 48 hours did not increase the conversion, and the enantioselectivity of the reaction decreased from 80.2% to 72.9%. The results of the reaction carried out at 0°C for 8 hours (entry 3) also were disappointing, because we obtained a decrease in conversion from 100% to 35% and in enantiomeric excess from 80.2% to 61.8%. A similar situation was seen with lower temperatures without an additive (see a chapter 9.2). This we cannot yet explain. Therefore, it can be concluded that room temperature and a time 24 hours are optimal for this system of catalyst-benzoic acid.

The next step in evaluating the effect of BzOH was to compare it to the two previously synthesized catalysts. These obtained data are shown in Table 11.

Table 11. Comparison of proline based and bicyclic catalysts with benzoic acid as an additive

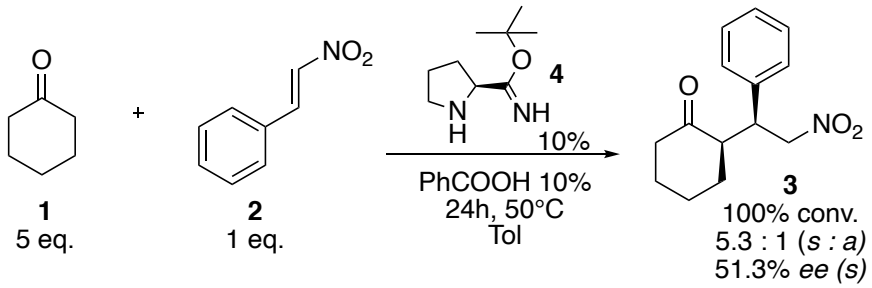


Entry	Catalyst	Conv. 24h[a]	Conv. 48h[a]	*syn* : *anti* [b]	*ee* (*syn*)[c]
1	Proline imidate **4**	100% (rt)	-	7.6 : 1	60.4%
2	Bicyclic imidate **5**	Traces (rt)	21% (75°C)	1.7 : 1	-[d]

[a] determined by ^{1}H NMR, by direct comparison of integrated alkene signals and product signals for the crude reaction; [b] determined by ^{1}H NMR for crude reaction; [c] determined by HPLC; [d] not determined

For proline imidate **4**, we noted a slight decrease in diastereoselectivity from 9.7:1 to 7.6:1 *syn* to *anti* ratio, but the most important was the increase in enantiomeric excess from 42.8% to 60.4%, compared to the experiment without additive (Table 2, entry 10). At the same time, benzoic acid did not help to improve the results for bicyclic catalyst **5**: conversion without additive 24% – conversion with it 21%; diastereoselectivity was 2.5:1 and became 1.7:1 as *syn* to *anti*.

The last experiment for a Michael reaction we conducted at elevated temperature to fully understand the effect of temperature on the reaction (Scheme 32).



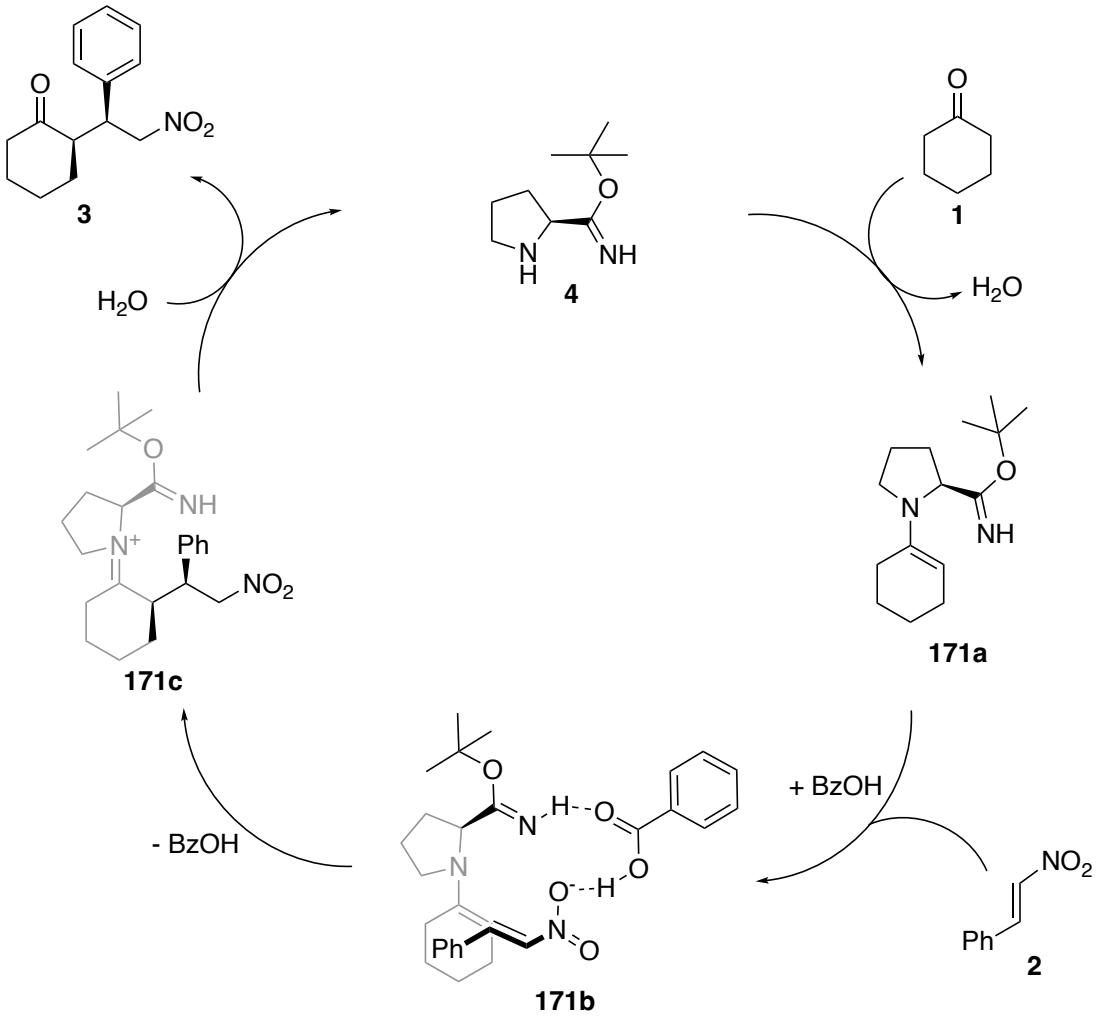
Scheme 32. Study of the reaction with benzoic acid at elevated temperature

The results were predictable: 100% conversion, reduction of diastereoselectivity (5.3:1 as *syn*:*anti*) and enantioselectivity (51.3%), compared to the same experiment at room temperature (Table 11, entry 1).

Therefore, it was determined that it was best to use 10% (0.1 equivalent) of benzoic acid as an additive along with 10% (0.1 equivalent) of proline imidate **4** in toluene at room temperature.

Based on the information about the role of benzoic acid [43][44] (see the introductory part, chapter 8.4) and previously described mechanism of Michael addition [55], a catalytic cycle for the developed Michael reaction was proposed (Scheme 33). First, an enamine **171a** is formed from the catalyst **4** and ketone **1**. Then, the transition state **171b** is formed from the alkene **2**, BzOH and intermediate

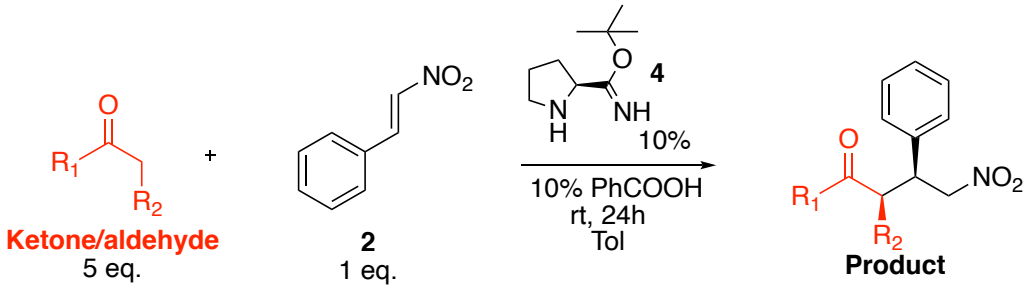
171a. At this stage, the key role is played by BzOH, which additionally activates nitroalkene **3** for the Michael reaction by forming H-bonds. After addition, iminium intermediate **171c** reacts with water to form the reaction product **3**.



Scheme 33. Proposed catalytic cycle for the developed Michael reaction

9.6. Scope

The final step was to examine the scope of catalyst **4** under the optimal conditions. This was started with evaluating carbonyl compounds that can act as nucleophiles (Scheme 34). Compared to the initial ketone screening we expanded the scope to aldehydes. The reaction products and all relevant information are presented in the Figure 14.



Scheme 34. General scheme of a reaction with carbonyl compounds as nucleophiles

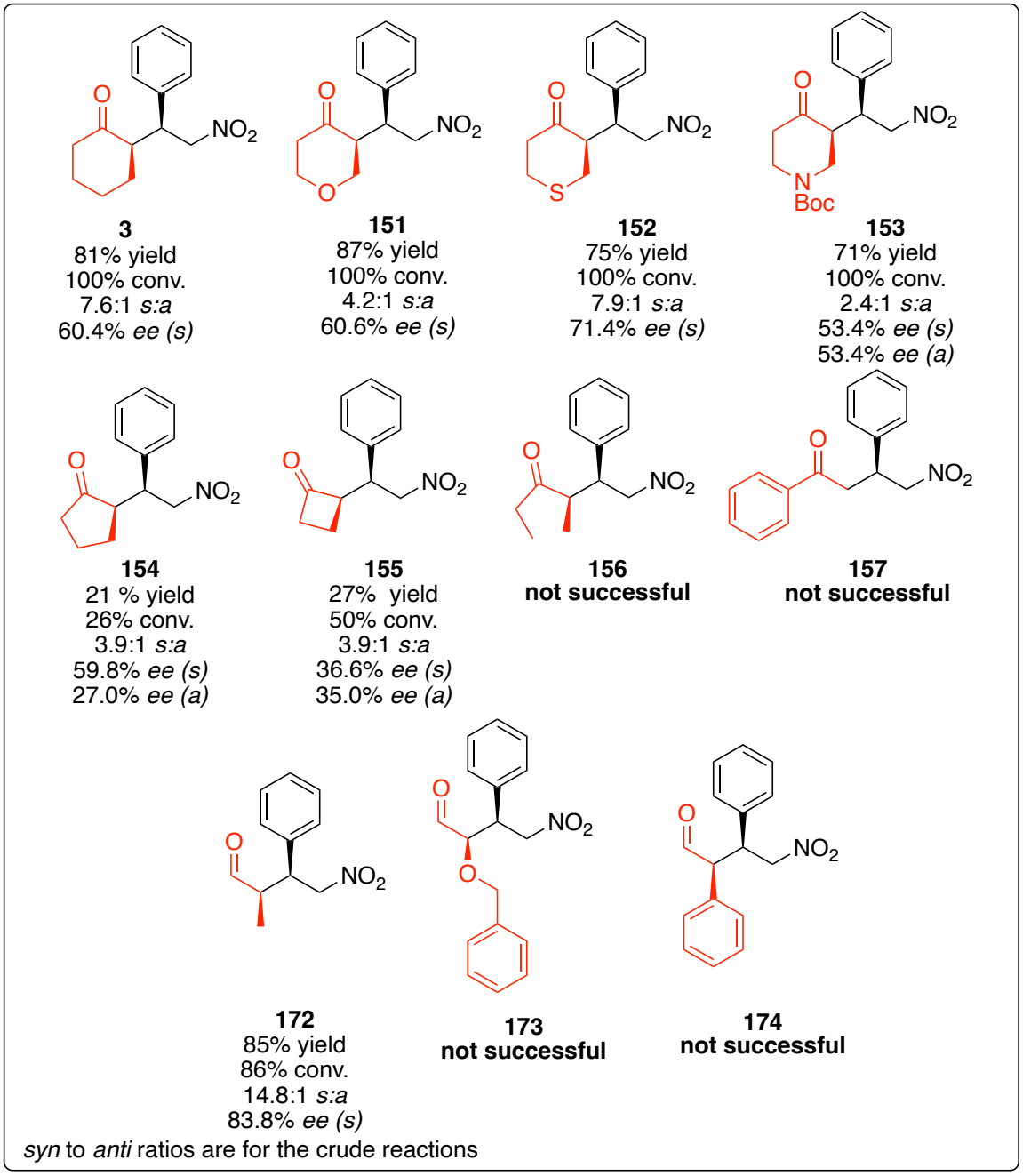
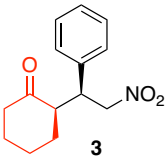
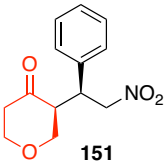
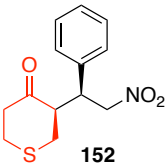
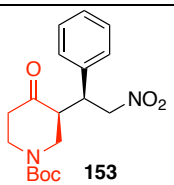
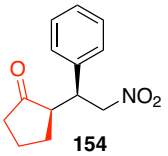
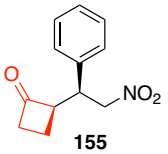
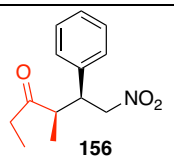
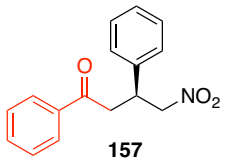


Fig. 14. Data of nucleophile screening

Comparing the results with the initial ketone screening, the conversion and enantioselectivity for most examples were significantly improved (Table 12).

Table 12. Comparison of ketone screening with and without benzoic acid

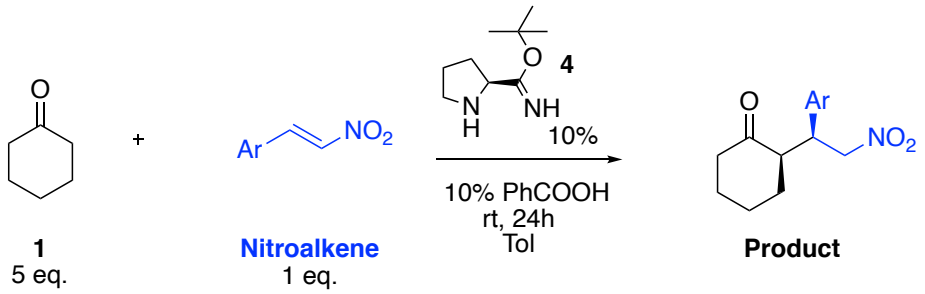
Entry	Product	Results without BzOH	Results without with 10% of BzOH
1	 3	62% yield 100% conv. 9.7 : 1 *syn : anti* 42.8% *ee (syn)*	81% yield 100% conv. 7.6 : 1 *syn : anti* 60.4% *ee (syn)*
2	 151	88% yield 100% conv. 5.8 : 1 *syn : anti* 25.8% *ee (syn)*	87% yield 100% conv. 4.2 : 1 *syn : anti* 60.6% *ee (syn)*
3	 152	25% yield 30% conv. 10 : 0 *syn : anti* 32.2% *ee (syn)*	75% yield 100% conv. 7.9 : 1 *syn : anti* 71.4% *ee (syn)*
4	 153	-[a]	71% yield 100% conv. 2.4 : 1 *syn : anti* 53.4% *ee (syn)* 53.4% *ee (anti)*
5	 154	6% conv. -[b] -[b] -[b]	21% yield 26% conv. 3.9 : 1 *syn : anti* 59.8% *ee (syn)* 27.0% *ee (anti)*
6	 155	27% yield 40% conv. 3.9 : 1 *syn : anti* 46.3% *ee (syn)* 15.8% *ee (anti)*	27% yield 50% conv. 3.9 : 1 *syn : anti* 36.6% *ee (syn)* 35.0% *ee (anti)*
7	 156	-[a]	-[a]

8	 157	-[a]	-[a]

syn to *anti* ratios are for the crude reactions; [a] no conversion; [b] not determined;

All cyclic six-membered ketones now had a complete conversion (entry 1-4). Moreover, they all had good enantiomeric excesses compare to use of no BzOH: from 53.4% for N-Boc-piperidin-4-one (entry 4) to 71.4% for tetrahydrothiopyran-4-one product (entry 3). For ketones with smaller ring size, we also saw an increase in conversion from 6% to 26% for cyclopentanone (entry 5) and from 40% to 50% for cyclobutanone (entry 6). The situation with enantioselectivity for these objects is interesting. In the reaction with cyclopentanone (entry 5) there is a good enantiomeric excess of the major *syn* product (59.8%) and a poor enantiomeric excess for the minor *anti*-product (17.0%). At the same time for cyclobutanone (entry 6), the enantiomeric excess for both products are quite low 36.6% and 35.0%. This is the only example where the addition of benzoic acid has worsened the enantiomeric excess for the *syn* product and increased the enantioselectivity for the *anti*-product. Reactions with acyclic ketones could not be catalyzed even with the additive (entry 7-8). This may be due to a different conformation of the alkyl chain (entry **7**) and the larger size of the substituents (entry **8**) compared to cyclic ketones. We were pleasantly surprised by the result of the reaction with propanal (Fig. 14, product **172**) – 86% conversion, *syn* to *anti* ratio 14.8 to 1 and 83.8% enantiomeric excess, which are the best results in our study. Unfortunately, reactions with other aldehydes gave no conversion. Diastereoselectivity in all cases except for N-Boc-piperidin-4-one product (entry 4; 2.4:1 as *syn* to *anti*) was high, and it should be noted that in this case both diastereomers had an equally good enantiomeric excess of 53.3%. This we cannot yet explain.

