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## Enantioselective auto- and cross catalytic reactions

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## CHAPTER 2

# From an autocatalytic design to a system with slow release of a catalyst and catalytic enantioselective synthesis of $\alpha$ -hydroxy acids

*In this chapter, design and experimental efforts towards an autocatalytic system based on amino acids are described. The goal was to take advantage of the bifunctional character of amino acids and to use them as autocatalysts to promote their own synthesis, starting from imino acid precursors. During this research, we found that acyclic imino acids are unstable and autocatalysis could not be accomplished. However, we discovered that corresponding salts formed from ketoacids and amines can be used as precursors for the synthesis of hydroxy acids through the slow release of amine catalysts and, the enantiopure hydroxy acids can be accessed via conventional proline based asymmetric catalysis.*

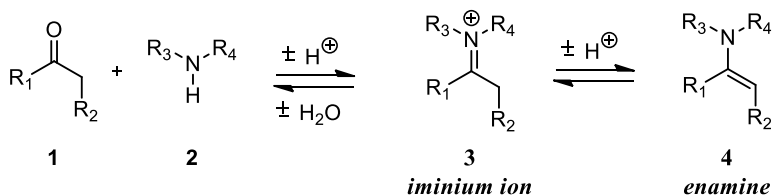
## 2.1 Introduction

Replication and homochirality are the fundamental characteristics of all living organisms.<sup>1-3</sup> Replication emerges from complex molecular networks of self-organized and dynamically interacting biomolecules.<sup>4-8</sup> Furthermore, the origin of homochirality of the biomolecules (L-amino acids and D-sugars) is directly associated with the 'origin of life' question.<sup>9</sup> From a chemical perspective, molecular self-replication processes function via autocatalytic, cross catalytic or collectively catalytic pathways, with additional information transfer (templating) from the product to the precursors.<sup>10-12</sup> Research in the area has led to the development of synthetic self-replicating systems involving nucleic acids, peptides, mixed protein-nucleic acid systems, as well as purely synthetic organic molecules.<sup>4-8</sup> Meanwhile, in the synthetic self-replicating systems developed over the last twenty years, homochirality has been predefined with the precursors employed being homochiral.<sup>4-8</sup>

The main goal of the project described in this chapter was to achieve enantioselective formation of amino acids from prebiotically relevant achiral (or chiral racemic) molecules, based on an autocatalytic processes. We choose amino acids to be used as molecules that are able to catalyse their own formation, thus acting as autocatalysts, based on the following considerations: amino acids are an inherently modular pool of chiral, organic, biologically important molecules relevant to the 'origin of life' question, and satisfy all of the requirements outlined above in order to perform asymmetric autocatalysis; amino acids with primary and secondary amino groups (especially proline) are known to be highly efficient organocatalysts for many asymmetric transformations;<sup>13</sup> the catalytic efficiency of amino acids is associated with the bifunctional structure of the molecule,<sup>14,15</sup> i.e. Lewis basicity of the amino group and the Brønsted acid carboxylic group; the mechanism of amino acid catalysis is based on the formation of an activated complex involving either, or both, iminium-enamine intermediate and hydrogen bond formation between the reaction precursors. In addition, amino acid based catalysts are potentially capable of providing a very high level of enantiodiscrimination.

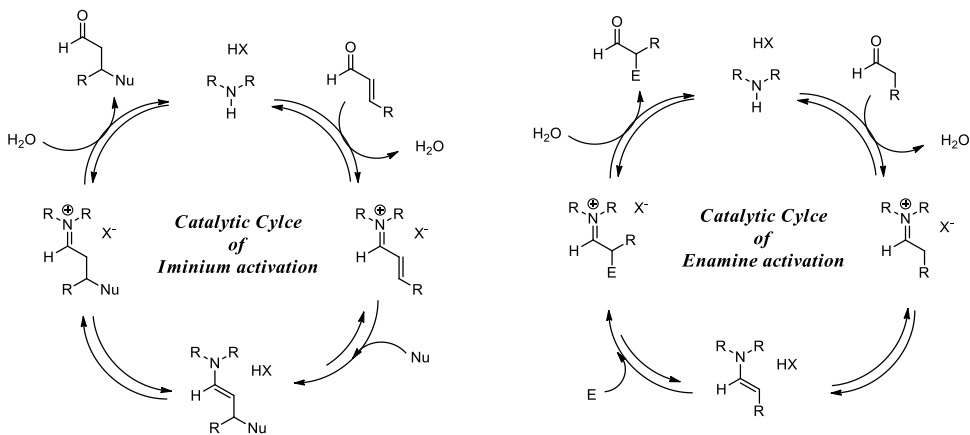
### 2.1.1 The imine-enamine catalysis in asymmetric synthesis: examples and mechanism

Enamine catalysis has proven to be a powerful method in organic synthesis and has a prominent role in organocatalysis field.<sup>16,17</sup> The basis of enamine catalysis is the reversible generation of enamines from a catalytic amount of amine and a carbonyl compound (Scheme 1). The formation of the enamine lowers the LUMO, as a consequence, the acidity of the C-H increase upon initial conversion of the carbonyl compound to iminium ion.<sup>16,18</sup>



*Scheme 1 - Enamine formation.*

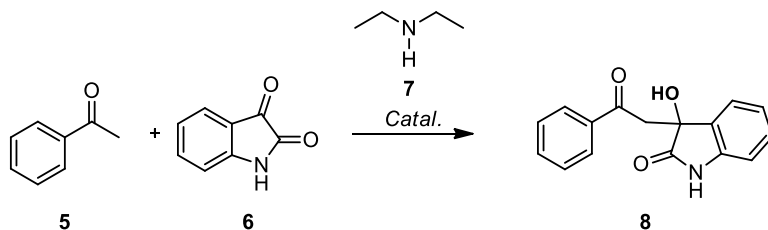
Enamines are among the most reactive neutral carbon nucleophiles, comparable to enolates.<sup>17</sup> The development of the enamine catalysis was contemporary to the development of the iminium catalysis (Scheme 2).<sup>19</sup>



*Scheme 2 - Parallels between iminium and enamine catalysis.*

The word enamine was coined for the first time by Wittig,<sup>20</sup> but at that time it was not considered as a reactive intermediate.

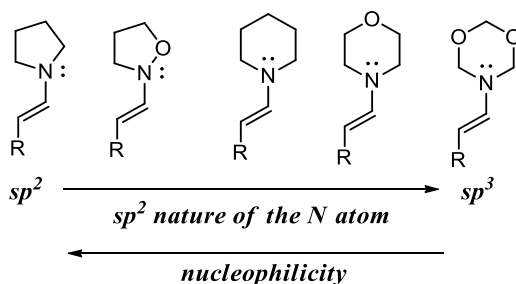
One of the first examples of enamine catalysis, where the enamine based reaction is not fully recognized, was reported by Lindwall and coworkers.<sup>21,22</sup> The reaction involved the condensation between acetophenone **5** and isantin **6**, using a catalytic amount of diethylamine **7** (Scheme 3).



*Scheme 3 - Lindwall secondary amine catalyzed aldol reaction.*

The first mechanistic proposal for an enamine based catalytic reaction was reported by Rutter, with regard to aldolase reactions.<sup>23</sup> The stoichiometric chemistry of enamines was developed by Stork,<sup>24</sup> which showed the utility of these kind of reactions in many useful transformations. The first useful enamine process was the intramolecular aldol reaction, the Hajos-Parrish-Eder-Sauer-Wiechert reaction.<sup>25</sup> Although this reaction was discovered in the 1970's, its potential was realized many years later when the group of List developed the first direct asymmetric intermolecular aldol reaction.<sup>23</sup>

In general, the nucleophilicity of enamines is related to the structure of the amine (Figure 1). Maximum overlap between the lone pair of the nitrogen with the C=C bond is required. Enamines derived from cyclic, five-membered ring amines, like pyrrolidine, are more nucleophilic than those derived from the piperidine. The high reactivity can be explained by the fact that the five-membered ring can better accept the  $sp^2$ -hybridized atoms compared to the six-membered rings.



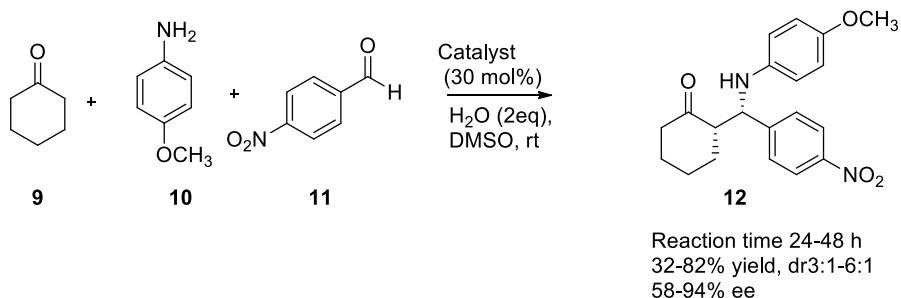
*Figure 1 - Reactivity profile of enamine.*

The reactivity order of the enamines is: pyrrolidine amine derivative > acyclic amine derivative > piperidine amine derivative.<sup>26</sup> Oxygen substituents reduce the reactivity of enamines, so morfoline derivative amines are less nucleophilic. Consequently, it is not surprising that the most used catalysts for enamine catalysis are based on the pyrrolidine skeleton. In enantioselective enamine catalysis, the approach of the enamine towards the electrophile can be subject to a steric or electronic effect of an activating group present on the enamine. Considering a relatively unreactive electrophile, like aldehydes, ketone or imines, an additional acid moiety in the structure of the molecule can promote the formation of the enamine. In the case of very basic and nucleophilic amines, like pyrrolidine, assistance from the acid moiety is not necessary.

Enamine catalysis, assisted by the presence of an acid, has been extensively studied by many groups.<sup>27–30</sup> A key step in enamine formation is the abstraction of the  $\alpha$ -proton from the initially formed iminium ion (Scheme 2). The presence of a strong acid as a co-catalyst stabilizes and promotes the formation of the iminium ion. On the other hand, a basic co-catalyst will assist the formation of the enamine. The basicity of the counter ion of the acid co-catalyst will determine the rate of the enamine formation. While a strong acid is beneficial for the first step (i.e. the formation of the iminium ion), a relatively strong base as a counter ion will promote the formation of the enamine, but this will compromise the formation of the iminium ion.

In comparison with the explosive growth of pyrrolidine-based organocatalysts in iminium and enamine catalysis, very little progress has been made in chiral primary amine-promoted organic reactions.<sup>31</sup>

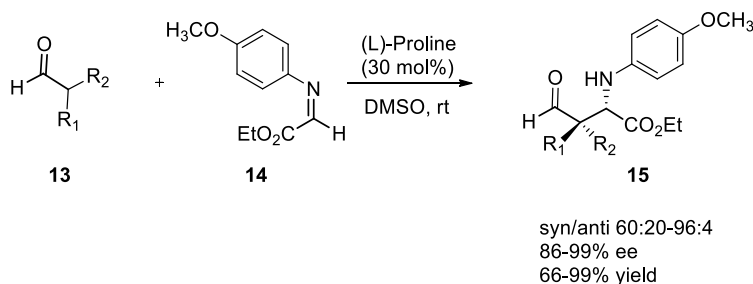
In the initial report on proline-catalyzed intermolecular aldol reactions in 2000,<sup>23</sup> it was shown that primary amino acids, such as phenylalanine and valine, were poor catalysts under the reaction conditions investigated. This seems to be reasonable as it is well accepted that a secondary enamine is better stabilized than its primary counterpart by hyperconjugation. In 2005, Córdova and co-workers<sup>32,33</sup> reported the first three-component asymmetric Mannich reaction (Scheme 4), catalyzed by primary amino acids. It was shown that simple primary amino acids, such as alanine, valine and serine, were remarkable catalysts for three-component asymmetric Mannich reactions between unmodified cyclohexanone **9**, *p*-anisidine **10**, and *p*-nitro aldehyde **11**, and the Mannich products were obtained with up to 90% *ee*.



**Scheme 4** - Three-component asymmetric Mannich reaction catalyzed by primary amino acids.

The Mannich reaction between an enolate (typically of an aldehyde, ketone, or ester) and an imine is a highly convenient and convergent method of accessing  $\beta$ -amino carbonyl compounds.<sup>18,34</sup> These Mannich adducts are important in the formation of  $\beta$ -amino alcohols and  $\beta$ -amino acid derivatives such as  $\beta$ -lactams and  $\beta$ -peptides. Very challenging is the formation of quaternary  $\beta$ -amino carbonyl compounds using an organocatalytic Mannich reaction. One of the first examples of formation of quaternary centers, using an organocatalytic Mannich reaction, was reported by Barbas *et al.*<sup>35</sup>

They performed L-Proline-catalyzed direct asymmetric Mannich reactions of N-PMP protected  $\alpha$ -imino ethyl glyoxylate **14** with various  $\beta,\beta$ -disubstituted aldehydes **13** to afford quaternary  $\alpha$ -formyl  $\beta$ -amino acid **15** derivatives with excellent yields and enantioselectivities (Scheme 5).



**Scheme 5** - L-proline-catalyzed quaternary Mannich reaction.

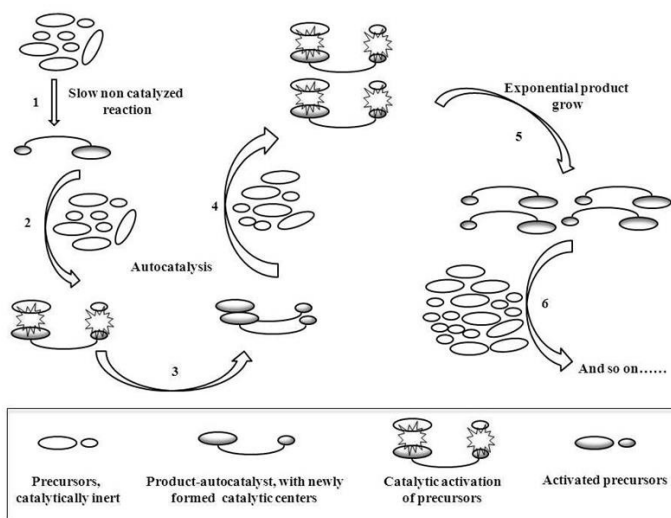
After this example, a few other examples of formation of quaternary stereocenters using Mannich reactions have been reported. Different substrates such as oxindoles<sup>36</sup> and thioesters<sup>37</sup> were used, and thiourea as the catalyst.

The construction of a chiral quaternary center represents one of the most challenging subjects in asymmetric synthesis, and has received continuing interest in our days.

## 2.2 Results and discussions

### 2.2.1 Strategy

In our design of an autocatalytic system, the synthetic route to the autocatalyst must involve a one step process in which two different catalytic functions are created (Scheme 6, step 1) and preserved in the final molecule, making it catalytically active towards its own precursors (Scheme 6, step 2). In addition, a templating effect based on self-recognition operating in the system (Scheme 6, steps 3 and 4), will ensure a further rate enhancement of the autocatalytic reaction and exponential product growth (Scheme 6, step 5).



*Scheme 6 - Proposed design for an asymmetric organo-autocatalytic system.*

The molecules that we choose as possible candidates for being an autocatalyst are the amino acids. The development of asymmetric autocatalytic reactions will be feasible if an autocatalytic molecule can be synthesized in one step and the following features are satisfied by the chosen autocatalyst molecule:



## System requirements

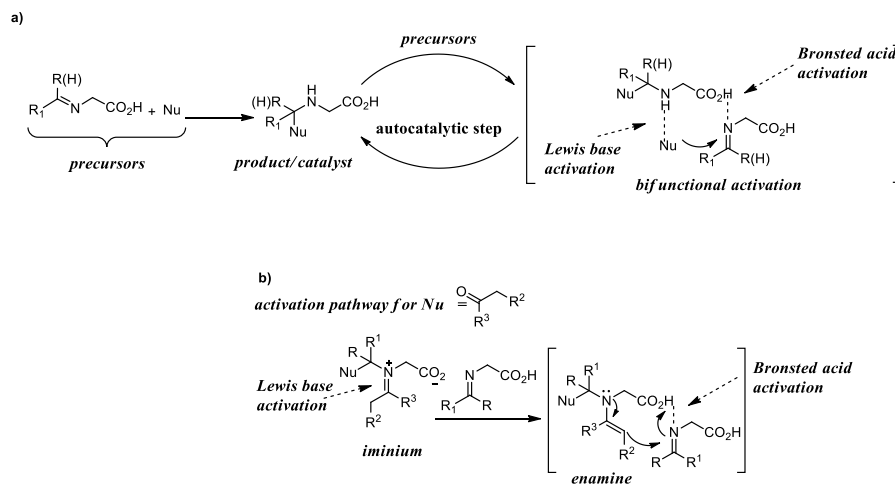
1. The autocatalyst must be chiral or form a chiral assembly.
2. The autocatalyst must have orthogonal catalytically active functional groups in its structure.
3. Positive asymmetric non-linear effect (+NLE) must be associated with the autocatalyst.<sup>14,15</sup>

(1) To achieve asymmetric autocatalysis the selected catalyst must be chiral as asymmetry can be generated only by a physical force or molecular asymmetry, which in turn can arise only from molecular chirality. (2) The presence of various functional groups in the structure of the autocatalyst is necessary to provide for the chemical activation of reaction precursors via non-covalent interactions and thus to perform catalysis. The co-existence of several orthogonal catalytic functionalities in the structure of the autocatalyst favours appearance of the following characteristics.

(3) In classical enantioselective catalysis, the enantiomeric excess (*ee*) of the product is linearly dependent on the *ee* of the catalyst, but some reactions deviate from linearity and demonstrate +NLE. This phenomenon allows for high *ee* to be obtained in a reaction even when using a catalyst of less than 100% enantiopurity. To obtain homochiral autocatalysis, starting from achiral or racemic precursors, a +NLE must be in operation in the autocatalytic system.<sup>14,38</sup>

In the current design, an autocatalytic cycle is based on a one-step synthetic route to amino acids using addition reactions of diverse nucleophiles to the electrophilic carbon of an imino acid (Scheme 7). The key element to the successful design is the synthesis of amino acids with the free carboxylic acid group, and formation of an amine moiety during the course of the reaction. The proposed system is expected to be autocatalytic due to the bifunctional molecular structure<sup>14,15</sup> of the amino acids. It is anticipated that, during the reaction the carboxylic acid of the amino acid will activate the electrophile by protonation/coordination with the nitrogen atom of the imine molecule. Concomitantly, the secondary amine will provide for activation of a nucleophile. In addition to double activation of the reactants, the reaction will also be favoured by the fact that both reactants are brought into close proximity.