The next step involved evaluating the reaction characteristics for different nitroalkenes (Scheme 35). The obtained data are shown in the Figure 15.



Scheme 35. General scheme of a reaction with nitroalkenes

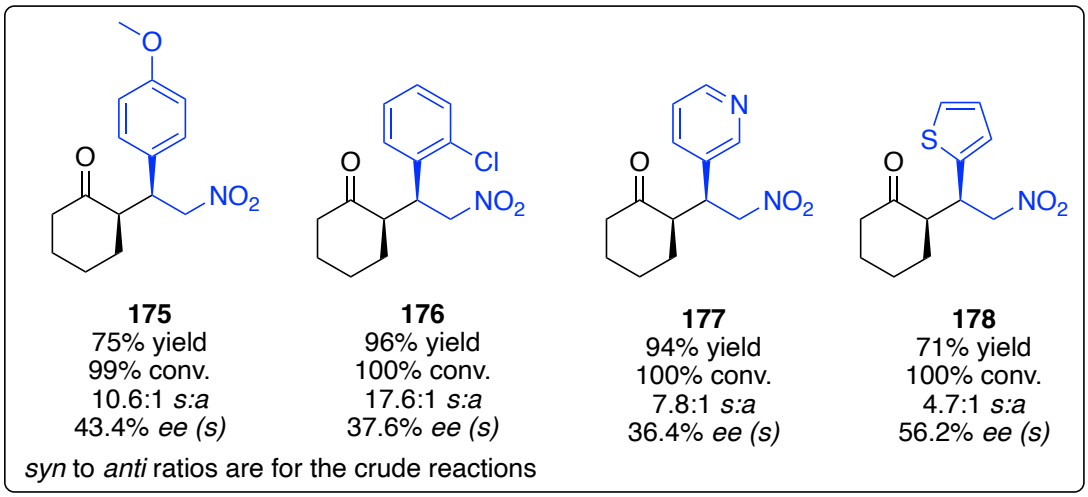
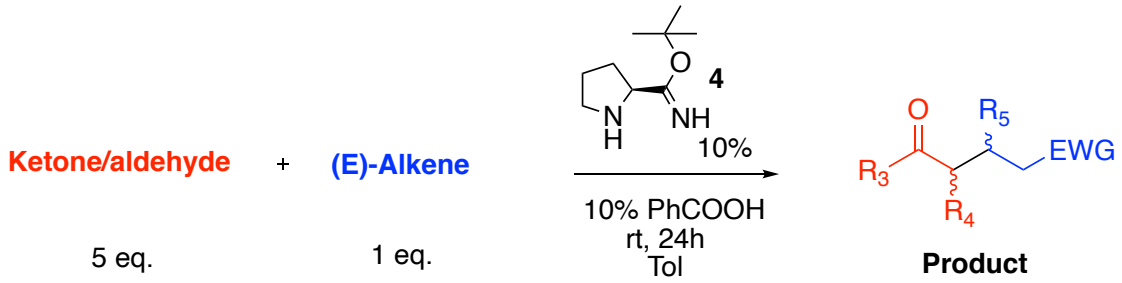


Fig. 15. Data of nitroalkene screening

Four aryl substituents of different natures were selected for experiments: (E)-1-methoxy-4-(2-nitroethenyl)benzene – *p*-substituted electron donor aromatic ring (**175**), (E)-1-chloro-2-(-2-nitroethenyl)benzene – *o*-substituted aromatic ring with negative inductive and positive mesomeric effects (**176**), (E)-3-(2-nitroethenyl)pyridine – electron poor aromatic ring (**177**) and (E)-2-(2-nitroethenyl)thiophene – electron donor aromatic five-membered ring (**178**). In all cases, the conversion was very high, indicating that the nature of the ketone is crucial for product formation. Diastereoselectivity was also high, from 4.7 : 1 (*syn : anti*) for the thiophene product **178** to 17.6 : 1 (*syn : anti*) for the *o*-chloro substituted benzene product **176**. This indicated that the nature of the aryl group does not significantly affect the ratio of diastereoisomers, and in general for the reaction is a

major *syn* product, regardless of the nature of the reagents. Enantioselectivity for products with six-membered aromatic rings is moderate. For product **175** formed from the alkene with a donor group in an aromatic ring enantiomeric excess is 43.4% and is 36.4% for a product **177** formed from an alkene with an electron poor ring. For the *o*-chloro substituted product **176**, we obtained an enantiomeric excess of 37.6%. The product **178** obtained from unsubstituted thiophene has an enantiomeric excess of 56.2%, which is similar with product obtained from cyclohexanone and nitroalkene with unsubstituted benzene core (Fig. 14).

At the end of study, it was decided to conduct experiments between different carbonyl compounds and Michael acceptors (Scheme 36; Fig. 16).



Scheme 36. General scheme of a reaction between different carbonyl compounds and Michael acceptors

Attempts to obtain products where the alkene is not a derivative of nitroethylene were unsuccessful (compounds **181-189**). Any attempts to change the nitro group to other groups led to a complete loss of conversion, which shows the importance of NO_2 as an EWG for the activation of the alkene. Only products **179** and **180** were obtained, where nitroalkenes were used. In the reaction where propanal was a nucleophile excellent results were obtained: conversion - 70%, *syn:anti* – 10.6:1 and a high enantiomeric excess for both diastereomers – 81.8% *syn* and 77.0% for *anti*. Unexpected results were obtained for the reaction between cyclobutanone and (E)-1-chloro-2-(2-nitroethenyl)benzene. The conversion was good – 64%, but

diastereoselectivity was almost completely lost – 1.6:1 as *syn:anti* and, for the first time, a better enantiomeric excess was recorded for the minor product – 46.8% for *anti* isomer compared to 15.2% for the major *syn* product.

Due to lack of time, other alkenes derivatives were not evaluated.

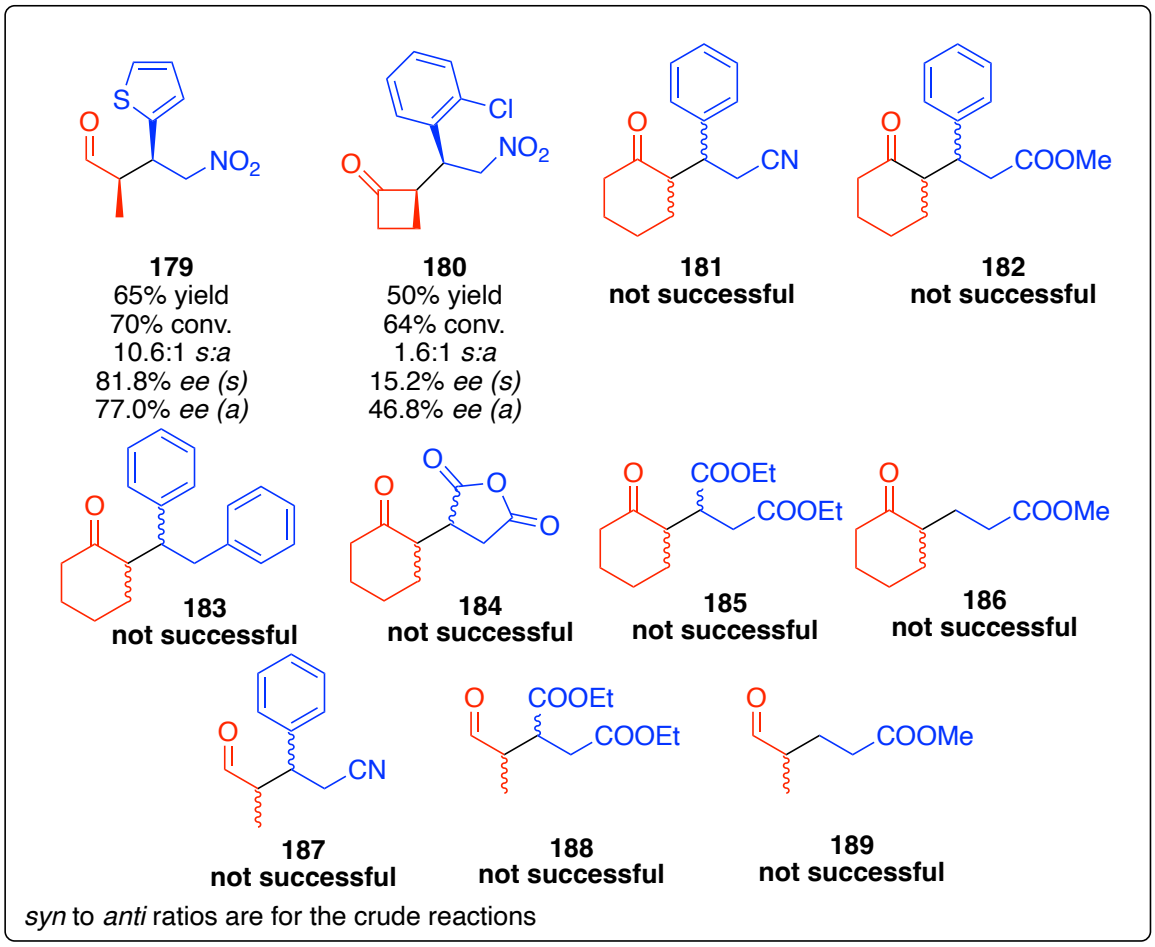


Fig. 16. Data of reactions between different carbonyl compounds and Michael acceptors

9.7. Conclusions and future work

In conclusion, the first study of aminonitriles as organocatalysts in a Michael reaction was carried out. During this research, *t*-butyl imidates with a proline core **4** and bicyclic core **5** were synthesized. Their characteristics were compared. Catalyst **5** did not show good results. Probably, this is because a more complex spatial structure makes it difficult to form a transition complex and the energy barrier of the reaction is higher. At the same time, proline imidate **4** with a simpler structure gave us a good conversion for a variety of substrates. Other proline imidates were unable to be synthesized.

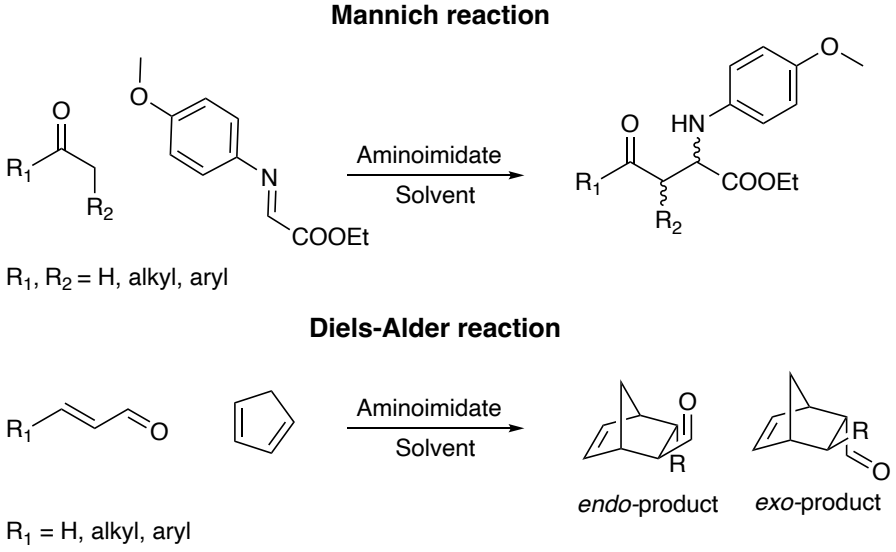
Various solvents were investigated for the reaction. It was determined that aprotic non-polar solvents such as cyclohexane and toluene were the best. Toluene was chosen as the main due to the best solubility properties. The effect of temperature on the reaction was investigated. As a result, it was determined that it is best to carry out the reaction at room temperature.

The way to improve conversion and enantioselectivity with additives was investigated. Additives of different nature were evaluated and determined that benzoic acid was the best. As a result, a transition state was proposed for the reaction including the role of the additive.

Finally, the scope of the Michael reaction catalyzed by *t*-butyl *L*-proline imidate was investigated. The best conversion results were obtained for cyclic six-membered ketones. Acyclic ketones did not undergo the reaction. The best enantioselectivity was observed for propane aldehyde.

The study of different alkenes showed that the nature of the aryl substituent affects the enantioselectivity and does not affect the conversion. We also found that the nitro group is absolutely needed as EWG, because the formation of the products was not observed when replacing it with other groups.

To conclude, we have demonstrated a second example of the use of imidates in organocatalysis (the first one was for an aldol reaction [46]). This work can be continued by studying the use of aminoimidates as an organocatalyst for other reactions, such as the Mannich reaction or Diels-Alder reaction (Scheme 37).



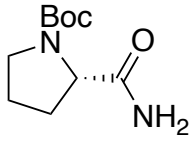
Scheme 37. Suggestions for the future work

10. Experimental

Unless otherwise noted, all compounds were bought from commercial suppliers and used without further purification. All reactions were performed in a flame dried flask, that was allowed to cool to rt under a N_2 atmosphere. NMR spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: $CDCl_3$ 7.26 ppm for ^1H NMR; $CDCl_3$ 77.0 ppm for ^{13}C NMR. Coupling constants (*J*) are quoted in Hertz. IR absorbances were recorded on a PerkinElmer UATR. Two FT-IR spectrometer using NaCl plates. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Optical rotations were carried out using a Bellingham + Stanley Single Wavelength Polarimeter ADP450 and $[\alpha]_D$ values are given in $deg \cdot cm^3 g^{-1} dm^{-1}$. TLC was performed on aluminum sheets coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, basic aq $KMnO_4$ or CAM stains. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich. Anhydrous solvents were acquired from a PureSolv PS-MD-7 solvent tower. High-performance liquid chromatography (HPLC) was performed using an Agilent 1100 series instrument using the chiral columns indicated and a range of wavelengths from 210.4–302.8nm for detection.

10.1. Experimental procedures

Boc-*L*-Prolinamide (148)



Boc-*L*-proline **147** (5.01 g, 23.3 mmol) and THF (70 mL) were added to a flask. To this flask, NEt_3 (3.25 mL, 23.3 mmol) was added and stirred, at room temperature. After 15 minutes, ethyl chloroformate (2.22 mL, 23.3 mmol) was added and the reaction was continued to be stirred at room temperature. After 1h, 7N solution of NH_3 in MeOH (5 mL), was added and the reaction was continued to be stirred overnight. After that, the reaction was deemed complete by ^{1}H NMR and the stirring stopped. The solvent was removed in *vacuo* and the solution was washed with H_2O (10 mL) and extracted with DCM (x3). The combined organic layers dried were over $MgSO_4$ and the solution was concentrated in *vacuo* to give the title compound **148** as a white solid in an 82% yield (4.11 g, 19.2 mmol). Melting point 107-108°C; lit. [56] 102-104°C.

IR (ATR): 2977, 1668, 1392, 1161 cm^{-1}.

$[\alpha]_D^{20}$ –32.34 (c=1.0 mg/mL, MeOH); lit. [46] $[\alpha]_D^{25}$ –44.7 (c=1.0 mg/mL, MeOH).