The mechanism of bifunctional activation of the reaction precursors by amino acids is illustrated with the example of the Mannich reaction using a ketone as a nucleophile (Scheme 7).



*Scheme 7 - a) An autocatalytic cycle for the synthesis of amino acids; b) activation pathway is shown on the example of an imino acid and a ketone as precursors for an autocatalytic reaction.*

## 2.2.2 Imino acid synthesis

Imino acids are the precursors for the synthetic route to amino acids outlined in our strategy above. However these types of compounds were not extensively explored. There are very few literature reports on the preparation and application of imino acids in organic synthesis.<sup>39–43</sup> This probably is related with anticipated problems in solubility, stability and isolation of these types of compounds. Thus the primary task was to develop and optimize an efficient synthetic route towards the synthesis of ternary and quaternary imino acids with structural variety presented in Figure 2. These imino acids in principle can be prepared based on simple condensation reactions of carbonyl compounds with amines, Bischler-Napieralski reactions, and mild oxidation procedures.<sup>39–43</sup>

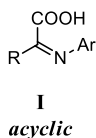
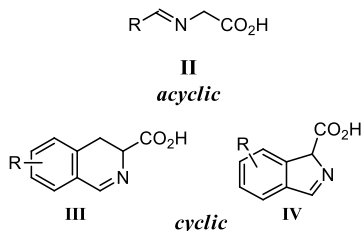
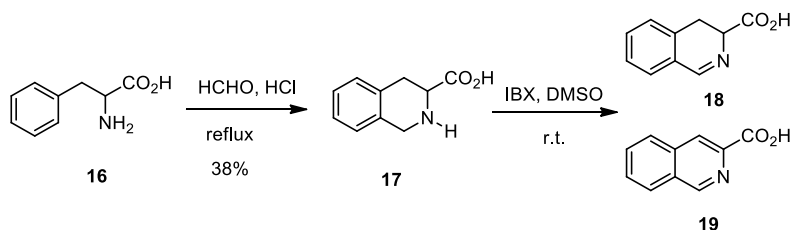
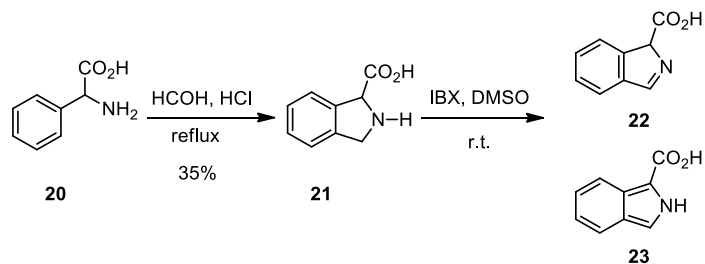
**Quaternary imino acids****Ternary imino acids**

Figure 2 - Variety of ternary and quaternary imino acids both with cyclic and acyclic structure.

We started out with synthesis of compound **18**. To synthesize imino acid **18** we decided to use Bieschler-Napieralsky reaction starting from phenylalanine **16**<sup>44</sup> (Scheme 8). The Bieschler-Napieralsky reaction provided compound **17** in moderate yield. Modest yield was due to complications during the isolation of the compound, which showed similar solubility in both water and organic solvents. In the next step, compound **17** was subjected to oxidation using IBX in DMSO (Scheme 8). This oxidation was reported by Nicolau *et al.*,<sup>41</sup> to be a useful methodology for the direct oxidation of primary and secondary amines. An additional advantage of this procedure was the potential for an easy purification of the final imino acid (by filtration of IBA).

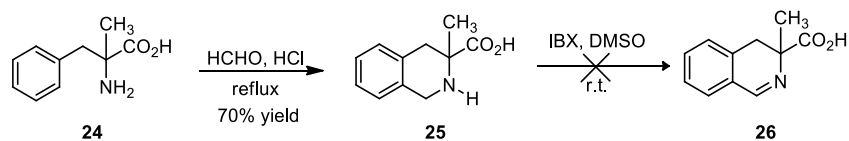
**Scheme 8**

Unfortunately, instead of the desired compound **18**, we found that mostly the over oxidized product **19** was formed during the reaction. Using lower loading of IBX (0.5 eq) provided starting material and fully oxidized product **19**. Other oxidizing agents such as TPAP<sup>45</sup> and POCl<sub>3</sub><sup>46</sup> were also tested in this reaction. However similar results were obtained, thus indicating that once compound **17** is obtained, it immediately oxidizes to the more stable aromatic compound **19**. Similar results were obtained when L-phenylglycine **20** was used as a starting material. Only the fully oxidized product **23** was obtained (Scheme 9).



Scheme 9

The problem of these substrates was the possibility of forming aromatic compounds, thus driving over oxidation. To overcome this problem we decided to use  $\alpha$ -methyl-D-phenylalanine **24** as a substrate for the Pictet–Spengler reaction, and follow with the oxidation reaction. The *N*-formylation of compound **24** was carried out using the literature procedure (Scheme 10).<sup>44</sup> Compound **25** was obtained with 70% yield and subjected to oxidation with IBX. However, in this case, a mixture of unidentified products were obtained. Changing the solvent, as well as the oxidizing agents,<sup>45,47</sup> did not result in the final desired product.

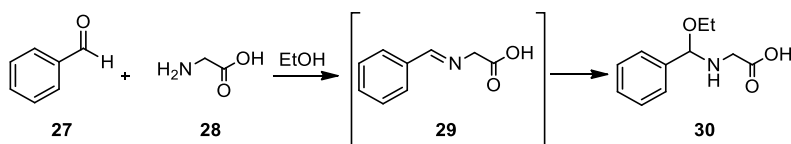


Scheme 10

The lack of success using this methodology led us to explore further options. Next, we attempted an oxidation reaction reported specifically for amino acids.<sup>48,49</sup> Two oxidation procedures using  $\text{NaIO}_4$  were performed. The first one was carried out in a mixture of DMSO/  $\text{H}_2\text{O}$ <sup>49</sup> and the second in  $\text{H}_2\text{O}$  at pH 8. In both cases, the presence of the desired product **26** was not identified.

Failure to synthesize cyclic imino acids led us towards the synthesis of linear imino acids. For this purpose, we decided to synthesize imino acid **29** via a condensation reaction of benzaldehyde **27** and glycine **28** (Scheme 11). The choice of the solvent for this reaction was based on the limited solubility of glycine. Carrying out the reaction in DMSO, DMF or neat led to the formation of a jelly like mixture, from which the desired compound could not be isolated.

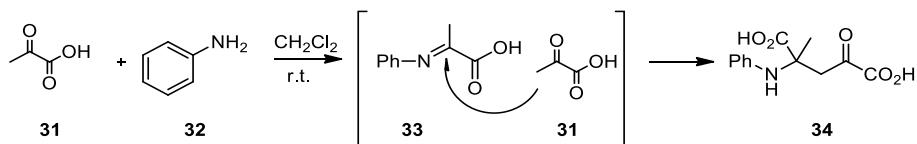
When the reaction was carried out in ethanol (Scheme 11), in which glycine was poorly soluble, little conversion of the starting material was observed. Surprisingly, according to the  $^1\text{H-NMR}$  data, instead of the desired imino acid **29**, the product of addition of the solvent EtOH to **29** was obtained. This result could be indicative that imino acids are far more reactive when compared to imines without a carboxylic acid moiety, which makes them inherently more reactive.



Scheme 11

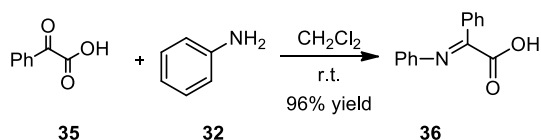
Our next approach was to use a condensation reaction of pyruvic acid **31** and aniline **32** in  $\text{CH}_2\text{Cl}_2$  (Scheme 12). We expected that an imino acid with a quaternary carbon would be less reactive than the corresponding ternary one.

However, instead of formation of the desired product **33**, dicarboxylic acid **34** was obtained, resulting from an addition of the enol of the pyruvic acid **31** to the imine **33**.



Scheme 12

To avoid this problem, we decided to perform a similar reaction using a non-enolizable ketone as the substrate, such as phenylglyoxylic acid **35** (Scheme 13). Indeed, this last attempt was a success, and the desired product, **36**,<sup>50</sup> was obtained as a white solid in good yield (96%).



Scheme 13

Using this approach, we could access different imino acids, containing electron donating and withdrawing groups, by changing the substituents on the aniline or on the keto acid. However, there was another problem we faced with this system. The imino acids were not stable, and slowly equilibrated back to the corresponding salts of amine and keto acid.

This effect was most pronounced for the aniline derivatives with electron withdrawing (EWG) substituents. Most probably, the electron donating substituent (EDG) increases the nucleophilicity of aniline thus favouring the formation of the imino acid product. On the other hand, the presence of EWG makes the aniline less nucleophilic but still basic enough to form the corresponding salts. (Figure 3).

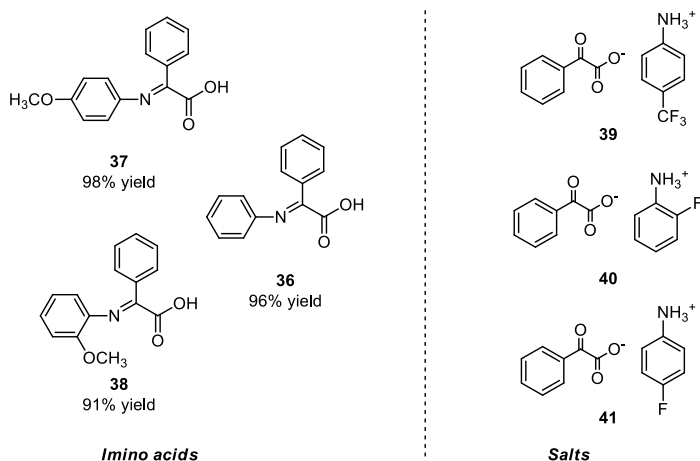
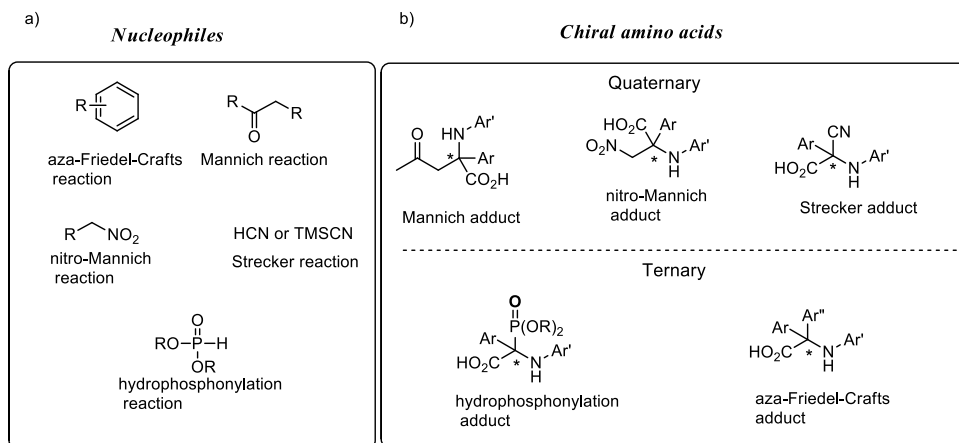


Figure 3 – Imino acids and salt compounds synthesized.

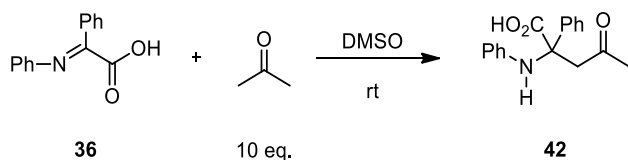
### 2.2.3 Towards autocatalytic synthesis of chiral amino acids using Mannich reaction

Following the synthesis of several imino acids, we proceeded to investigate their application in our design of an autocatalytic reaction. Varying the structure of the nucleophiles, in combination with the range of newly synthesized imino acids, different types of reactions could be studied, such as *Mannich condensation*,<sup>51</sup> *aza-Friedel-Crafts*,<sup>52</sup> *hydrophosphonylation*<sup>53</sup> and *Strecker reaction* (Figure 4).<sup>54</sup>



**Figure 4** - Structural variety of nucleophiles (a) for application in autocatalytic synthesis of amino acids (b) Indication for different class of autocatalytic reactions to be explored is given under the chemical structures.

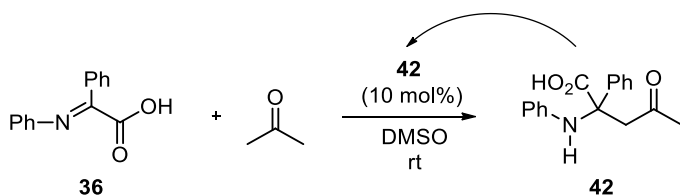
Due to time restraints imino acids were only tested in Mannich reactions. The question at the forefront of this strategy was: would it be possible to form quaternary amino acids? Initially, the Mannich reaction between the imino acid **36** and acetone (10 eq.) as the nucleophile, in the absence of any catalyst, was carried out to determine if a blank reaction would occur. DMSO was the solvent of choice, firstly, because it is one of the most commonly used solvents in Mannich reactions, and secondly, due to the poor solubility of the imino acid in any other organic solvent (Scheme 14).



**Scheme 14** - Synthesis of quaternary amino acids using Mannich reaction.

Intriguingly, after 73 hours, clean  $^1\text{H-NMR}$  spectrum of the crude reaction mixture was obtained, showing the formation of the product **42**. Unfortunately, all attempts to purify the crude reaction mixture failed to give the desired product. At this point, the kinetics of the reaction were followed by  $^1\text{H-NMR}$  spectroscopy in order to gain knowledge of the kinetic profile of the product formed during the reaction.

For this purpose two different experiments were designed: 1) to follow the rate of the original reaction; 2) to follow the rate of the original reaction seeded with 10 mol% of the product. The idea behind the 2<sup>nd</sup> experiment was to determine if autocatalysis is operating in this system. Due to difficulties in the product isolation we decided at first to seed the reaction with 10 mol% of crude reaction mixture containing of product formed after 73h. In both of the reactions, DMSO- $d_6$  was used as the solvent and DCE was added as an internal standard. Interestingly, the rate of the 2<sup>nd</sup> reaction (seeded) was found to be twice that of the 1<sup>st</sup> reaction (blank) (Scheme 15, Figure 5).



Scheme 15 – Seeding experiment.

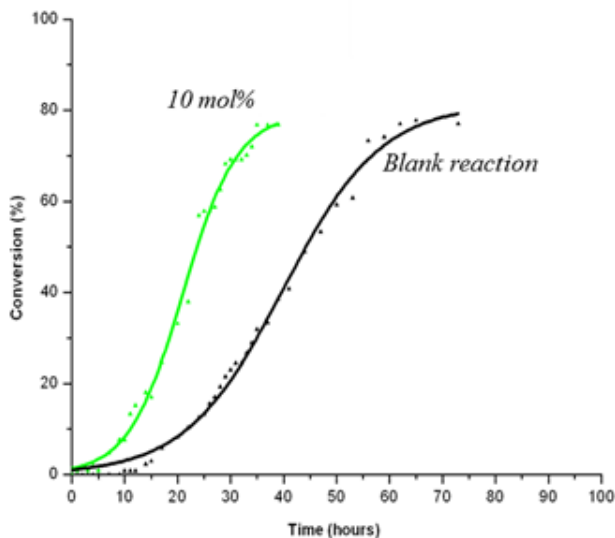
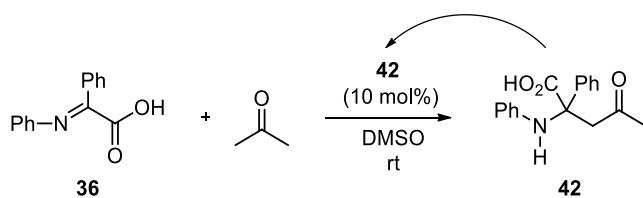


Figure 5 - Kinetic profile of the blank reaction and the reaction with 10 mol% of catalyst.



In autocatalytic reactions, the concentration-time profile shows an initial stage of the reaction where there is slow formation of the product, known as an induction or a lag period.<sup>55</sup> When the concentration of the product increases, the autocatalytic cycle begins to operate. Since in each cycle the amount of the product doubles, the product concentration increases exponentially, until reaching a certain concentration when all of the reactants are consumed. The result of this process, in terms of concentration-time profile, is a sigmoidal or S-shaped curve. Indeed, such a profile was obtained for our reactions, with a shorter lag time in the case of the reaction with 10 mol% of catalyst (Figure 6). The seeding experiment was also carried out using different amounts of catalyst (25, 50 mol%, Table 1, entries 5-6 and 8-9). However, the rate of the reaction did not accelerate any further than that observed in the reaction seeded with 10 mol% of catalyst (Table 1, entries 4,5 and 6). Furthermore, the reaction never reached full conversion, with a maximum of ~80% conversion observed.

Table 1



Entry	Acetone (y eq.)	Seed, RM 42 (x mol %)	Time (hours)
1	10	-	73
2	30	-	50
3 <sup>a</sup>	10	-	61
4	10	10	40
5	10	25	40
6	10	50	40
7	30	10	37
8	30	25	37
9	30	50	37

<sup>a</sup>The concentration of the reaction was increased to 0.5 M.

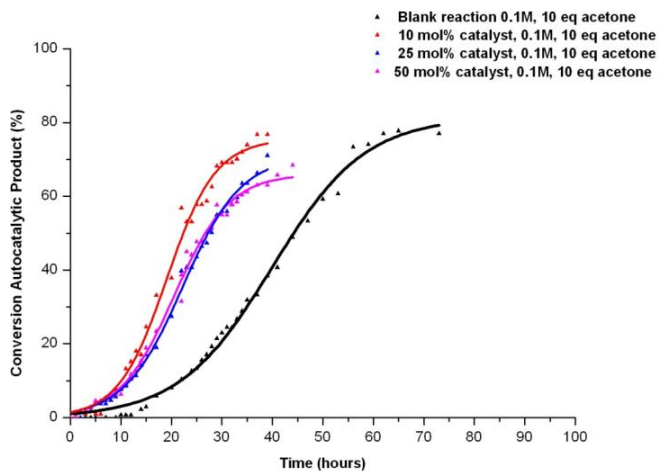


Figure 6 - Kinetic profile of the blank and “catalytic” reactions using 10 eq. of acetone.

Another important parameter affecting the rate of the reaction, in need of consideration, was the amount of acetone required.