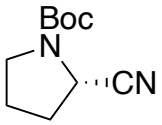
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 – 5.77 (m, 2H), 4.34 – 4.03 (m, 1H), 3.54 – 3.07 (m, 2H), 2.35 – 1.73 (m, 4H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.2 and 175.1 (rotamers), 155.7 and 154.7 (rotamers), 80.5 and 80.3 (rotamers), 61.0 and 59.7 (rotamers), 47.2 and 47.0 (rotamers), 31.2, 28.4, 24.6 and 23.8 (rotamers).

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{10}H_{18}N_2NaO_3$ – 237.1210; found: $C_{10}H_{18}N_2NaO_3$ – 237.1205.

^{1}H NMR data agree with the literature [46].

Boc-*L*-Proline Nitrile (149)



A flask containing Boc-*L*-proline amide **148** (4.02 g, 18.8 mmol) and NEt_3 (5.78mL, 41.4 mmol) in THF (60 mL) was cooled to 0°C and stirred. After 30 minutes of stirring, TFAA (3.92 mL, 28.2 mmol) was added and the reaction continued to be stirred at 0 °C. After 2 hours the reaction was warmed to room temperature and continued to be stirred. After stirring overnight the reaction was deemed complete by TLC (100% EtOAc; CAM stain) and the stirring was stopped. The solvent was removed in *vacuo*. The crude yellow oil was redissolved in EtOAc, washed with 2M HCl and extracted with EtOAc (x3) from the HCl wash. The organic layers were combined, washed with saturated $NaHCO_3$ and then with brine. Organic layers were combined, dried over Na_2SO_4 and filtered. The solution was concentrated in *vacuo* to give the crude product as orange oil. The crude oil was further purified by column chromatography (gradient from Hex to EtOAc) to give **149** as a pale yellow oil in a 95 % yield (3.51 g, 17.9 mmol).

IR (ATR): 2980, 1694, 1387, 1158 cm^{-1}.

$[\alpha]_D^{20}$ –72.77 (c=1.0 mg/mL, MeOH); lit. [46] $[\alpha]_D^{20}$ –91.15 (c=1.3 mg/mL, MeOH).

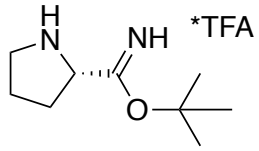
^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm: 4.60 - 4.40 (1 H, m), 3.58-3.25 (2 H, m) 2.30 – 1.95 (4 H, m), 1.50 - 1.45 (9 H, m).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.8 and 153.2 (rotamers), 119.2, 81.6 and 81.1 (rotamers), 47.3 and 47.1 (rotamers), 46.1 and 45.8 (rotamers), 31.7 and 30.9 (rotamers), 28.4 and 28.3 (rotamers), 24.7 and 23.9 (rotamers).

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{10}H_{16}N_2NaO_2$ - 219.1104; found: $C_{10}H_{16}N_2NaO_2$ - 219.1102.

^{1}H NMR data agree with the literature [46].

t-Butyl *L*-Proline imidate trifluoroacetate (150)



The flask with Boc-*L*-proline nitrile **149** (1.0 g, 5.1 mmol), TFA (17.00 mL, 229.5 mmol) was added, and the flask was cooled to 0°C. Upon consumption of the starting material (Hex : EtOAc = 8 : 2; CAM stain), *t*-BuOH (0.97 mL, 10.2 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was left stirring overnight. Stirring was stopped and the solvent was removed in *vacuo*. Trituration with DIPE-Hex provided the salt **150** as a yellow solid in a 77 % yield (1.1 g, 3.9 mmol). Melting point 87-89°C; lit. [46] 88-90°C.

IR (ATR): 1661, 1177, 1131 cm^{-1}.

$[\alpha]_D^{20}$ –44.36 (c=1.0 mg/mL, DCM); lit. [46] $[\alpha]_D^{25}$ –47.23 (c=1.0 mg/mL, DCM).

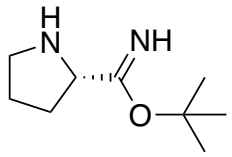
^{1}H NMR (400 MHz, Methanol-d_4) δ 4.12 (dd, J = 8.5, 6.8 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.36 – 3.24 (m, 1H), 2.43 – 2.31 (m, 1H), 2.06 – 1.85 (m, 3H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 167.6, 59.7, 52.2, 52.1, 46.4, 30.5, 28.5, 24.7. (TFA signals are absent)

HRMS (ESI) *m*/*z* $[M + H]^+$ calculated for $C_9H_{19}N_2O$ - 171.1492; found: $C_9H_{19}N_2O$ – 171.1493.

^{1}H NMR data agree with the literature [46].

t-Butyl *L*-Proline imidate (4)



The free *L*-proline imidate **4** was liberated by dissolving the salt **150** (1.0 g, 3.9 mmol) in DCM and stirring over K_2CO_3 (2.69 g, 19.5 mmol) for 1 hour before filtering and concentrating in *vacuo*. The crude product was purified by column chromatography (gradient from DCM to MeOH; TLC – DCM : MeOH = 8 : 2 and CAM stain); the free base imidate **4** was obtained as yellow solid in a 62 % yield (0.4 g, 2.4 mmol). Melting point 68-69°C.

IR (ATR): 2965, 1657, 1518, 1454, 1226 cm^{-1}.

$[\alpha]_D^{20}$ –51.54 (c=1.0 mg/mL, MeOH).

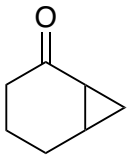
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.40 (br s, 1H), 3.60 (dd, *J* = 8.9, 5.5 Hz, 1H), 2.98 (dt, *J* = 10.3, 6.8 Hz, 1H), 2.86 (dt, *J* = 10.3, 6.4 Hz, 1H), 2.26 (br s, 1H), 2.12 – 2.01 (m, 1H), 1.91 – 1.79 (m, 1H), 1.77 – 1.54 (m, 2H), 1.32 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.3, 61.2, 50.2, 47.3, 30.8, 28.8, 26.3.

HRMS (ESI) *m*/*z* $[M + H]^+$ calculated for $C_9H_{19}N_2O$ - 171.1492; found: $C_9H_{19}N_2O$ – 171.1492.

^{1}H NMR data agree with the literature [46].

Bicyclo[4.1.0]heptan-2-one (158)



To a flame-dried three-necked flask, equipped with an efficient stirrer, inert gas inlet, thermometer and dropping funnel was added DMSO (50 mL). Vigorous stirring was started and NaH (60% in oil – 5.00 g, 125 mmol) was added carefully in small portions to keep the reaction mixture temperature within the range of 20-35°C by external cooling. Followed by trimethylsulfoxonium iodide (27.5 g, 125 mmol) was carefully added in small portions. The white suspension obtained was stirred for an additional 30 min, the reaction mixture was cooled to 20°C and a solution of 2-cyclohexen-1-one (6.47 mL, 62.5 mmol) in DMSO (10 mL) was slowly added with vigorous stirring to control the internal temperature at 20°C. The reaction mixture was stirred for 30 min at r.t. and for an additional 2h at 50°C, then it was checked by TLC (Hex : Et_2O = 8 : 2; CAM stain), cooled and poured onto 60 g of ice. The suspension formed was filtered, and the filtrate thoroughly extracted with Et_2O (x3). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting compound **158** was dried under vacuum at rt and then directly used for the next step (4.9 g with 90% purity, 64% yield). The form of pure matter - colorless oil.

IR (ATR): 3016, 2933, 2863, 1684, 1348, 1244, 875 cm^{-1}

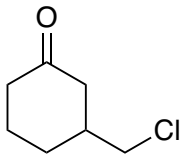
^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.31 – 2.21 (m, 1H), 2.10 – 1.81 (m, 3H), 1.76 – 1.50 (m, 4H), 1.18 (q, *J* = 5.3 Hz, 1H), 1.10 – 1.02 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.5, 36.8, 25.9, 21.3, 17.8, 17.5, 10.3.

HRMS (ESI) *m*/*z* $[M + Na]^+$ calculated for $C_7H_{10}NaO$ – 133.0624; found: $C_7H_{10}NaO$ – 133.0624.

^{1}H NMR data agree with the literature [57].

3-(Chloromethyl)cyclohexanone (159)



Compound **158** (4.70 g, 42.7 mmol) and pyridinium hydrochloride (14.8 g, 0.13 mol) were dissolved in MeCN (60 mL), transferred in the flask, and refluxed for 60h. The reaction was monitored by TLC (Hex : Et_2O = 8 : 2; CAM stain). When complete, the reaction was poured into brine (100 mL) and extracted with Et_2O (x3). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (gradient from Hex to Et_2O). The product **159** was obtained as colorless oil in a 51 % yield (3.2 g, 21.8 mmol).

IR (ATR): 2950, 1707, 1225, 721, 498 cm^{-1}

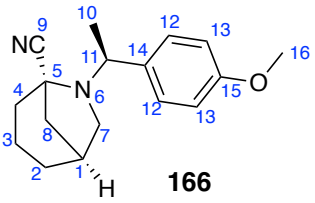
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.57 – 3.41 (m, 2H), 2.49 – 2.42 (m, 1H), 2.42 – 2.31 (m, 1H), 2.31 – 1.99 (m, 4H), 2.00 – 1.92 (m, 1H), 1.74 – 1.45 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.3, 49.4, 45.4, 41.1, 40.8, 28.7, 24.6.

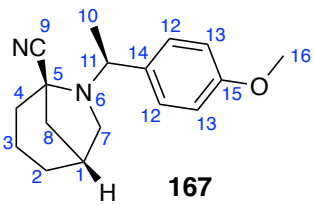
HRMS (ESI) *m*/*z* $[M + Na]^+$ calculated (as 3:1) for $C_7H_{11}{}^{35}ClNaO$ – 169.0391 and $C_7H_{11}{}^{37}ClNaO$ – 171.0361; found (as 3:1): $C_7H_{11}{}^{35}ClNaO$ – 169.0392 and $C_7H_{11}{}^{37}ClNaO$ – 171.0361.

^{1}H NMR data agree with the literature [58].

(1*S*,5*R*)-6-((*S*)-1-(4-Methoxyphenyl)ethyl)-6-azabicyclo[3.2.1]octane-5-carbonitrile (166) and **(1*R*,5*S*)-6-((*S*)-1-(4-methoxyphenyl)ethyl)-6-azabicyclo[3.2.1]octane-5-carbonitrile (167)**



166



167

To a solution of 3-chloromethylcyclohexanone **159** (3.11 g, 21.2 mmol) in MeOH (19 mL), (*S*)-1(4-methoxyphenyl)ethylamine (3.31 mL, 22.4 mmol) and acetone cyanohydrin (5.81 mL, 63.6 mmol) were added. The mixture obtained was refluxed for 40h, then poured into 126 mL of 10% aqueous NaOH solution and extracted with DCM (x3). The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (gradient from Hex to Et_2O; TLC – Hex : Et_2O = 8 : 2, UV) to afford 52% (1.5 g, 5.5 mmol) of **167** (eluting first), and 45% (1.3 g, 4.8 mmol) of **166** (eluting second).

166: melting point 57-58°C (pile yellow solid)

IR (ATR): 2938, 2862, 2234, 1511, 1244, 1034, 833 cm^{-1}

$[\alpha]_D^{20}$ –5.83 (c=0.61 mg/mL, $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 2H, H-12), 6.88 – 6.82 (m, 2H, H-13), 4.04 (q, *J* = 6.6 Hz, 1H, H-11), 3.78 (s, 3H, H-16), 3.32 (dd, *J* = 9.3, 6.0 Hz, 1H, H-7), 2.73 (d, *J* = 9.3 Hz, 1H, H-7), 2.44 – 2.24 (m, 2H, H-1,8), 2.24 – 2.14 (m, 1H, H-4), 1.79 (d, *J* = 10.6 Hz, 1H, H-8), 1.75 – 1.48 (m, 5H, H-2,3,4), 1.44 (d, *J* = 6.6 Hz, 3H, H-10).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.3 (C-9), 135.8 (C-15), 129.5 (C-12), 121.8 (C-14), 113.6 (C-13), 57.7 (C-5), 57.0 (C-11), 55.3 (C-16), 53.9 (C-7), 45.6 (C-8), 33.5 (C-4), 33.1 (C-1), 30.1 (C-2), 23.0 (C-10), 18.7 (C-3).

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{17}H_{22}N_2NaO$ – 293.1624; found: $C_{17}H_{22}N_2NaO$ – 293.1628.

167: melting point 84-85°C (white solid)

IR (ATR): 2940, 2860, 2236, 1510, 1242, 1033, 833 cm^{-1}.

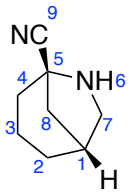
$[\alpha]_D^{20}$ –31.49 (c=0.56 mg/mL, $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H, H-12), 6.88 – 6.80 (m, 2H, H-13), 4.06 (q, *J* = 6.6 Hz, 1H, H-11), 3.79 (s, 3H, H-16), 3.01 (dd, *J* = 9.8, 5.8 Hz, 1H, H-7), 2.47 – 2.37 (m, 1H, H-8), 2.33 (ddd, *J* = 13.9, 5.1, 2.9 Hz, 1H, H-4), 2.29 – 2.17 (m, 2H, H-1,7), 1.88 (d, *J* = 10.8 Hz, 1H, H-8), 1.85 – 1.74 (m, 1H, H-4), 1.73 – 1.51 (m, 5H, H-3,10), 1.51 – 1.43 (m, 2H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.6 (C-9), 138.0 (C-15), 128.1 (C-12), 124.0 (C-14), 113.8 (C-13), 59.2 (C-11), 56.9 (C-5), 56.6 (C-7), 55.3 (C-16), 45.9 (C-8), 33.3 (C-1), 32.9 (C-2), 30.0 (C-4), 24.2 (C-10), 19.2 (C-3).

HRMS (ESI) *m/z* [M + Na]$^+$ calculated for $C_{17}H_{22}N_2NaO$ – 293.1624; found: $C_{17}H_{22}N_2NaO$ – 293.1626.

(1*R*,5*S*)-6-Azabicyclo[3.2.1]octane-5-carbonitrile (168)



The compound **167** (0.80 g) was dissolved in TFA (8.0 mL), transferred to the flask, and stirred at r.t. for 1h. TFA was evaporated under reduced pressure when the reaction was deemed complete by ^{1}H NMR. The residue was dissolved in water, extracted with Et_2O (x3) and K_2CO_3 was added to the basic reaction of solution. The target product was extracted with Et_2O (x3) from the basic solution. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The product **168** was obtained as a white solid in a 64 % yield (0.26 g, 1.90 mmol). Melting point 76-77°C. The configuration of the compound was determined by the optical rotation for the nitrile-derived acid hydrochloride. Data in agreement with literature [51].

IR (ATR): 3348, 3282, 2934, 2879, 2228, 1677, 1459, 1204, 1126, 1006, 739 cm^{-1}

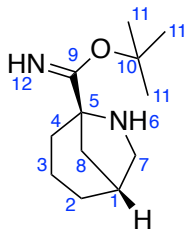
$[\alpha]_D^{20}$ –22.20 (c=0.70 mg/mL, $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.15 (dd, *J* = 10.2, 5.4, 1H, H-7), 2.95 (d, *J* = 10.2 Hz, 1H, H-7), 2.36 – 2.43 (m, 1H, H-1), 2.20 – 2.09 (m, 1H, H-8), 1.88 – 1.74 (m, 3H, H-8,4), 1.73 – 1.59 (m, 2H, H-3), 1.59 – 1.38 (m, 2H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 122.9 (C-9), 55.6 (C-5), 51.0 (C-7), 43.5 (C-8), 37.3 (C-4), 35.1 (C-1), 29.9 (C-2), 18.5 (C-3).

HRMS (ESI) *m/z* $[M + H]^+$ calculated for $C_8H_{13}N_2$ – 137.1073; found: $C_8H_{13}N_2$ – 137.1072.

(1*R*,5*S*)-*t*-Butyl 6-Azabicyclo[3.2.1]octane-5-carbimidate (5)



The nitrile **168** (0.2 g, 1.5 mmol) was dissolved in TFA : *t*-BuOH = 3 : 1 (1.5 mL : 0.5 mL) and stirred for 16h at 45°C. The reaction was monitored by NMR of reaction mixture after evaporation.