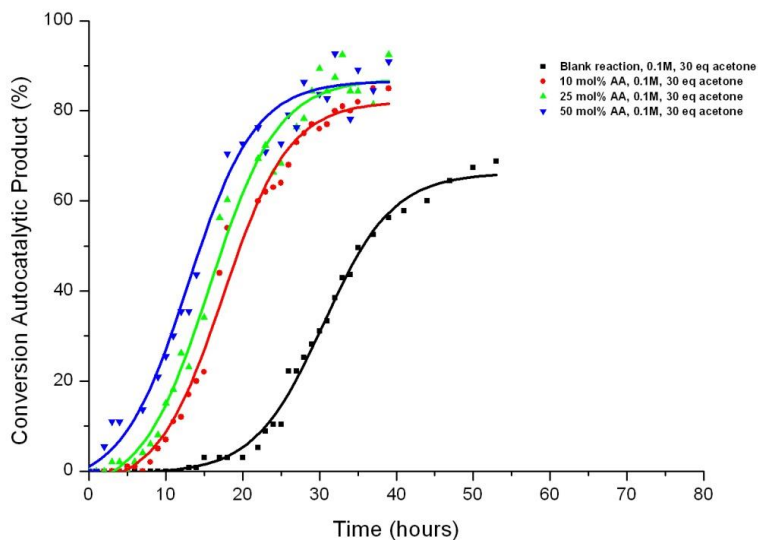


Figure 7 - Kinetic profile of the blank and “catalytic” reactions using 30 eq. of acetone.

Typically, a Mannich reaction is a bimolecular reaction and the reaction rate is expected to be dependent on the concentrations of both reagents. Therefore, the blank and seeded reactions, using 30 eq. of acetone, were performed (Table 1, Figure 7), and the results showed an acceleration in the reaction rates in comparison to the results obtained using 10 eq. of acetone. Moreover, this effect was much more pronounced in the case of the blank reaction than for the catalytic reaction (compare entries 1,2 with entries 4,7).

Although the initial kinetic data suggested an autocatalytic profile for the product formation, based on the crude  $^1\text{H-NMR}$  data, questions remained as to why the product could not be isolated from the reaction mixture and why full conversion could not be reached. However, more careful analysis of the reaction kinetics indicated that the system was more complex than initially assumed. Following further analysis of how the reaction developed over time, it was found that no reaction occurred for the first 5 hours, with only peaks associated with the starting reagents present in the  $^1\text{H-NMR}$  spectrum. However, after 5 hours new peaks began to appear in the aromatic region of the spectrum, while no changes were observed in the aliphatic region (Figure 8).

At first, we reasoned that it was an effect of *Z/E* isomerization of the imino acid **36**, and after reaching a 1:1 ratio of the isomers, the Mannich reaction (with acetone) follows.

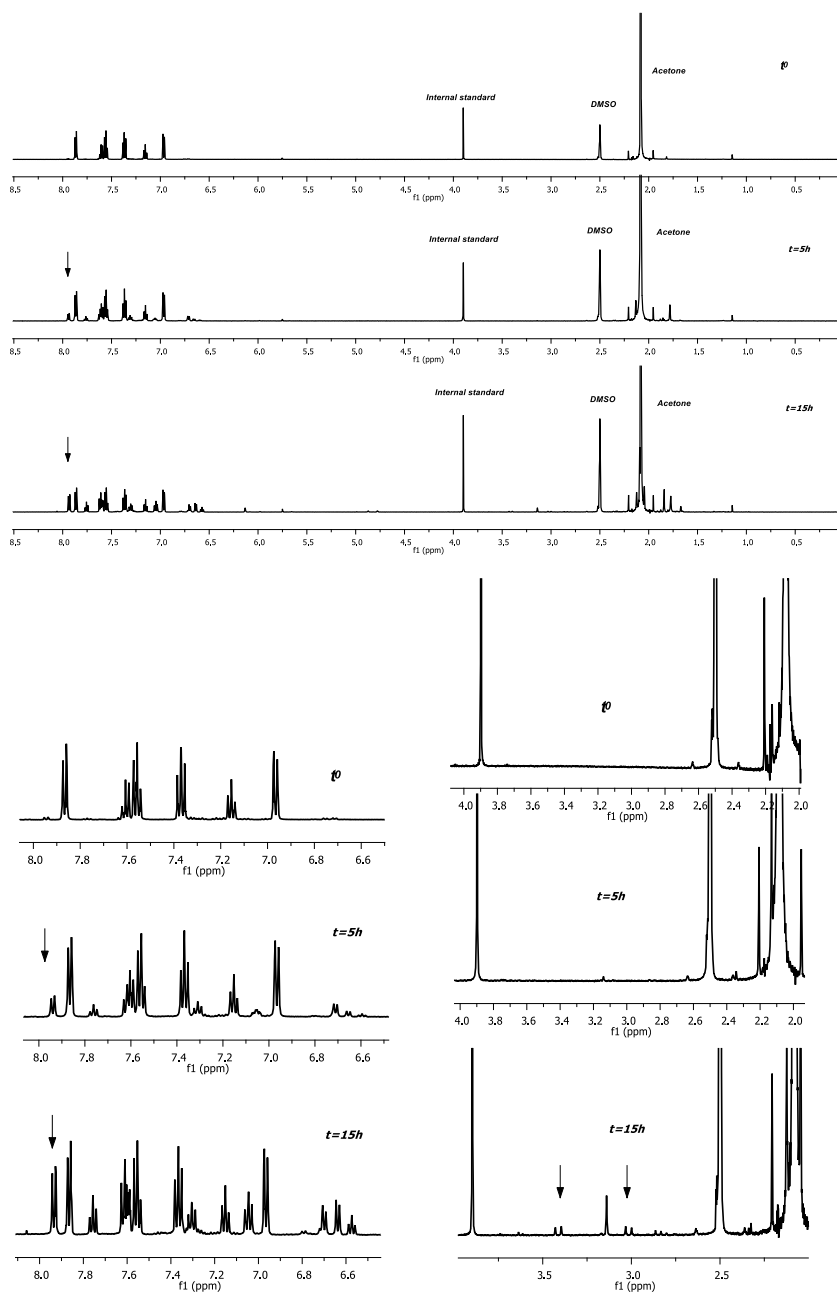


Figure 8 -  $^1\text{H-NMR}$  spectra of the reaction mixture at  $t_0$ , after 5 hours and after 15 hours.

Unfortunately, we realised that during the initial 5 h the imino acid hydrolyses to amine and keto acid, followed by formation of the salts, a fate which was previously observed when attempting to form the imino acids using electron poor aniline derivatives. In the  $^1\text{H-NMR}$  spectra, the initial doublet peak at 7.86 ppm corresponds to the imino acid. After 5 hours, a second doublet began to appear at 7.94 ppm and other peaks (2 doublets and one triplet) in the region between 6.71-6.56 ppm. From comparison with the  $^1\text{H-NMR}$  of the starting materials, the newly formed peaks were identified as precursors of the iminoacid **36**: the phenylglyoxylic **35** and aniline **32**. The starting materials were in equilibrium with the corresponding salt.

It is well known that aldol reactions can be catalyzed by primary or secondary amines.<sup>56-59</sup> Therefore, we deduced that in our reaction system, imino acid is formed initially which, under the reaction conditions, is then hydrolyzed back to the starting materials. The starting materials are in equilibrium with the corresponding salts, but the equilibrium is mostly shifted towards the salt. Nevertheless, after 5h from the start of the reaction, a small amount of free aniline **32** is still present, in addition to the imino acid **36**, keto acid **35**. Free aniline **32** reacts with acetone, forming the corresponding enamine **43**, which then goes on to perform nucleophilic attack on the keto acid **35**, leading to the formation of the aldol product, hydroxy acid **44**. Subsequently, the aniline **32** is released back into the reaction mixture. This hypothesis was further supported by the presence of distinctive peaks at 4.87 and 4.78 ppm, in the  $^1\text{H-NMR}$  spectra, corresponding to the enamine molecule (Figure 9).

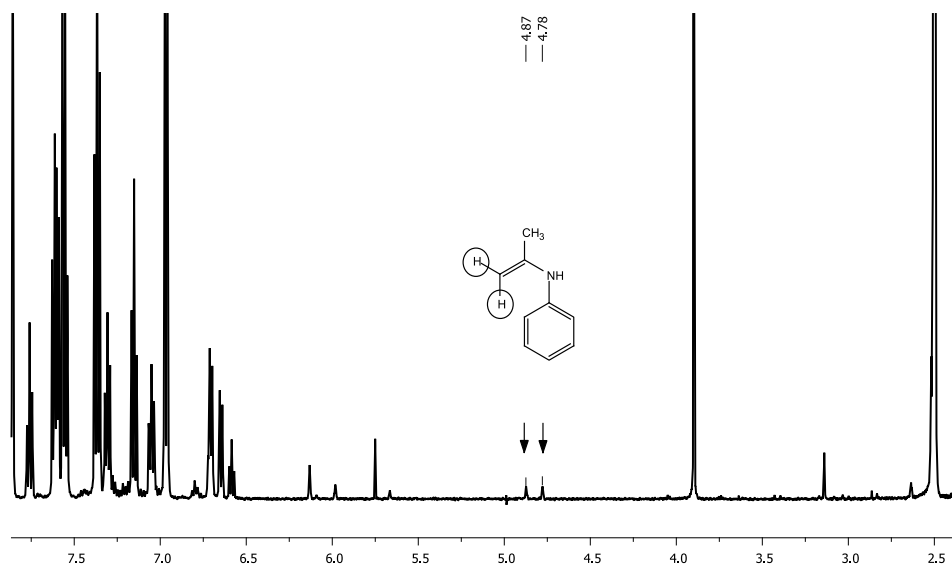
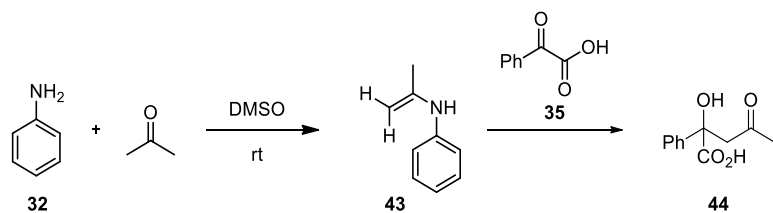


Figure 9 -  $^1\text{H-NMR}$  spectra of the reaction mixture, showing peaks corresponding to the enamine.