^{1}H NMR (400 MHz, Chloroform-*d*) 9.19 (br s, 1H), 8.49 (br s, 1H), 5.87 (br s, 1H), 3.43 – 3.63 (m, 2H), 2.42 – 2.63 (m, 1H), 2.20 – 2.35 (m, 2H), 2.02 – 1.70 (m, 5H), 1.56 – 1.70 (m, 1H), 1.32 (s, 9H) – spectrum information for the TFA salt of **5**.

The TFA was evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and stirred with K_2CO_3 (1.04 g; 7.50 mmol) for 10 minutes at r.t. An inorganic residue was removed by filtration, and the filtrate was evaporated. The pure product **5** was obtained as a white solid in an 73 % yield (0.23 g, 1.09 mmol). Melting point 114-115°C.

IR (ATR): 3311, 2927, 2865, 1658, 1518, 1456, 1231 cm^{-1}

$[\alpha]_D^{20}$ –23.20 (c=0.6 mg/mL, MeOH).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (br s, 1H, H-12), 3.07 (dd, *J* = 10.4, 4.7 Hz, 1H, H-7), 3.01 (d, *J* = 10.4 Hz, 1H, H-7), 2.30 – 2.24 (m, 1H, H-1), 2.15 (app. td, *J* = 12.9, 5.7 Hz, 1H, H-4), 1.76 – 1.66 (m, 2H, H-3,8), 1.66 – 1.38 (m, 4H, H-2,4,8), 1.29 (s, 9H, H-11).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 175.8 (C-9), 66.9 (C-5), 51.2 (C-7), 50.1 (C-10), 42.8 (C-3), 36.1 (C-1), 33.8 (C-4), 30.5 (C-2), 28.8 (C-11), 19.4 (C-8).

HRMS (ESI) *m/z* $[M + H]^+$ calculated for $C_{12}H_{23}N_2O$ – 211.1805; found: $C_{12}H_{23}N_2O$ – 211.1806.

10.2. General procedure for racemic Michael reaction

D/L-Proline (75.0 μmol, 0.15 eq.), ketone (5.0 mmol, 10.0 eq.) and an alkene (0.5 mmol, 1.0 eq.) were dissolved in 4 mL of DMSO. The reaction solution was stirred at room temperature for 24 hours, after which the reaction was analyzed by TLC. After completion of the reaction, it was quenched with 8 mL saturated NH_4Cl solution and extracted with EtOAc (x3). The organic layers were collected, dried by Na_2SO_4, and concentrated to give the crude Michael product.

The procedure is based on the conditions described in the literature [22].

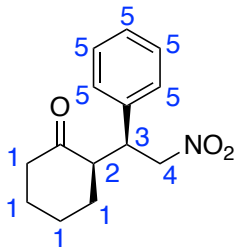
All products were purified by column chromatography (conditions the same as for chiral compounds) and HPLC conditions were determined for pure products.

10.3. General procedure for imidate catalyzed Michael reaction

Proline-imidate **4** (0.025 mmol, 0.1 eq.) and benzoic acid (0.025 mmol, 0.1eq) were dissolved in 1 mL of toluene along with ketone (1.250 mmol, 5 eq.) and stirred for 15 minutes. Alkene (0.250 mmol, 1.0 eq.) was added to the reaction solution and stirred at room temperature for 24 hours, after which, the reaction was analyzed by TLC and NMR (for conversion and *syn* to *anti* diastereoselectivity). Then the reaction was quenched with 2 mL saturated NH_4Cl solution and extracted with DCM (x3). The organic layers were collected, washed with 0.7M (1g/10mL) K_2CO_3 solution (x1), dried by Na_2SO_4, and concentrated to give the crude Michael product.

All products were purified by column chromatography and enantiomeric excess was determined by HPLC for pure products.

(R)-2-[(S)-2-Nitro-1-phenylethyl]cyclohexanone (3)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 81% (white solid; melting point 118-120°C; lit. [59] 128-130°C); ratio *syn:anti* 27.5:1.0; *ee* (*syn*) 60.4%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 1 mL/min, λ = 254 nm, 30°C).

IR (ATR): 2977, 1707, 1550, 1380, 1130, 702 cm^{-1}.

$[\alpha]_D^{20}$ +14.4 (c=0.58 mg/mL, $CHCl_3$); lit. [59] **$[\alpha]_D^{25}$** +19.1 (c=1.0 mg/mL, $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.39 – 7.22 (m, 3H, H-5), 7.22 – 7.08 (m, 2H, H-5), 4.93 (dd, *J* = 12.6, 4.5 Hz, 1H, H-4), 4.62 (dd, *J* = 12.6, 9.9 Hz, 1H, H-4), 3.75 (td, *J* = 10.0, 4.5 Hz, 1H, H-3), 2.73 – 2.62 (m, 1H, H-2), 2.52 – 2.25 (m, 2H, H-1), 2.13 – 2.01 (m, 1H, H-1), 1.83 – 1.48 (m, 4H, H-1), 1.31 – 1.15 (m, 1H, H-1).

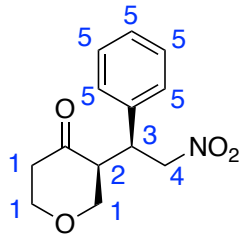
Detected *anti* isomer signal: δ 4.02 – 3.97 (m, 1H, H-3).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 212.1, 135.9, 129.1, 128.3, 127.9, 79.0, 52.6, 44.0, 42.9, 33.3, 28.6, 25.1.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{14}H_{17}NNaO_3$ – 270.1101; found: $C_{14}H_{17}NNaO_3$ – 270.1103.

^{1}H NMR (*syn*) data agree with the literature [48b].

(S)-3-[(S)-2-Nitro-1-phenylethyl]-tetrahydro-pyran-4-one (151)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 87% (white solid); ratio *syn:anti* 10.1:1.0; *ee* (*syn*) 60.6%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 15:85, flow rate 1 mL/min, λ = 210 nm, 25°C).

IR (ATR): 2977, 2831, 1711, 1552, 1380, 703 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.37 – 7.26 (m, 3H, H-5), 7.19 – 7.14 (m, 2H, H-5), 4.92 (dd, *J* = 12.7, 4.6 Hz, 1H, H-4), 4.63 (dd, *J* = 12.7, 10.1 Hz, 1H, H-4), 4.18 – 4.09 (m, 1H, H-3), 3.87 – 3.62 (m, 3H, H-1,2), 3.26 (dd, *J* = 11.6, 8.9 Hz, 1H, H-1), 2.92 – 2.82 (m, 1H, H-1), 2.71 – 2.61 (m, 1H, H-1), 2.55 (dt, *J* = 13.9, 4.0 Hz, 1H, H-1).

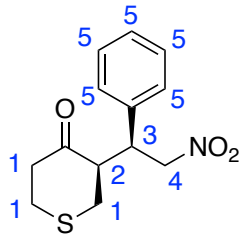
Detected *anti* isomer signals: δ 4.89 – 4.83 (m, 1H, H-4), 3.95 (dt, *J* = 8.9, 6.0 Hz, 1H, H-2), 3.52 – 3.45 (m, 1H, H-1), 2.97 (dt, *J* = 8.6, 5.6 Hz, 1H, H-1), 2.52 – 2.43 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 207.5, 136.3, 129.4, 128.4, 128.0, 78.8, 71.7, 69.1, 53.4, 43.1, 41.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{13}H_{15}NNaO_4$ – 272.0893; found: $C_{13}H_{15}NNaO_4$ – 272.0893.

^{1}H NMR (*syn*) data agree with the literature [48b].

(R)-3-[(S)-2-Nitro-1-phenylethyl]-tetrahydro-thiopyran-4-one (152)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 75% (white solid); ratio *syn:anti* 7.8:1.0; *ee* (*syn*) 71.4%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 15:85, flow rate 0.95 mL/min, λ = 210 nm, 25°C).

IR (ATR): 2971, 2917, 1706, 1549.8, 1549.6, 1380, 702 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.38 – 7.26 (m, 3H, H-5), 7.20 – 7.15 (m, 2H, H-5), 4.73 (dd, *J* = 12.8, 4.6 Hz, 1H, H-4), 4.62 (dd, *J* = 12.8, 9.8 Hz, 1H, H-4), 3.97 (td, *J* = 10.2, 4.6 Hz, 1H, H-3), δ 3.08 – 3.00 (m, 1H, H-2), 3.00 – 2.92 (m, 2H, H-1), 2.92 – 2.75 (m, 2H, H-1), 2.60 (ddd, *J* = 13.9, 4.1, 1.8 Hz, 1H, H-1), 2.44 (dd, *J* = 13.9, 9.4 Hz, 1H, H-1).

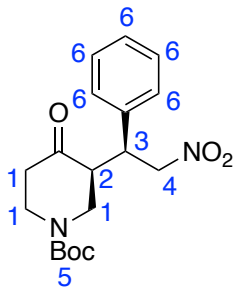
Detected *anti* isomer signals: δ 4.92 – 4.77 (m, 2H, H-4), 4.18 – 4.11 (m, 1H, H-3), 3.15 – 3.09 (m 1H, H-2).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 209.6, 136.6, 129.4, 128.4, 128.3, 78.7, 55.1, 44.6, 43.6, 35.2, 31.7.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{13}H_{15}NNaO_3S$ – 288.0665; found: $C_{13}H_{15}NNaO_3S$ – 288.0669.

^{1}H NMR (*syn*) data agree with the literature [48b].

(S)-*t*-Butyl 3-[(S)-2-Nitro-1-phenylethyl]-4-oxopiperidine-1-carboxylate (153)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 71% (white solid); ratio *syn:anti* 3.8:1.0; *ee* (*syn*) 53.4%, *ee* (*anti*) 53.4%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 mL/min, λ = 210 nm, 25°C)

IR (ATR): 2977, 2928, 1689, 1551, 1421, 1366, 1240, 1161, 731, 701 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.36 – 7.22 (m, 3H, H-6), 7.22 – 7.14 (m, 2H, H-6), 4.91 (dd, *J* = 12.7, 4.6 Hz, 1H, H-4), 4.59 (dd, *J* = 12.7, 9.8 Hz, 1H, H-4), 4.19 (brs, 1H, H-3), 3.81 (brs, 2H, H-1,2), 3.29 – 3.05 (m, 1H, H-1), 2.88 – 2.60 (m, 2H, H-1), 2.57 – 2.39 (m, 2H, H-1), 1.60 – 1.08 (m, 9H, H-5).

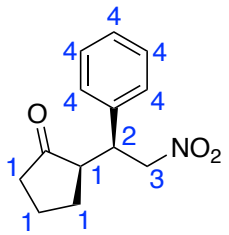
Detected *anti* isomer signals: δ 4.96 – 4.82 (m, 1H, H-4), 3.45 – 3.33 (m, 1H), 3.29 – 3.05 (m, 1H), 2.35 (t, *J* = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 208.5, 154.2, 136.6, 129.3, 129.1, 128.3, 128.2, 128.1, 80.8, 79.0, 44.3, 41.9, 41.9, 40.9, 28.3.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{18}H_{24}N_2NaO_5$ – 371.1577; found: $C_{18}H_{24}N_2NaO_5$ – 371.1586.

^{1}H NMR (*syn*) data agree with the literature [48b].

(R)-2-[(S)-2-Nitro-1-phenylethyl]cyclopentanone (154)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 21% (white solid); ratio *syn:anti* 6.0:1.0; *ee* (*syn*) 59.8%, *ee* (*anti*) 17.0%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 1 mL/min, λ = 210 nm, 25°C).

Difference in preparation of racemic compound compared to the general procedure: we used 50% of catalysts and the reaction was carried out at 50°C.

IR (ATR): 2967, 1732, 1550, 1380, 1155, 702 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.36 – 7.21 (m, 3H, H-4), 7.21 – 7.11 (m, 2H, H-4), 5.33 (dd, *J* = 12.9, 5.6 Hz, 1H, H-3), 4.70 (dd, *J* = 12.9, 9.8 Hz, 1H, H-3), 3.68 (td, *J* = 9.5, 5.6 Hz, 1H, H-2), 2.45 – 2.29 (m, 2H, H-1), 2.18 – 2.06 (m, 1H, H-1), 1.98 – 1.77 (m, 2H, H-1), 1.77 – 1.62 (m, 1H, H-1), 1.54 – 1.39 (m, 1H, H-1).

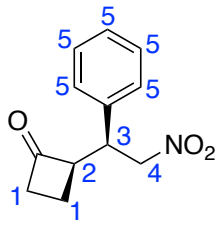
Detected *anti* isomer signals: δ 5.01 (d, *J* = 7.8 Hz, 2H, H-3), 3.85 – 3.78 (m, 1H, H-2), 2.54 – 2.46 (m, 1H, H-1), 2.29 – 2.22 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 218.6, 137.8, 129.0, 128.1, 128.0, 78.4, 50.6, 44.3, 38.8, 28.4, 20.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{13}H_{15}NNaO_3$ – 256.0944; found: $C_{13}H_{15}NNaO_3$ – 256.0942.

^{1}H NMR (*syn*) data agree with the literature [49].

(R)-2-[(S)-2-Nitro-1-phenylethyl]cyclobutanone (155)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 27% (pile yellow oil); ratio *syn:anti* 2.4:1.0; *ee* (*syn*) 36.6%, *ee* (*anti*) 35.0%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK AS-H column (IPA:Hexane 25:75, flow rate 0.7 mL/min, λ = 210 nm, 25°C).

IR (ATR): 2923, 1775, 1551, 1379, 1086, 702 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.38 – 7.26 (m, 3H, H-5), 7.21 – 7.15 (m, 2H, H-5), 5.06 (dd, *J* = 12.8, 4.6 Hz, 1H, H-4), 4.63 (dd, *J* = 12.8, 9.9 Hz, 1H, H-4), 3.76 – 3.65 (m, 1H, H-3), 3.65 – 3.52 (m, 1H, H-2), 3.15 – 2.87 (m, 2H, H-1), 2.10 – 1.98 (m, 1H, H-1), 1.78 – 1.60 (m, 1H, H-1).

Anti isomer signals: δ 7.38 – 7.26 (m, 3H, H-5), 7.21 – 7.15 (m, 2H, H-5), 4.92 – 4.76 (m, 2H, H-4), 3.76 – 3.65 (m, 2H, H-2,3), 3.15 – 2.87 (m, 1H, H-1), 2.68 – 2.57 (m, 1H, H-1), 2.22 – 2.10 (m, 1H, H-1), 1.78 – 1.60 (m, 1H, H-1).

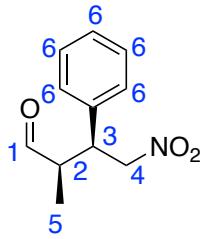
^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 208.7, 137.0, 129.2, 128.3, 127.7, 78.3, 61.1, 44.6, 44.4, 15.9.

Detected *anti* isomer signals: δ 136.6, 129.2, 128.3, 77.7, 61.5, 45.1, 44.3, 14.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{12}H_{13}NNaO_3$ – 242.0788; found: $C_{12}H_{13}NNaO_3$ – 242.0786.

^{1}H NMR (*syn*) data agree with the literature [49].

(2R,3S)-2-Methyl-4-nitro-3-phenylbutanal (172)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 85% (pile yellow oil); ratio *syn:anti* 4.6:1.0 (epimerization over time *syn* in *anti*); *ee* (*syn*) 83.8%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 mL/min, λ = 210 nm, 25ºC).

IR (ATR): 2975, 2731, 1723, 1551, 1380, 702 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 9.70 (d, *J* = 1.8 Hz, 1H, H-1), 7.36 – 7.25 (m, 3H, H-6), 7.22 – 7.11 (m, 2H, H-6), 4.84 – 4.71 (m, 1H, H-4), 4.71 – 4.62 (m, 1H, H-4), 3.80 (td, *J* = 9.1, 5.7 Hz, 1H, H-3), 2.86 – 2.70 (m, 1H, H-2), 0.98 (d, *J* = 7.2 Hz, 3H, H-5).

Anti isomer signals: δ 9.52 (d, *J* = 1.8 Hz, 1H, H-1), 7.36 – 7.25 (m, 3H, H-6), 7.22 – 7.11 (m, 2H, H-6), 4.84 – 4.71 (m, 2H, H-4), 3.80 (td, *J* = 9.1, 5.7 Hz, 1H, H-3), 2.86 – 2.70 (m, 1H, H-2), 1.20 (d, *J* = 7.2 Hz, 2H, H-5).