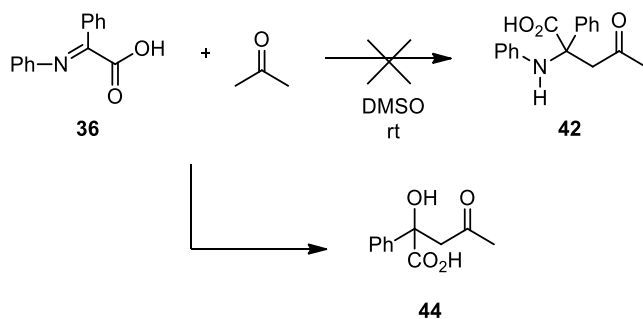
After elucidating the events of the reaction, slight modifications were made to the isolation procedure, and the product was isolated. Indeed, following full characterization, the product proved to be the quaternary hydroxy acid **44**, and not the corresponding amino acid as original suspected (Scheme 16).



Scheme 16 - Aniline catalyst for the aldol reaction between acetone and phenylglyoxylic acid **35**.

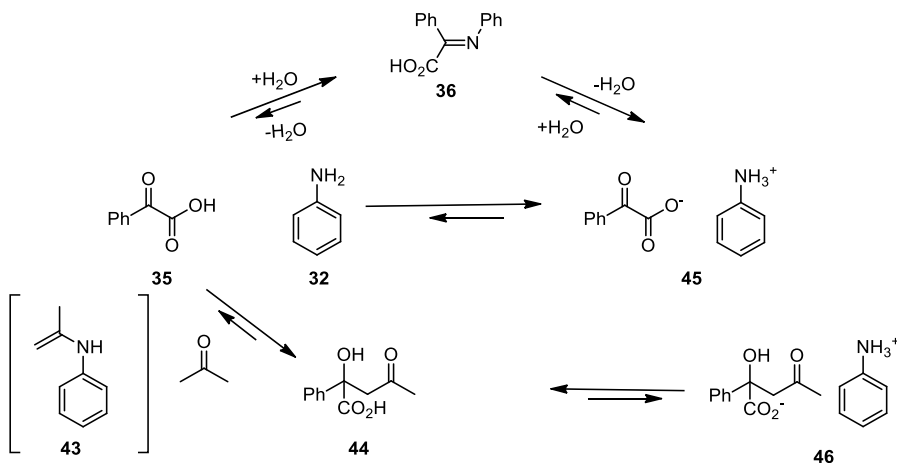
#### 2.2.4 Slow release of a catalyst during hydroxy acid formation

After establishing that, in our designed system, no amino acid formation or Mannich reaction took place (Scheme 17), the question still remains as to what was the origin of the sigmoidal kinetic curves observed for the reaction rate and why the reaction was accelerated by seeding the experiment.



Scheme 17

We rationalized these results by the following (Scheme 18): initially, the reaction started with the imino acid **36**. After a few hours, hydrolysis takes place, leading to an equilibria between imino acid **36**/keto acid **35** and aniline **32**/the corresponding salts **45**. These equilibria are shifted towards the salts **45**. A small amount of free aniline **32**, present in this equilibria, can act as a catalyst for an aldol reaction by forming the catalytically active enamine **43** with acetone. Once one molecule of enamine is formed, it reacts with the keto acid **35**, leading to the formation of the corresponding hydroxy acid **44** and subsequent release of the aniline **32** molecule.



Scheme 18 - Slow release of the catalyst in a self-replicating system.

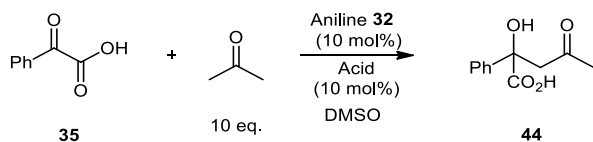
The lag time observed during the kinetic profile is explained by the time needed for equilibria to be established and enamine to be formed.

Overall, this appears to be a conventional catalysis profile and exponential product growth or a rate increase upon seeding is unexpected. However, since the equilibria is mainly shifted towards the salt formation, initially there is only a small amount of aniline **32** catalyst present for the reaction being trapped in the form of salt **45**, thus being inactive. However, we hypothesize that once a molecule of hydroxy acid **44** is formed, it is less acidic compared to the original keto acid **35** and thus does not form the salt with released molecule of aniline **32**. Therefore, as more molecules of the hydroxy acid product **44** are formed during the reaction, more molecules of aniline **32** catalyst become available for enamine catalysis (Scheme 18). As a result, we have a system of catalytic product formation in which the catalyst is not present initially but is slowly released from the substrate during the course of the reaction. This phenomenon is responsible for the observed kinetic behavior of the reaction discussed in 2.2.3.

To get more insight into this catalytic aniline catalysed aldol reaction, further experiments were carried out. The first experiment performed, involved the reaction between acetone and keto acid **35** in DMSO, using a catalytic amount of aniline **32** (Table 2). When 10 mol% of aniline **32** was employed, full conversion to the hydroxy acid product **44** was obtained after 8 days (Table 2, entry 1). Performing the same reaction without any aniline present, but using 10 mol% of the hydroxy acid **44**, did not generate any product, thus indicating that autocatalysis does not occur in this instance (Table 2, entry 2). Intriguingly, however, when a combination of both the hydroxy acid **44** (10 mol %) and aniline **32** (10 mol %) were added to the same reaction mixture, the reaction was complete after just 3 days. This is a marked increase in the rate of the reaction, in comparison to the 8 days required when aniline was used as the sole catalyst (Table 2, entry 3).



Table 2



Entry	Acid (10 mol%)	Amine (10 mol%)	Time (days)
1	-	Aniline	8 days
2	<b>44</b>	-	-
3 <sup>a</sup>	<b>44</b>	Aniline	3 days
4	Mandelic Acid	Aniline	12 days
5	<b>44</b> (60 % <i>ee</i> )	Aniline	3 days

Unless noted the results are for reactions that proceeded with full conversion. <sup>a</sup>The reaction performed with 5 mol% of catalyst gave the same results.

We were intrigued to discover if this phenomenon is specific to this product molecule or if any structurally similar hydroxy acid compound would also work as a rate enhancing catalyst. In order to examine this, a further experiment was carried using mandelic acid (10 mol%, entry 4). In this case, the reaction time increased to 12 days, indicating that indeed the product of the reaction, hydroxy acid **44**, is specifically required, in combination with aniline, for rate enhancement to occur.

The effect of adding 10 mol % of enantioenriched hydroxy acid **44** to the reaction mixture was also explored, in order to determine if asymmetric induction would occur. <sup>60-62</sup> The enantioenriched hydroxy acid **44** (60% *ee*) was obtained by reacting ketoacid **33** and acetone, in the presence of an L-proline catalyst (see section 2.2.5). However, no asymmetric induction was observed in this case (Table 2, entry 5).

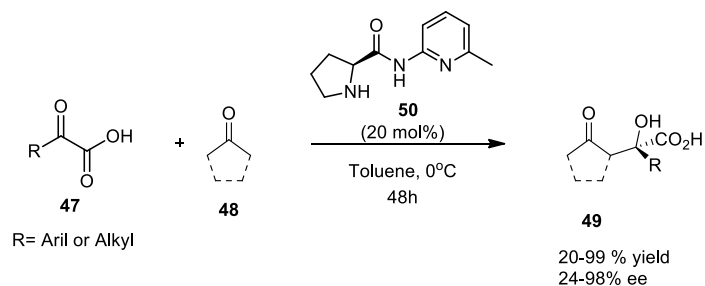
So far, the nature of this symbiotic effect of the hydroxy acid product **44** and aniline catalyst, which leads to sufficient rate enhancement (from 8 to 3 days), is uncertain. Further studies are required to understand the nature of this phenomenon.