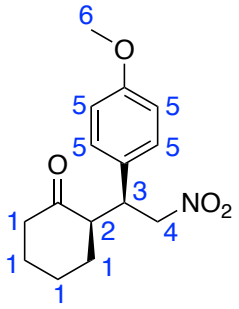
^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 202.4, 136.6, 129.2, 128.3 & 128.2 *syn/anti*, 128.2, 78.2, 48.5, 44.1, 12.2.

Detected *anti* isomer signals: δ 202.5, 136.9, 129.2, 128.3 & 128.2 *syn/anti*, 48.8, 44.9, 11.8.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{11}H_{13}NNaO_3$ – 230.0788; found: $C_{11}H_{13}NNaO_3$ – 230.0788.

^{1}H NMR (*syn*) data agree with the literature [60].

(R)-2-[(S)-1-(4-Methoxyphenyl)-2-nitroethyl]cyclohexanone (175)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 75% (white solid); ratio *syn:anti* 10.0:1.0; *ee* (*syn*) 43.3%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 0.5 mL/min, λ = 254 nm, 25ºC).

IR (ATR): 2941, 2863, 1706, 1550, 1514, 1251, 832 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.11 – 7.02 (m, 2H, H-5), 6.87 – 6.79 (m, 2H, H-5), 4.90 (dd, *J* = 12.4, 4.6 Hz, 1H, H-4), 4.57 (dd, *J* = 12.4, 10.0 Hz, 1H, H-4), 3.77 (s, 3H, H-6), 3.70 (td, *J* = 9.9, 4.6 Hz, 1H, H-3), 2.69 – 2.58 (m, 1H, H-2), 2.51 – 2.31 (m, 2H, H-1), 2.11 – 2.01 (m, 1H, H-1), 1.82 – 1.47 (m, 4H, H-1), 1.29 – 1.14 (m, 1H, H-1).

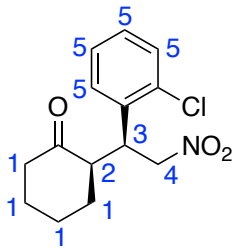
Detected *anti* isomer signals: δ 7.19 – 7.13 (m, 2H, H-5), 6.86 – 6.81 (m, 2H, H-5), 4.79 (dd, *J* = 12.7, 9.7 Hz, 1H, H-4), 3.93 – 3.87 (m, 1H, H-3), 1.43 – 1.34 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 212.2, 159.1, 129.6, 129.3, 114.4, 79.2, 55.3, 52.8, 43.3, 42.8, 33.2, 28.6, 25.1.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{15}H_{19}NNaO_4$ – 300.1206; found: $C_{15}H_{19}NNaO_4$ – 300.1210.

^{1}H NMR (*syn*) data agree with the literature [61].

(R)-2-[(S)-1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone (176)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 96% (white solid; melting point 67-69°C lit. [59] 64-66°C); ratio *syn:anti* 20.0:1.0; *ee* (*syn*) 37.6%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 1 mL/min, λ = 254 nm, 25°C).

IR (ATR): 2941, 2863, 1706, 1550, 1379, 755 cm^{-1}.

$[\alpha]_D^{20}$ +15.30 (c=0.58 mg/mL, $CHCl_3$); lit. [59] **$[\alpha]_D^{25}$** +45.3 (c=1.0 mg/mL, $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.39 – 7.34 (m, 1H, H-5), 7.30 – 7.15 (m, 3H, H-5), 4.95 – 4.83 (m, 2H, H-4), 4.32 – 4.22 (m, 1H, H-3), 2.97 – 2.84 (m, 1H, H-2), 2.50 – 2.32 (m, 2H, H-1), 2.14 – 2.04 (m, 1H, H-1), 1.85 – 1.51 (m, 4H, H-1), 1.44 – 1.17 (m, 1H, H-1).

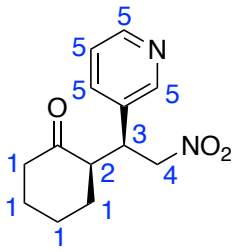
Detected *anti* isomer signal: δ 4.69 – 4.62 (m, 1H, H-3).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 211.8, 135.5, 134.6, 130.5, 129.0, 127.5, 77.3, 51.8, 42.9, 33.2, 28.6, 25.4.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated (as 3:1) for $C_{14}H_{16}{}^{35}ClNNaO_3$ – 304.0711 and $C_{14}H_{16}{}^{37}ClNNaO_3$ – 306.0681; found (as 3:1): $C_{14}H_{16}{}^{35}ClNNaO_3$ – 304.0709 and $C_{14}H_{16}{}^{37}ClNNaO_3$ – 306.0685.

^{1}H NMR (*syn*) data agree with the literature [49].

(R)-2-[(S)-2-Nitro-1-(pyridin-3-yl)ethyl]cyclohexanone (177)



Flash columned with a gradient from Hex to EtOAc; isolated yield – 94% (yellow solid); ratio *syn:anti* 5.1:1.0; *ee* (*syn*) 36.4%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 20:80, flow rate 0.75 mL/min, λ = 254 nm, 25ºC).

IR (ATR): 2942, 2864, 1706, 1550, 1428, 1379, 1131, 717 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 8.52 (dd, *J* = 4.8, 1.7 Hz, 1H, H-5), 8.46 (d, *J* = 2.3 Hz, 1H, H-5), 7.53 (dt, *J* = 7.8, 2.0 Hz, 1H, H-5), 7.29 – 7.25 (m, 1H, H-5), 4.94 (dd, *J* = 12.9, 4.6 Hz, 1H, H-4), 4.68 (dd, *J* = 12.9, 9.9 Hz, 1H, H-4), 3.80 (td, *J* = 9.6, 4.6 Hz, 1H, H-3), 2.76 – 2.65 (m, 1H, H-2), 2.53 – 2.32 (m, 2H, H-1), 2.14 – 2.05 (m, 1H, H-1), 1.85 – 1.50 (m, 4H, H-1), 1.25 (qd, *J* = 12.7, 3.5 Hz, 1H, H-1).

Detected *anti* isomer signals: δ 8.54 – 8.48 (m, 2H, H-5), 7.67 (dt, *J* = 7.9, 1.9 Hz, 1H, H-5), 4.91 – 4.83 (m, 2H, H-4), 3.94 – 3.88 (m 1H, H-3), δ 2.80 – 2.72 (m, 1H, H-2), 2.35 – 2.23 (m, 2H, H-1), 1.97 – 1.87 (m, 1H, H-1), 1.43 – 1.31 (m, 1H, H-1).

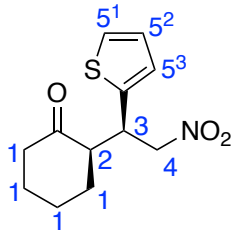
^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 211.2, 150.0, 149.4, 135.8, 133.6, 123.8, 78.2, 52.3, 42.8, 41.7, 33.3, 28.4, 25.2.

Detected *anti* isomer signals: δ 149.1, 136.2, 123.7, 53.3, 42.5, 41.5, 30.8, 27.4.

HRMS (ESI) *m/z* $[M + H]^+$ calculated for $C_{13}H_{17}N_2O_3$ – 249.1234; found: $C_{13}H_{17}N_2O_3$ – 249.1233.

^{1}H NMR (*syn*) data agree with the literature [61].

(R)-2-[(R)-2-Nitro-1-(thiophen-2-yl)ethyl]cyclohexanone (178)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 71% (yellow solid); ratio *syn:anti* 5.2:1.0; *ee* (*syn*) 56.2%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IA column (IPA:Hexane 10:90, flow rate 1 mL/min, λ = 254 nm, 25°C).

IR (ATR): 2939, 2863, 1705, 1551, 1379, 1129, 705.6 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.20 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5^1), 6.92 (dd, *J* = 5.2, 3.5 Hz, 1H, H-5^2), 6.86 (dd, *J* = 3.5, 1.3 Hz, 1H, H-5^3), 4.88 (dd, *J* = 12.7, 4.7 Hz, 1H, H-4), 4.64 (dd, *J* = 12.7, 9.4 Hz, 1H, H-4), 4.12 (td, *J* = 9.1, 4.8 Hz, 1H, H-3), 2.71 – 2.61 (m, 1H, H-2), 2.51 – 2.24 (m, 2H, H-1), 2.18 – 2.02 (m, 1H, H-1), 1.95 – 1.78 (m, 2H, H-1), 1.73 – 1.57 (m, 2H, H-1), 1.47 – 1.21 (m, 1H, H-1).

Detected *anti* isomer signals: δ 7.19 (m, 1H, H-5^1), 4.92 – 4.75 (m, 2H, H-4), 4.23 – 4.17 (m, 1H, H-3), 2.79 – 2.71 (m, 1H, H-2).

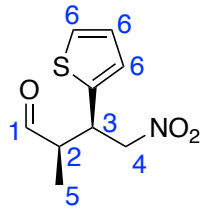
^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 211.3, 140.6, 127.0, 126.8, 125.1, 79.3, 53.5, 42.7, 39.5, 32.9, 28.4, 25.2.

Detected *anti* isomer signals: δ 126.9, 125.4, 78.2, 53.6, 42.4, 39.6, 30.8, 27.3.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_{12}H_{15}NNaO_3S$ – 276.0665; found: $C_{12}H_{15}NNaO_3S$ – 276.0669.

^{1}H NMR (*syn*) data agree with the literature [62].

(2R,3R)-2-Methyl-4-nitro-3-(thiophen-2-yl)butanal (179)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 65% (yellow oil); ratio *syn:anti* 3.7:1.0; *ee* (*syn*) 81.8%, *ee* (*anti*) 77.0%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 1.3 mL/min, λ = 210 nm, 25°C).

IR (ATR): 2974, 2731, 1723, 1553, 1380, 706 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 9.68 (s, 1H, H-1), 7.25 – 7.20 (m, 1H, H-6), 6.98 – 6.85 (m, 2H, H-6), 4.81 – 4.59 (m, 2H, H-4), 4.27 – 4.19 (m, 1H, H-3), 2.87 – 2.72 (m, 1H, H-2), 1.11 (d, *J* = 7.4 Hz, 3H, H-5).

Anti isomer signals: δ 9.60 (s, 1H, H-1), 7.25 – 7.20 (m, 1H, H-6), 6.98 – 6.85 (m, 2H, H-6), 4.81 – 4.59 (m, 2H, H-4), 4.19 – 4.12 (m, 1H, H-3), 2.87 – 2.72 (m, 1H, H-2), 1.25 (d, *J* = 7.4 Hz, 3H, H-5).

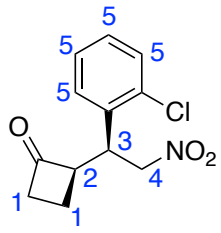
^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 201.8, 138.9, 127.2, 126.9, 125.4, 78.5, 48.9, 39.5, 11.6.

Anti isomer signals: δ 202.1, 139.3, 127.3, 126.9, 125.5, 78.1, 49.1, 40.2, 11.9.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated for $C_9H_{11}NNaO_3S$ – 236.0352; found: $C_9H_{11}NNaO_3S$ – 236.0362.

^{1}H NMR (*syn*) data agree with the literature [63].

(R)-2-[(S)-1-(2-Chlorophenyl)-2-nitroethyl]cyclobutanone (180)



Flash columned with a gradient from Hex to Et_2O; isolated yield – 50% (yellow oil); ratio *syn:anti* 1.6:1.0; *ee* (*syn*) 15.2%, *ee* (*anti*) 46.8%. Enantiomeric excess determined from pure product using Chiral HPLC analysis: CHIRALPAK IC column (IPA:Hexane 10:90, flow rate 0.7 mL/min, λ = 210 nm, 25°C).

IR (ATR): 2922, 1774, 1550, 1378, 1083, 1039, 756 cm^{-1}.

^{1}H NMR (400 MHz, Chloroform-*d*) (*syn*): δ 7.47 – 7.35 (m, 1H, H-5), 7.30 – 7.15 (m, 3H, H-5), 5.04 (dd, *J* = 12.9, 4.6 Hz, 1H, H-4), 4.92 – 4.80 (m, 1H, H-4), 4.29 – 4.19 (m, 1H, H-3), 3.88 – 3.76 (m, 1H, H-2), 3.19 – 2.92 (m, 2H, H-1), 2.13 – 1.99 (m, 1H, H-1), 1.79 – 1.60 (m, 1H, H-1).

Anti isomer signals: δ 7.47 – 7.35 (m, 1H, H-5), 7.30 – 7.15 (m, 3H, H-5), 4.92 – 4.80 (m, 2H, H-4), 4.40 (q, *J* = 7.4 Hz, 1H, H-3), 3.88 – 3.76 (m, 1H, H-2), 3.19 – 2.92 (m, 1H, H-1), 2.76 – 2.63 (m, 1H, H-1), 2.27 – 2.16 (m, 1H, H-1), 1.79 – 1.60 (m, 1H, H-1).

^{13}C NMR (101 MHz, Chloroform-*d*) (*syn*): δ 208.4, 134.7, 134.2, 130.5, 129.4 & 129.3 *syn/anti*, 128.4, 127.7 & 127.6 *syn/anti*, 76.6, 60.6, 45.2, 44.5, 16.0.

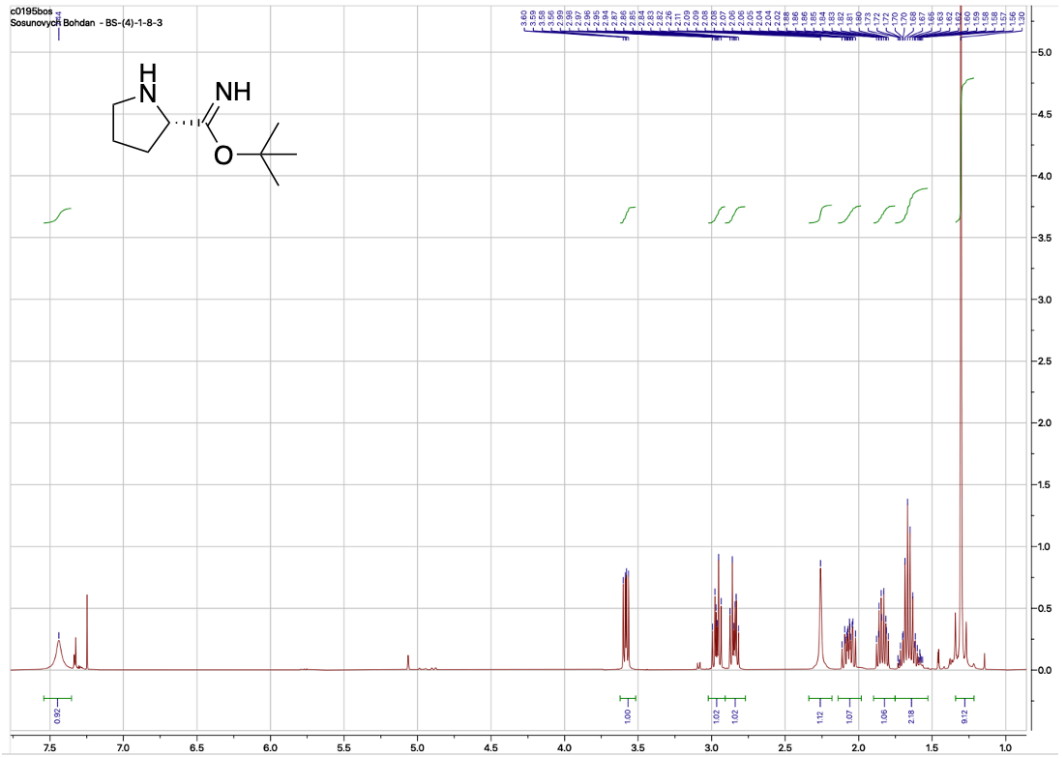
Detected *anti* isomer signals: δ 208.2, 134.6, 130.4, 129.4 & 129.3 *syn/anti*, 127.7 & 127.6 *syn/anti*, 60.2, 14.7.

HRMS (ESI) *m/z* $[M + Na]^+$ calculated (as 3:1) for $C_{12}H_{12}{}^{35}ClNNaO_3$ – 276.0398 and $C_{12}H_{12}{}^{37}ClNNaO_3$ – 278.0368; found (as 3:1): $C_{12}H_{12}{}^{35}ClNNaO_3$ – 276.0401 and $C_{12}H_{12}{}^{37}ClNNaO_3$ – 278.0377.

^{1}H NMR (*syn*) data agree with the literature [49].

10.4. Appendix

Fig. 17. ^{1}H and ^{13}C NMR ($CDCl_3$) of *L*-proline imidate **4**



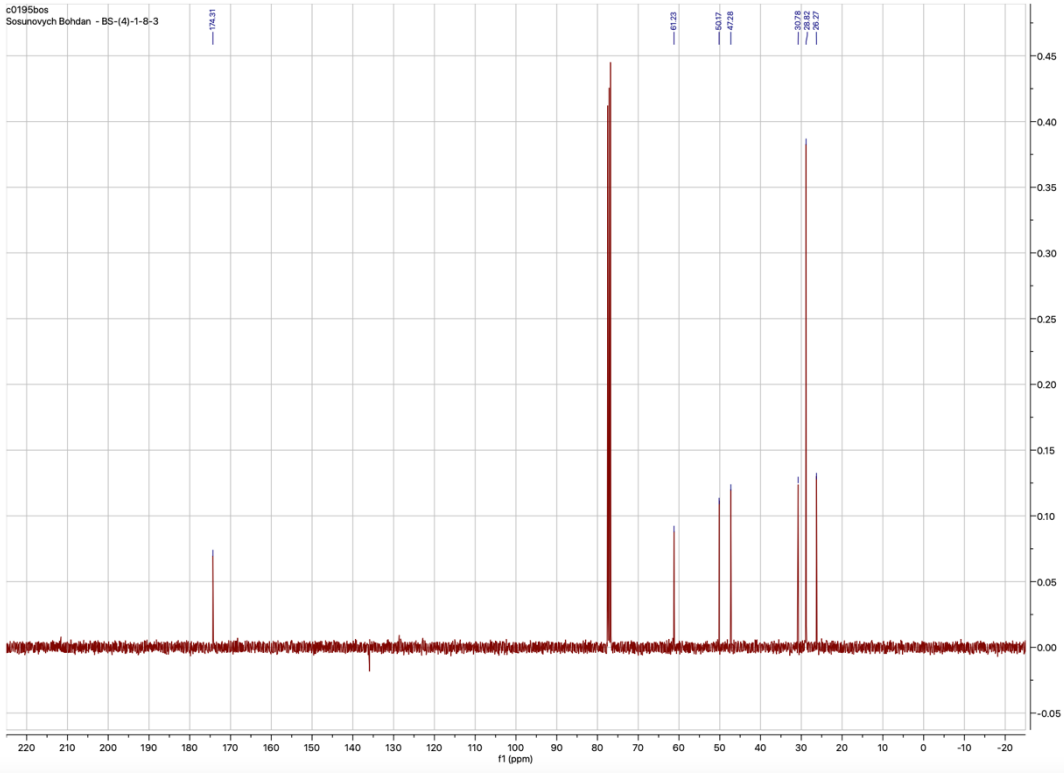
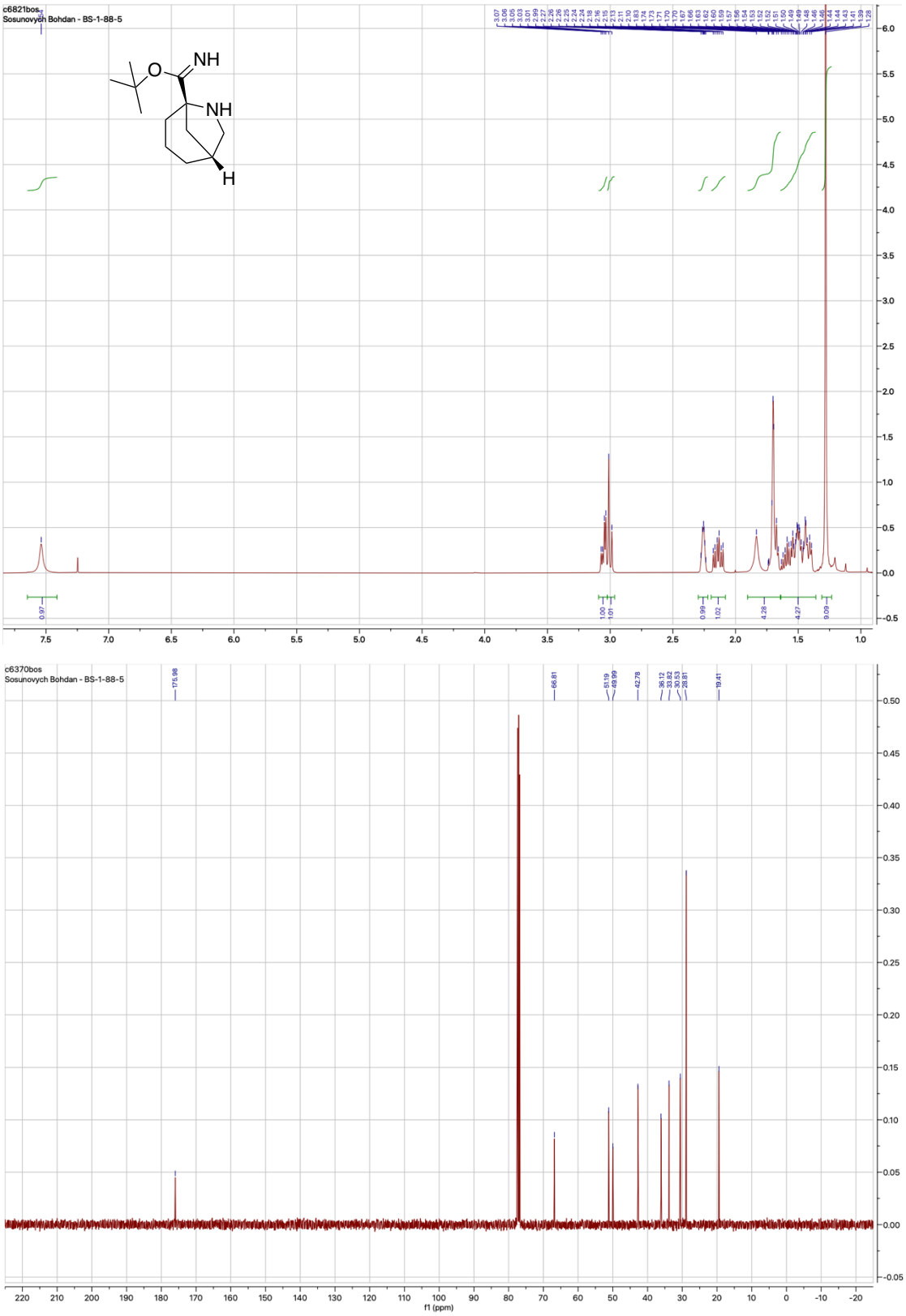
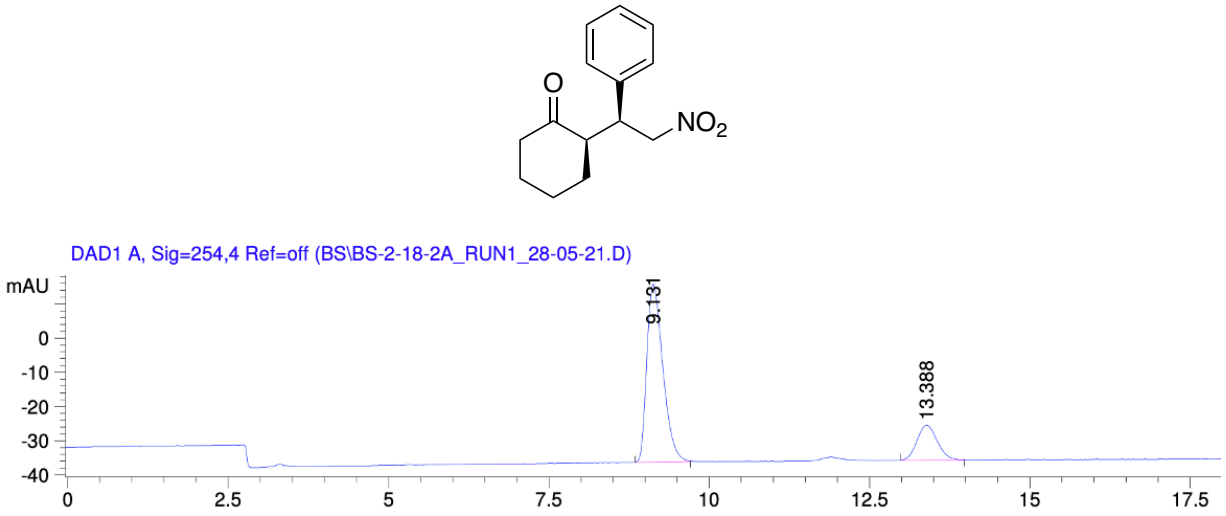


Fig. 18. ^{1}H and ^{13}C NMR ($CDCl_3$) of bicyclic imidate **5**





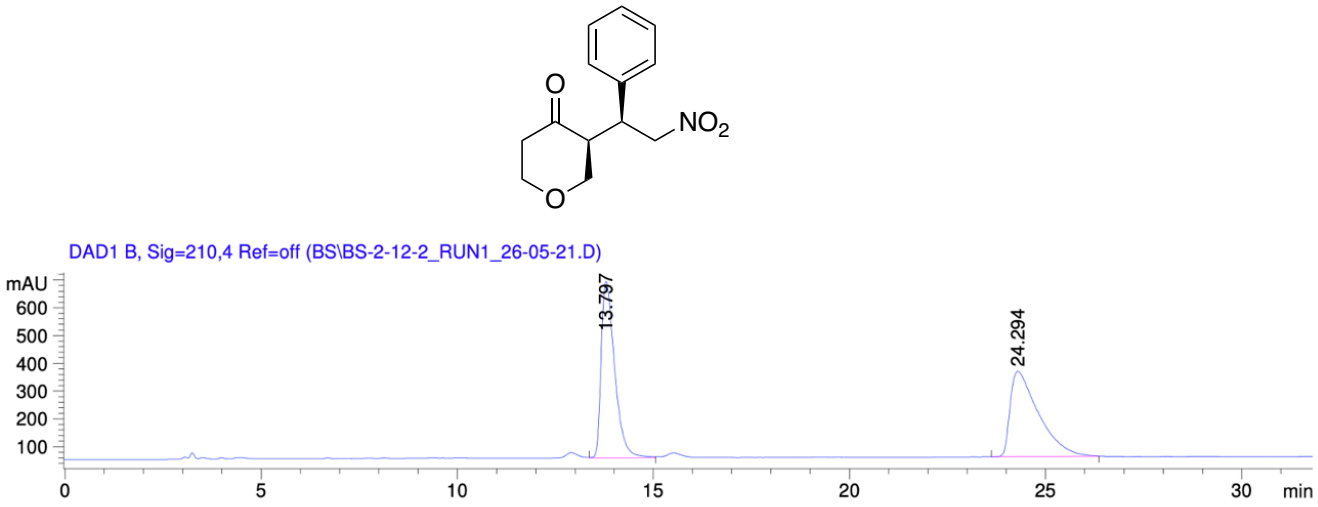
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.131	BB	0.2711	906.64490	52.06992	80.1737
2	13.388	BB	0.3432	224.20638	10.24839	19.8263
Totals :				1130.85127	62.31831	

Fig. 19. HPLC trace of enantioenriched **3**

Anti isomer traces were not detected.

Retention times agree with the literature [64]

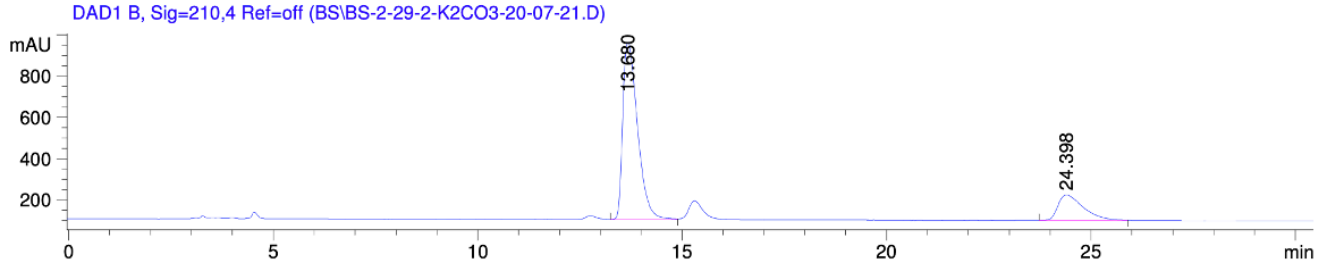


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.797	VB	0.3643	1.51483e4	634.98511	49.4392
2	24.294	BB	0.7056	1.54920e4	307.60867	50.5608
Totals :				3.06403e4	942.59378	

Fig. 20. HPLC trace of racemic **151**

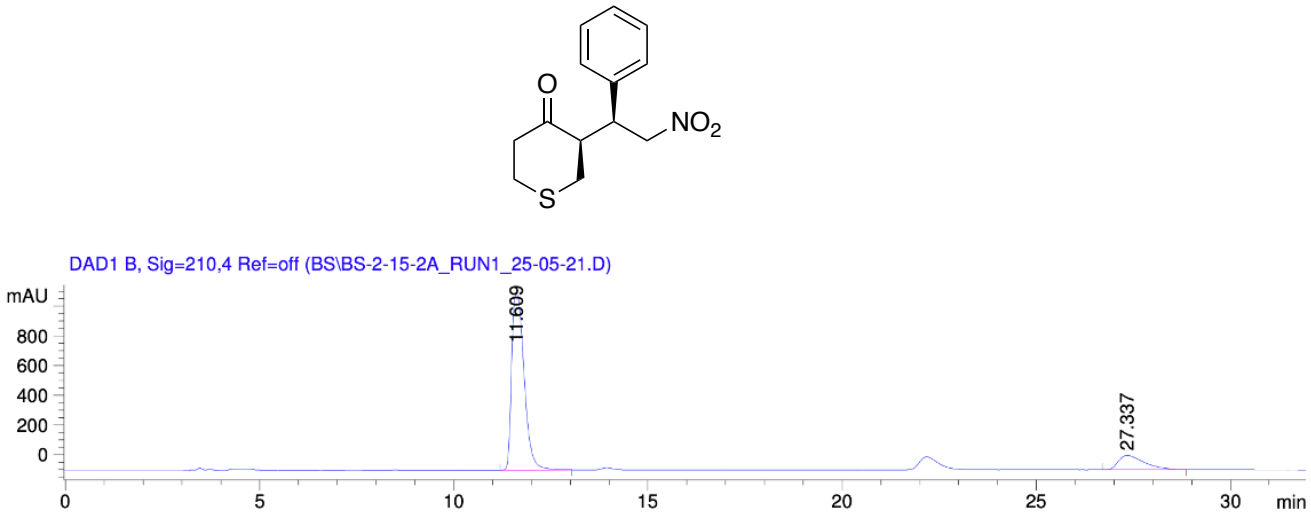
Retention time of minor *anti* isomer traces: 12.9 and 15.5 minutes.



Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.680	VB	0.3872	2.15790e4	858.54150	80.3249
2	24.398	BB	0.6524	5285.64746	123.23447	19.6751
Totals :				2.68646e4	981.77598	

Fig. 21. HPLC trace of enantioenriched **151**



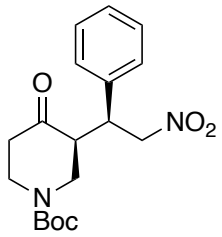
Signal 2: DAD1 B, Sig=210,4 Ref=off

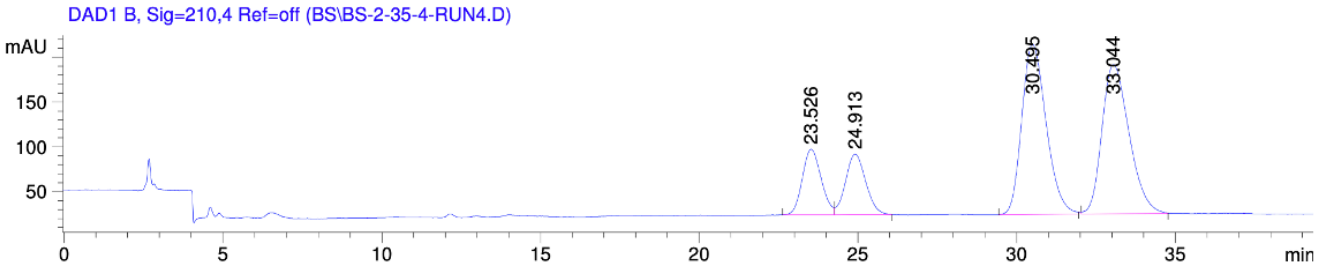
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.609	BB	0.3533	2.65987e4	1187.68689	85.6685
2	27.337	BB	0.6714	4449.70117	95.88362	14.3315
Totals :				3.10484e4	1283.57051	

Fig. 22. HPLC trace of enantioenriched **152**

Retention time of minor *anti* isomer traces: 14.0 and 22.3 minutes.