## 2.2.5 The organocatalytic enantioselective aldol reaction

The catalytic asymmetric aldol reaction is an important strategy for C-C bond formation in organic synthesis.<sup>63-70</sup> The chiral  $\beta$ -hydroxy carbonyl compounds, produced from this transformation, have a broad range of applications as building blocks for synthetic organic chemistry, as well as precursors for pharmaceutical compounds.<sup>71</sup>

The Hajos-Parrish-Eder-Sauer-Wiechert reaction is an example of an intramolecular aldol reaction catalyzed by the small organic molecule, L-proline.<sup>23,25,72-74</sup> This particular reaction marks the beginning of organocatalysis, and also of modern asymmetric catalysis. Since then, many chiral organocatalysts have been discovered for the direct aldol reaction.<sup>56,57,75-82</sup> Aldol reactions using ketones, instead of aldehydes, are of particular interest due to the more challenging quaternary stereocenter formation and also their lower reactivity as a consequence of steric hindrance. In particular, if ketoesters are used as substrates for aldol reactions, quaternary hydroxy acids can be formed. In the last number of years, examples of aldol reactions between  $\alpha$ -ketoesters and aldehydes have been reported.<sup>79</sup>

In general, the keto esters used contained electron-withdrawing groups in order to activate the keto function. More challenging is the reaction between keto acids and ketones. So far, only one example of an organocatalyzed aldol reaction, between ketones and keto acids, has been reported by the group of Gong *et al.* (Scheme 19).<sup>60,61</sup> In this report, the authors showed that they could achieve excellent enantioselectivities, using an L-prolinamide derivative **50** as a catalyst. Despite the high levels of enantioselectivities obtained, the catalyst employed is complex and requires several synthetic steps for preparation.



*Scheme 19* - Aldol reaction based on molecular recognition.



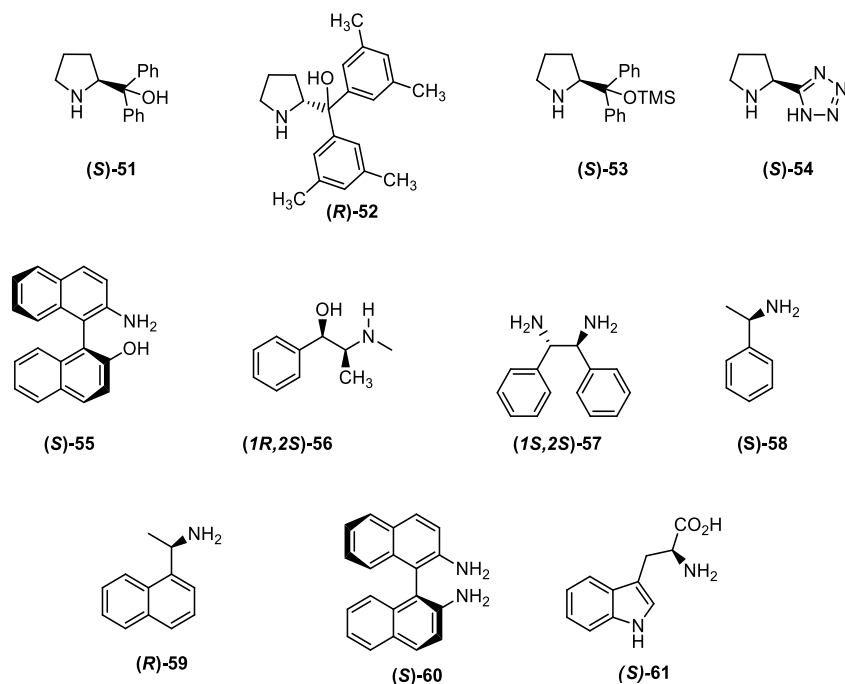
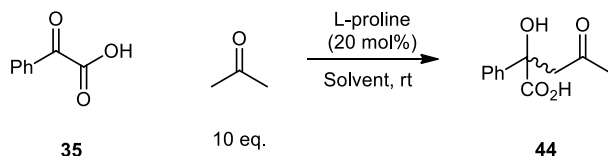


Figure 10 - Structures of chiral organocatalysts used during the screening.

L-proline was initially selected because it was reported to be a good catalyst for aldol reactions of  $\alpha$ -keto esters with aldehydes.<sup>79</sup> We obtained the desired product, in good yield and enantioselectivity (Table 3, entry 1), using L-proline as the catalyst and toluene as the solvent. With the intention of increasing the enantioselectivity and reducing the reaction time, which was relatively long in the case of L-proline (6 days) due to its low solubility in toluene, more soluble derivatives of proline were screened, such as **51**, **52**, **53**, **54** (Table 3, entries 2-5). Unfortunately, none of the commercially available proline derivatives showed significant improvements for both the rate and the enantioselectivity of the reaction, when compared to proline itself. Only the tetrazole derivative **S-52** (Table 3, entry 5) catalyzed the reaction in a relatively short reaction time, but the enantioselectivity decreased to 35%. Primary amine types of catalysts were also tested (Table 3, entries 7-12).

Some of them furnished the product, however longer reaction times were required and lower enantioselectivities were obtained. Thus, the simple L-proline proved to be the best catalyst for this reaction. Encouraged by these results, the role of the solvent was examined next (Table 4).

Table 4: Solvents screening



Entry	Solvent <sup>a</sup>	Reaction time <sup>b</sup>	Yield (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	Toluene	6 days	85	70
2	Acetone	48 h	98	25
3	NMP	24 h	80	5
4 <sup>e</sup>	DMSO	5 days	60	25
5	H <sub>2</sub> O	-	-	-
6	Toluene 10 eq. H <sub>2</sub> O	-	-	-

Unless noted the results are for reactions that proceeded with full conversion <sup>a</sup>A mixture of 2-hydroxy-4-oxo-2-phenylpentanoic acid **35** (0.5 mmol), L-proline (20 mol%), and acetone (1.0 mL) in solvent (3 mL) was stirred till complete conversion at room temperature; <sup>b</sup> Reaction progress was monitored by <sup>1</sup>H NMR; <sup>c</sup> Isolated yield; <sup>d</sup> Determined by <sup>1</sup>H NMR using (*R*)-1-(naphthalen-1-yl)ethanamine **59** as chiral solvating agent; <sup>e</sup> After 5 days 70% conversion was achieved.

Shorter reaction times, but lower enantioselectivity, were obtained using more polar aprotic solvents such as acetone and *N*-methyl 2-pyrrolidinone (Table 4, entries 2 and 3). When DMSO was used as a solvent, a longer reaction time was required and poor enantioselectivity were obtained (Table 4, entry 4). The addition of water, or carrying out the reaction in water, resulted in no product formation (Table 4, entries 5 and 6). After a brief solvent screening, it was clear that the optimal solvent for proline-catalysed (20 mol %) reaction is toluene. Next, we investigated the scope of the reaction by testing additional keto acid derivatives (Figure 11). The aldol reaction proceeded smoothly with the different keto acids, affording the aldol adducts **62**, **63**, **64**, with a quaternary stereocenter, in good yield and moderate enantioselectivity.

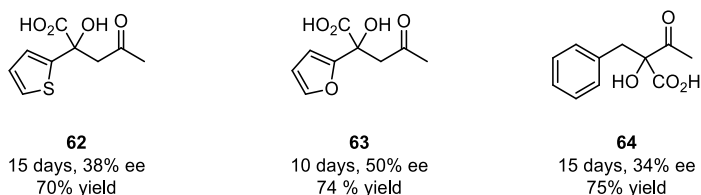
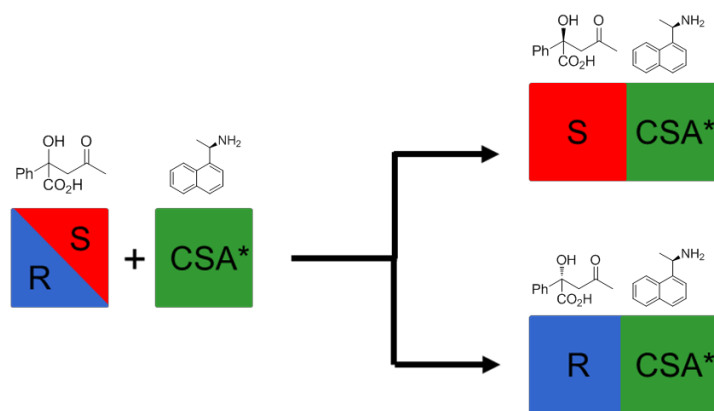
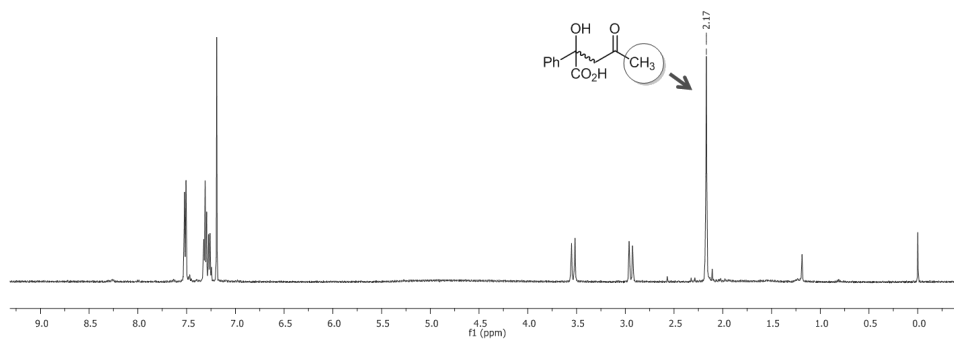
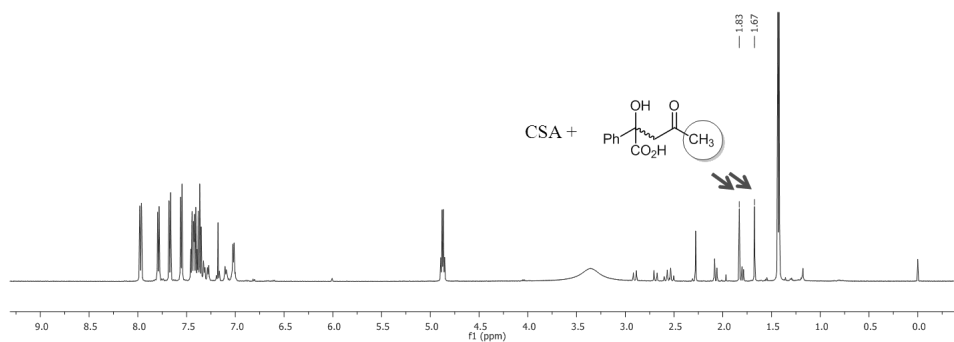


Figure 11 – Aldol products synthesized.