Retention times agree with the literature [65]



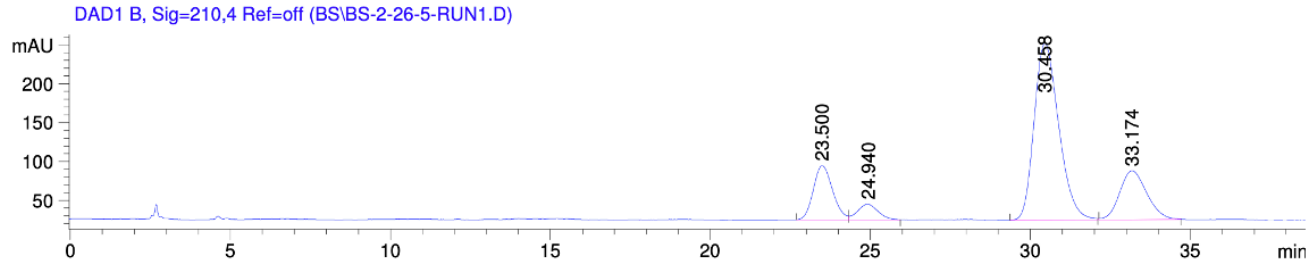


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.526	BV	0.6031	3033.95068	73.27061	11.6387
2	24.913	VB	0.6281	2994.60425	67.69376	11.4878
3	30.495	BB	0.7704	1.01300e4	189.87624	38.8605
4	33.044	BB	0.8544	9909.09570	166.48235	38.0130
Totals :				2.60677e4	497.32295	

Fig. 23. HPLC trace of racemic **153**

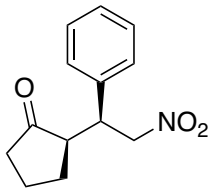
Retention time of minor *anti* isomer traces: 23.5 and 24.9 minutes.

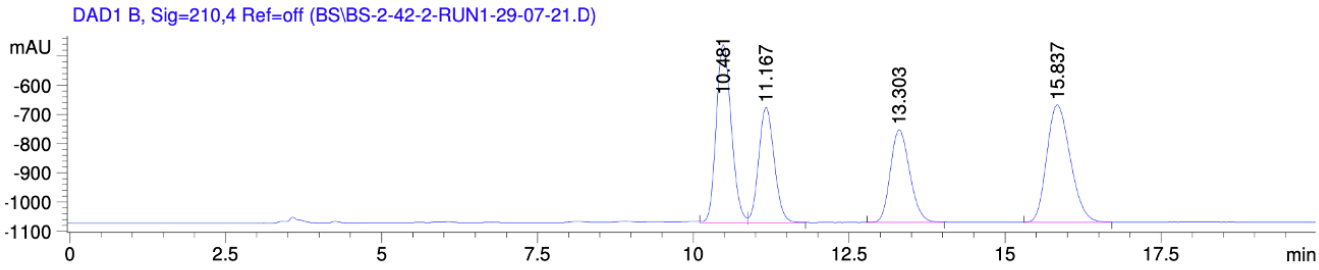


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.500	BV	0.6125	2911.44336	69.53360	14.8227
2	24.940	VV	0.5483	886.20184	19.94725	4.5118
3	30.458	BB	0.8225	1.21469e4	226.94003	61.8422
4	33.174	BB	0.7653	3697.23218	62.75798	18.8233
Totals :				1.96418e4	379.17887	

Fig. 24. HPLC trace of enantioenriched **153**



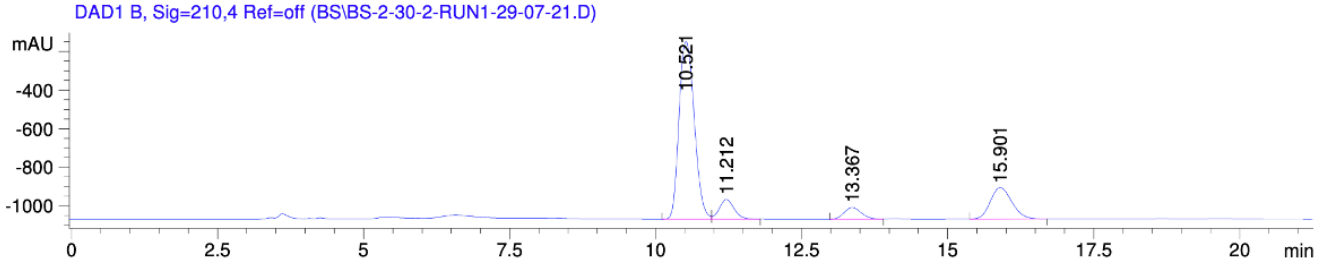


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.481	VV	0.2652	1.02835e4	608.53192	29.7616
2	11.167	VB	0.2707	6840.10156	393.77805	19.7960
3	13.303	BB	0.3383	6848.79980	316.64307	19.8212
4	15.837	BB	0.4113	1.05805e4	401.63190	30.6212
Totals :				3.45529e4	1720.58493	

Fig. 25. HPLC trace of racemic **154**

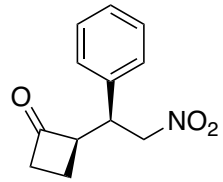
Retention time of minor *anti* isomer traces: 11.2 and 13.3 minutes.

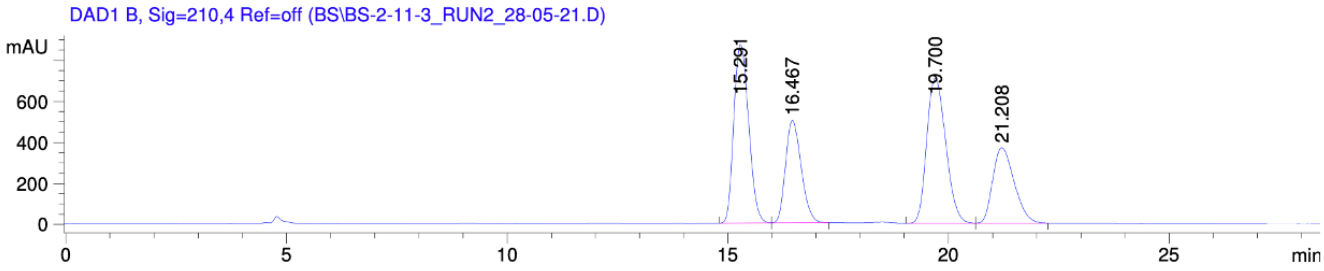


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.521	BV	0.2899	1.66797e4	918.52490	69.6380
2	11.212	VB	0.2734	1794.26526	101.89684	7.4911
3	13.367	BV	0.3220	1272.81470	60.87047	5.3140
4	15.901	BB	0.3965	4205.24756	163.29239	17.5570
Totals :				2.39520e4	1244.58460	

Fig. 26. HPLC trace of enantioenriched **154**



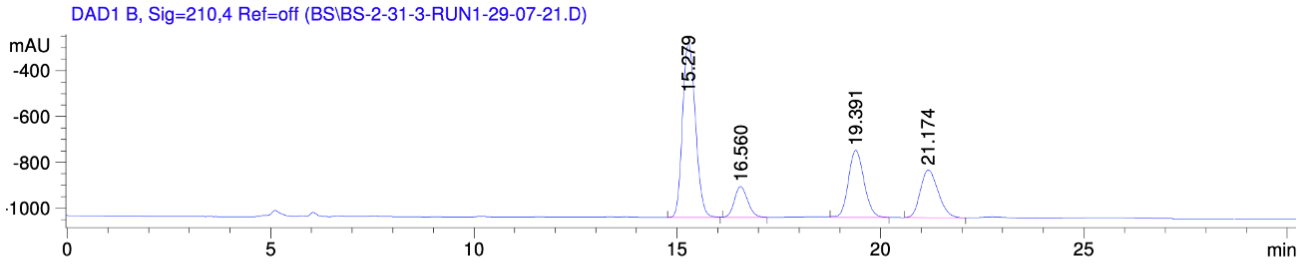


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.291	BV	0.3716	2.04112e4	870.41644	30.7447
2	16.467	VB	0.3846	1.23562e4	499.51392	18.6117
3	19.700	VV	0.4673	2.11921e4	707.84137	31.9210
4	21.208	VB	0.5282	1.24298e4	367.83472	18.7226
Totals :				6.63894e4	2445.60645	

Fig. 27. HPLC trace of racemic **155**

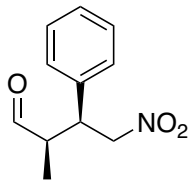
Retention time of minor *anti* isomer traces: 16.5 and 21.2 minutes.

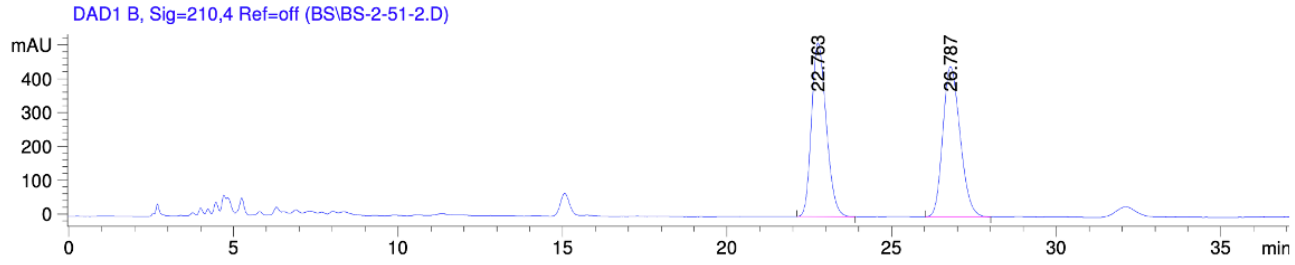


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.279	BB	0.3498	1.67807e4	759.43610	49.4399
2	16.560	BB	0.3459	3044.25562	134.57545	8.9691
3	19.391	BB	0.4191	7799.30322	292.49927	22.9786
4	21.174	BB	0.4796	6317.36621	207.29028	18.6124
Totals :				3.39416e4	1393.80110	

Fig. 28. HPLC trace of enantioenriched **155**



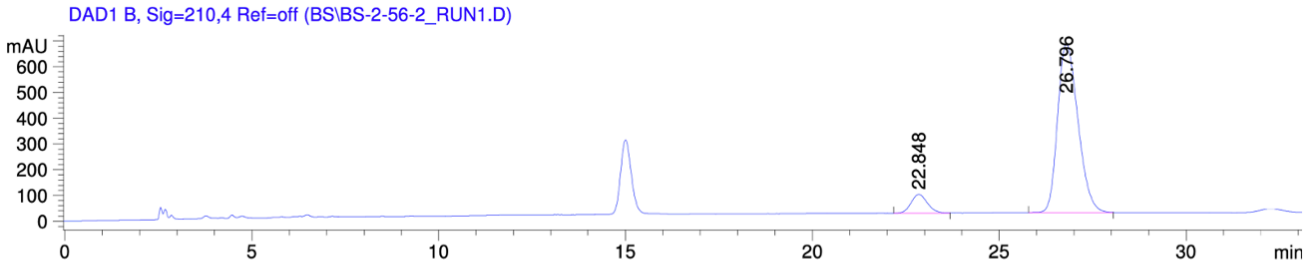


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.763	BB	0.4857	1.60160e4	513.77661	49.5807
2	26.787	BB	0.5698	1.62868e4	444.20007	50.4193
Totals :				3.23028e4	957.97668	

Fig. 29. HPLC trace of racemic **172**

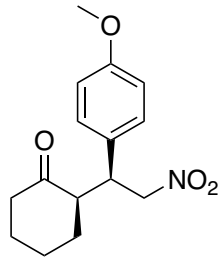
Retention time of minor *anti* isomer traces: 15.1 and 32.1 minutes.

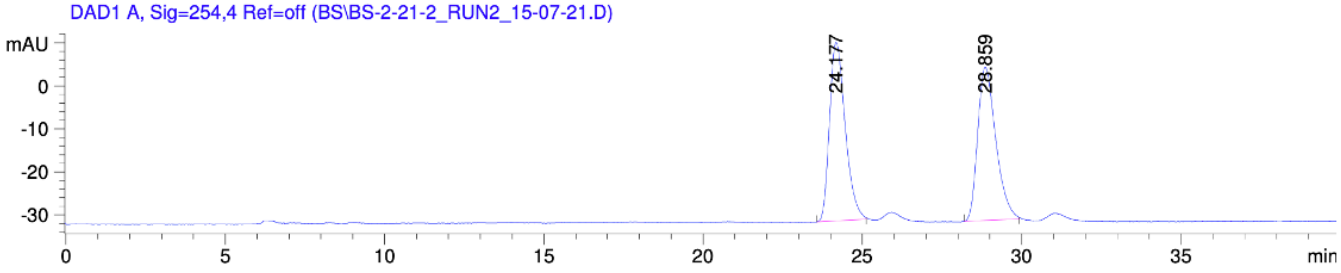


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.848	BB	0.4627	2197.29102	72.68048	8.1448
2	26.796	BB	0.5955	2.47807e4	654.79443	91.8552
Totals :				2.69780e4	727.47491	

Fig. 30. HPLC trace of enantioenriched **172**



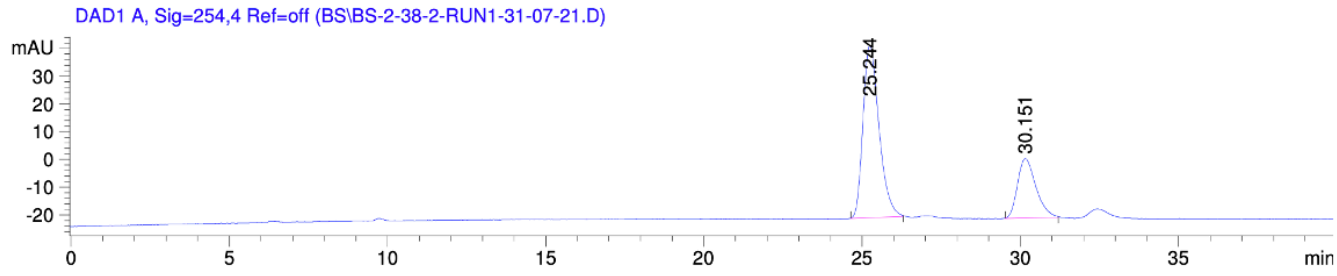


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.177	BB	0.5221	1421.80518	41.45721	50.2136
2	28.859	BB	0.6023	1409.70728	35.57922	49.7864
Totals :				2831.51245	77.03643	

Fig. 31. HPLC trace of racemic **175**

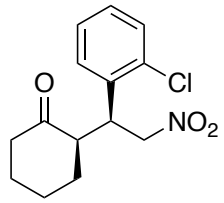
Retention time of minor *anti* isomer traces: 25.9 and 31.1 minutes.

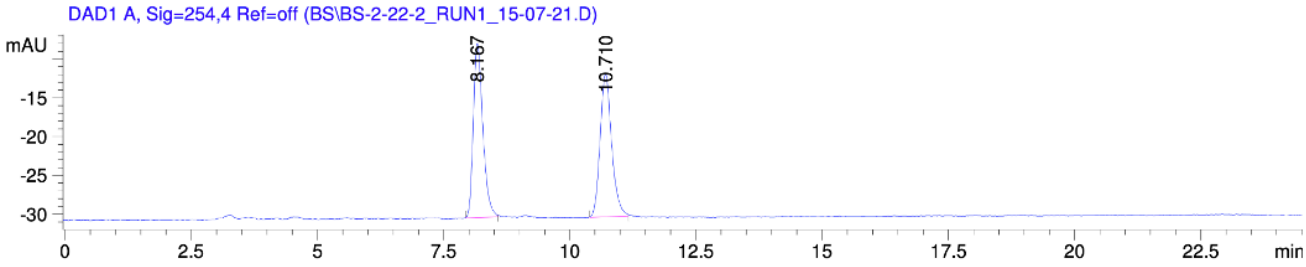


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.244	BB	0.5275	2188.70923	62.05999	71.6411
2	30.151	BB	0.5460	866.39148	21.41722	28.3589
Totals :				3055.10071	83.47721	

Fig. 32. HPLC trace of enantioenriched **175**



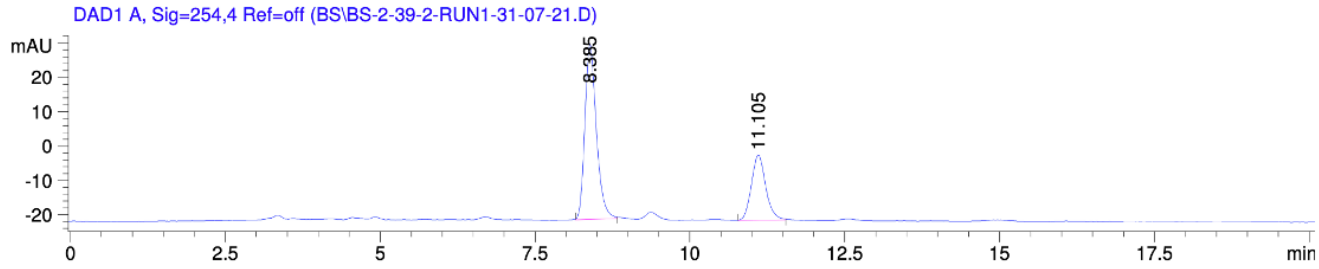


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.167	BB	0.1992	294.93860	22.46553	50.1633
2	10.710	BB	0.2454	293.01840	18.44093	49.8367
Totals :				587.95700	40.90646	

Fig. 33. HPLC trace of racemic **176**

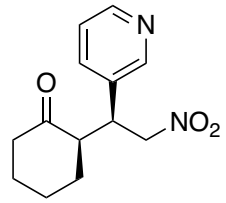
Anti isomer traces were not detected.

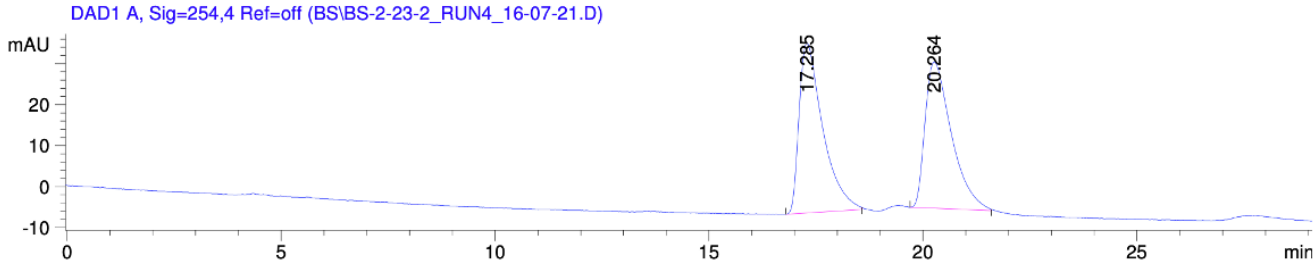


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.385	BB	0.1994	671.00269	51.03154	68.7619
2	11.105	BB	0.2493	304.83170	18.98849	31.2381
Totals :				975.83438	70.02002	

Fig. 34. HPLC trace of enantioenriched **176**



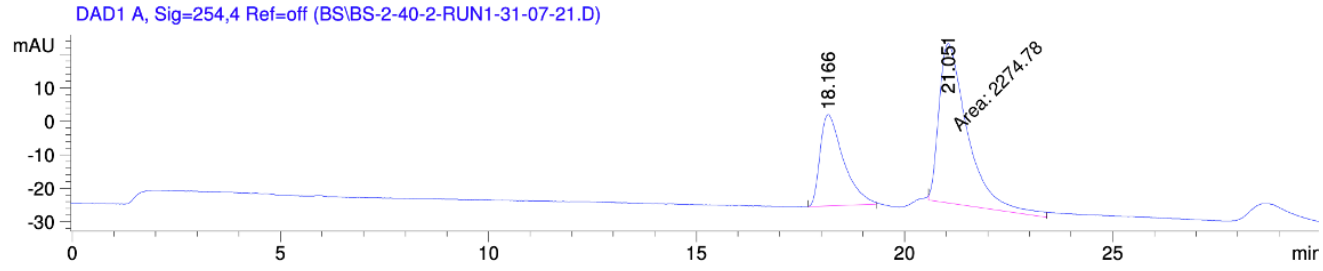


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.285	BB	0.5638	1594.28320	41.53807	50.9514
2	20.264	BB	0.6109	1534.74548	35.74903	49.0486
Totals :				3129.02869	77.28710	

Fig. 35. HPLC trace of racemic **177**

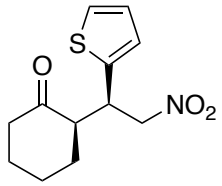
Retention time of minor *anti* isomer traces: 19.4 and 27.8 minutes.

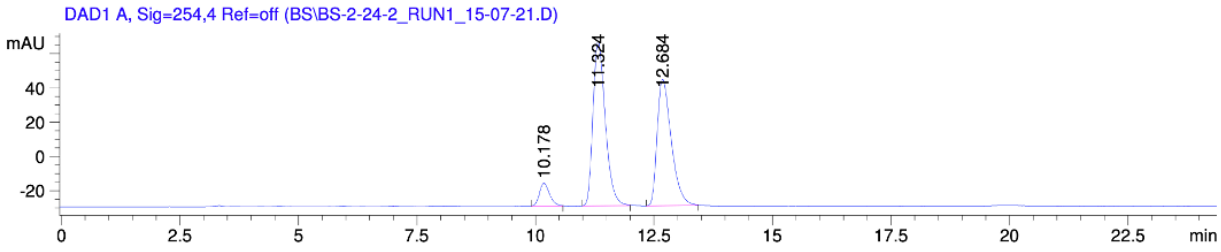


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.166	BB	0.5533	1059.40222	27.26358	31.7740
2	21.051	MM	0.7966	2274.78198	47.59598	68.2260
Totals :				3334.18420	74.85957	

Fig. 36. HPLC trace of enantioenriched **177**



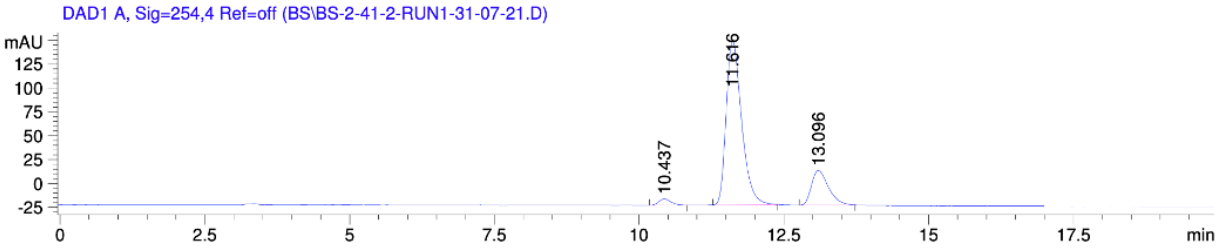


Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.178	BB	0.2287	204.35374	13.49066	5.8972
2	11.324	BB	0.2814	1735.22485	95.76899	50.0746
3	12.684	BB	0.3175	1525.70239	73.69756	44.0282
Totals :				3465.28099	182.95722	

Fig. 37. HPLC trace of racemic **178**

Retention time of minor *anti* isomer traces: 10.2 and 11.3 (overlapped) minutes.

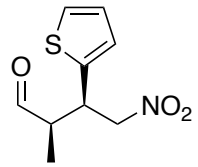


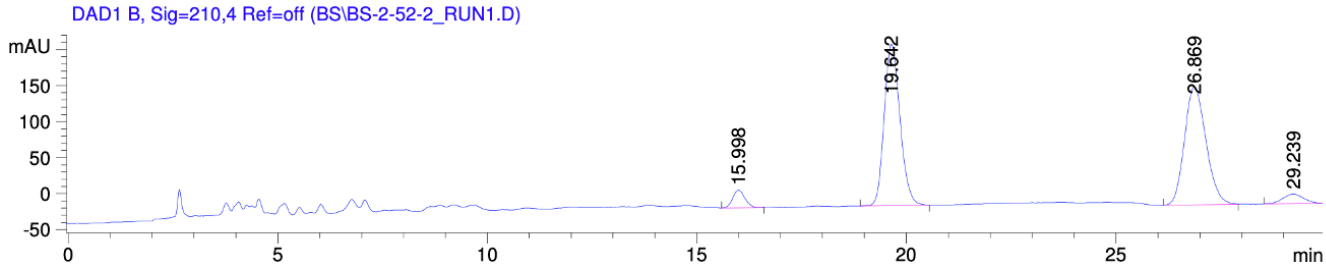
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.437	BB	0.2273	98.26952	6.61412	2.4349
2	11.616	BB	0.2845	3194.82837	172.15773	79.1603
3	13.096	BB	0.3098	742.80127	36.43693	18.4049
Totals :				4035.89916	215.20878	

Fig. 38. HPLC trace of enantioenriched **178**

The *ee* calculations for the *syn* isomer were based on the information that 16% (5.2:1 as *syn* to *anti*) of the *anti* isomer present in the mixture.



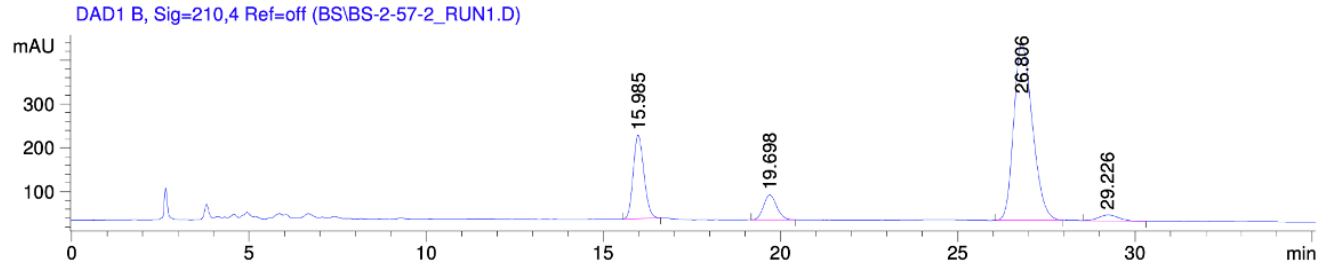


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.998	BB	0.3157	502.18137	24.43897	3.9579
2	19.642	BB	0.4076	5889.77539	224.82584	46.4202
3	26.869	BB	0.5564	5831.51807	164.16266	45.9610
4	29.239	BBA	0.4235	464.48700	13.29966	3.6608
Totals :				1.26880e4	426.72712	

Fig. 39. HPLC trace of racemic **179**

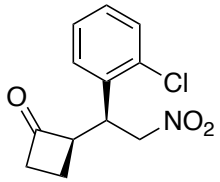
Retention time of minor *anti* isomer traces: 16.0 and 29.2 minutes.

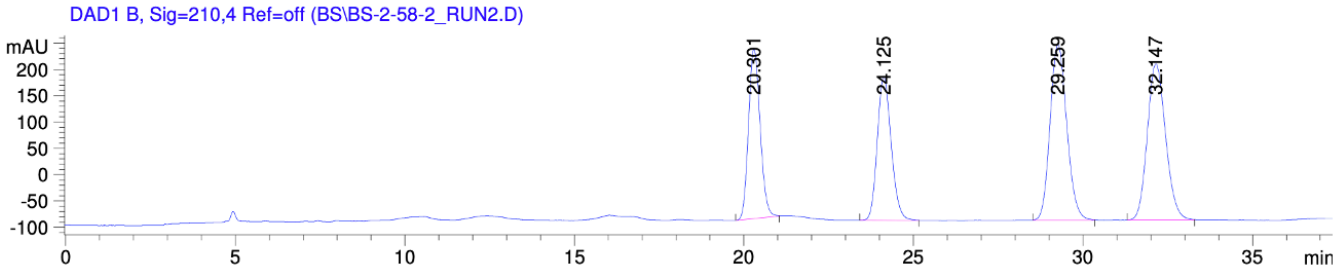


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.985	BB	0.3227	3997.18066	190.56300	19.2049
2	19.698	BB	0.4037	1484.21570	57.00915	7.1311
3	26.806	BB	0.5713	1.48146e4	402.57941	71.1786
4	29.226	BB	0.4689	517.28516	13.32544	2.4854
Totals :				2.08133e4	663.47700	

Fig. 40. HPLC trace of enantioenriched **179**



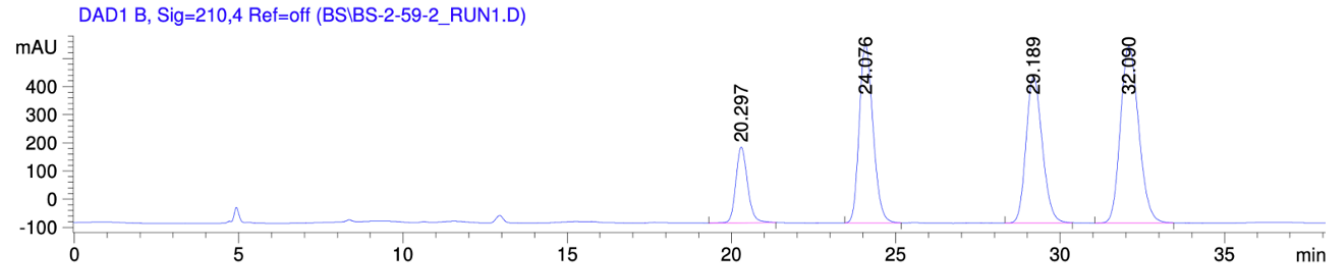


Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.301	BB	0.3712	7663.61523	322.55090	20.2163
2	24.125	BB	0.4447	7780.64209	272.87363	20.5250
3	29.259	BB	0.5239	1.13738e4	333.51102	30.0036
4	32.147	BB	0.5846	1.10901e4	296.34375	29.2552
Totals :				3.79082e4	1225.27930	

Fig. 41. HPLC trace of racemic **180**

Retention time of minor *anti* isomer traces: 20.3 and 24.1 minutes.



Signal 2: DAD1 B, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.297	BB	0.3798	6661.75781	268.17746	9.9070
2	24.076	BB	0.4557	1.84176e4	632.53235	27.3896
3	29.189	BB	0.5311	1.78715e4	519.81226	26.5774
4	32.090	BB	0.6060	2.42923e4	627.06793	36.1261
Totals :				6.72431e4	2047.59000	

Fig. 42. HPLC trace of enantioenriched **180**

11. Abbreviations

Ac	Acetyl
Ar	Aryl
ATR	Attenuated total reflection
atm	Atmosphere(s)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bz	Benzoyl
CAM	Ceric ammonium molybdate
conv.	Conversion
DCM	Dichloromethane
DFT	Density-functional theory
Dioxane	1,4-Dioxane
DIPE	Diisopropyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric Ratio
ee	Enantiomeric excess
eq	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
Hex	Hexane
His	Histidine
HRMS	High resolution mass spectrometry

HPLC	High performance liquid chromatography
IPA	Isopropyl alcohol
i-Pr	Isopropyl
IR	Infrared spectroscopy
Me	Methyl
MS	Mass spectrometry
NMR	Nuclear molecular resonance
Ph	Phenyl
Phe	Phenylalanine
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
Pr	Propyl
Py	Pyridine
RNA	Ribonucleic acid
rt	Room temperature
t-Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	Toluene
Ts	Toluenesulfonyl
Tyr	Tyrosine
UV	Ultraviolet
Val	Valine

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