As mentioned previously, an alternative technique to determine the *ee* of the  $\beta$ -hydroxy carbonyl compounds, was utilized for these experiments, using  $^1\text{H-NMR}$  analysis with chiral shift reagents/chiral solvating agent. Enantiomers cannot be distinguished in an achiral medium, but diastereomers are easily distinguishable because the resonance of the diastereomeric protons is anisochronous. The well-known method applied to determine the enantioselectivity, using NMR techniques, was to add a chiral auxiliary to the sample which converts the mixture of enantiomers to diastereomers. The integration of the diastereomeric mixture is a direct measure that can be related to the *ee* of the compounds in question. Commonly, three types of chiral auxiliaries are used<sup>83–88</sup> to pre-form diastereomers before the NMR analysis:<sup>89</sup> chiral lanthanide shift reagents,<sup>90</sup> chiral solvating agents<sup>91</sup> and chiral derivatizing agents. For the purpose of direct *ee* analysis of  $\beta$ -substituted hydroxy carboxylic acids, a chiral primary amine, (*R*)-1-(naphthalen-1-yl)ethanamine **59**, was used, which was added to an NMR sample of the crude reaction product (Figure 12). The formation of diastereomeric complexes, as a result of hydrogen bonding interactions between the acid moiety of the  $\beta$ -hydroxy acid and the amine moiety, proved to be a simple method to determine the enantioselectivity of the reaction. A clear splitting of the  $\text{CH}_3$  signal (at 2.17 ppm) of the acetone moiety was observed after the addition of 4 equivalents of CSA to the corresponding  $\beta$ -hydroxy acid (Figure 12).



Diastereoisomeric complexes

*a**b*

**Figure 12** - *ee* determination using CSA, a)  $^1\text{H-NMR}$  of the hydroxyl acid **44**; b)  $^1\text{H-NMR}$  of the hydroxyl acid **44** after the addition of CSA.

## 2.3 Conclusions

In this chapter, our strategy and design of an autocatalytic reaction, based on bifunctional amino acid molecules to be used as autocatalysts, was presented. As a result of these studies, we found that the imino acid molecules, which were intended to be used as reagents for autocatalytic amino acid synthesis, are highly unstable and reactive: cyclic imino acids are prone to over-oxidation and linear imino acids are prone to hydrolyse to the corresponding carbonyl compounds and amines, followed by salt formation. As a consequence of imino acid hydrolysis, fortunately we have discovered an interesting system, displaying an unusually slow release of a catalyst, trapped in the substrate molecule, for the synthesis of hydroxy acid compounds. The results have been supported by kinetic studies and NMR analysis. This concept of slow catalyst release, in some way, relates to enzyme catalysis and has potential for further development towards new and interesting applications.

For racemic synthesis of hydroxy acids, catalyzed by aniline, we found that the product of the reaction has a significant rate-accelerating effect when used in combination with the aniline catalyst. As of now, the effect of the product on the reaction rate is uncertain and further studies are required. In addition, we have developed a proline catalyzed enantioselective synthesis of chiral hydroxy acids, with quaternary stereocenters, with enantioselectivities of up to 70% achieved.

## 2.4 Experimental section

### 2.4.1 General Remarks

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. Toluene anhydrous was purchased from Sigma Aldrich and used without any further purification. Acetone was dried over anhydrous  $K_2CO_3$ . All the reagents were purchased from Sigma Aldrich or Alfa Aesar and used without purification. Chromatography was performed using silica gel P60 (230-400 mesh) and aluminium oxide 90 neutral (70-230 mesh ASTM) from Merck. Progress and products of the reactions were determined by: thin layer chromatography (TLC) performed on Merk silica gel 60 TLC-plates F254 and components were visualized by UV and using potassium permanganate and/or ninhydrin staining, GC-MS (GC, HP6890; MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA).

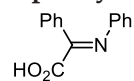


Mass spectra were recorded on a LTQ Orbitrap XL (ESI<sup>+</sup>). <sup>1</sup>H- and <sup>13</sup>C-NMR were obtained with Varian VXR500 (500 and 125 MHz, respectively), 400 (400 and 100.59 MHz respectively) spectrometers equipped with a 5 mm z-gradient broadband probe, using CDCl<sub>3</sub> and DMSO-d<sub>6</sub> as solvent. Chemical shifts (δ) are reported in ppm, relative to the residual solvent peak (CHCl<sub>3</sub>: δ = 7.26 ppm for <sup>1</sup>H-NMR, δ = 77.16 ppm for <sup>13</sup>C-NMR; DMSO: δ=2.50 ppm for <sup>1</sup>H-NMR, δ = 39.51 ppm for <sup>13</sup>C-NMR). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Enantiomeric excesses were determined by <sup>1</sup>H-NMR using (*R*)-(+)-1-(1-Naphthyl)ethylamine **59** as chiral solvating agent.

### 2.4.2 General Procedure for the synthesis of imino acid

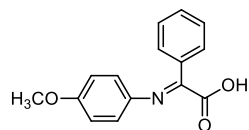
To a solution of ketoacid (0.01 mol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added the corresponding aniline (0.01 mol). The resulting mixture was stirred at room temperature for 1-8h till the formation of a precipitate. The solid was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub>, to afford the desired iminoacid that can be used without further purification.

#### 2-phenyl-2-(phenylimino)acetic acid (**36**)



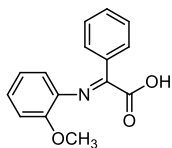
Compound **36** was obtained following the general procedure, as a white solid in 96% yield. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.66 – 7.50 (m, 3H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 2H). <sup>13</sup>C-NMR (126 MHz, DMSO-d<sub>6</sub>) δ 166.03, 161.28, 149.78, 133.43, 131.95, 129.41, 129.24, 128.99, 128.88, 127.62, 124.67, 119.6. HRMS (ESI<sup>+</sup>, *m/z*); calcd for C<sub>14</sub>H<sub>12</sub>NO<sub>2</sub>[M + H]<sup>+</sup>: 226.08626, found 226.08563.

#### 2-((4-methoxyphenyl)imino)-2-phenylacetic acid (**37**)



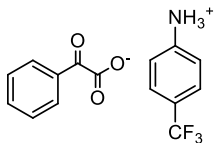
Compound **37** was obtained following the general procedure, as a light yellow solid in 98% yield. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.83 (d, *J* = 6.7 Hz, 2H), 7.62 – 7.47 (m, 3H), 6.96 (q, *J* = 9.1 Hz, 4H), 3.76 (s, 3H). <sup>13</sup>C-NMR (126 MHz, DMSO-d<sub>6</sub>) δ 166.98, 160.93, 156.78, 142.71, 134.36, 134.00, 131.52, 129.27, 129.00, 128.92, 127.46, 121.43, 114.66, 114.13, 55.21. HRMS (ESI<sup>+</sup>, *m/z*); calcd for C<sub>15</sub>H<sub>14</sub>NO<sub>3</sub>[M + H]<sup>+</sup>: 256.0815, found 256.0815.

### 2-((2-methoxyphenyl)imino)-2-phenylacetic acid (38)



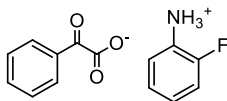
Compound **38** was obtained following the general procedure, as a white solid in 91% yield.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.63 – 7.53 (m, 2H), 7.36 – 7.25 (m, 3H), 7.23 – 7.19 (m, 2H), 6.91 (d,  $J = 2.7$  Hz, 2H), 3.89 – 3.85 (m, 3H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ )  $\delta$  168.04, 166.22, 150.49, 137.43, 135.31, 135.11, 130.55, 130.33, 128.21, 128.19, 127.84, 120.45, 119.83, 113.38, 56.79. HRMS ( $\text{ESI}^+$ ,  $m/z$ ); calcd for  $\text{C}_{15}\text{H}_{14}\text{NO}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 256.0805, found 256.0807.

### 4-(trifluoromethyl)benzenaminium 2-oxo-2-phenylacetate (39)



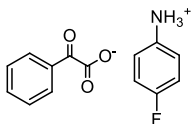
Compound **39** was obtained following the general procedure, as a white solid in 90% yield.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.94 (d,  $J = 7.2$  Hz, 1H), 7.77 (t,  $J = 7.4$  Hz, 1H), 7.62 (t,  $J = 7.7$  Hz, 1H), 7.30 (d,  $J = 8.5$  Hz, 1H), 6.64 (d,  $J = 8.5$  Hz, 1H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{DMSO-d}_6$ )  $\delta$  188.70, 166.09, 152.18, 135.14, 131.84, 129.43, 129.28, 126.73, 126.25, 126.21, 126.18, 126.14, 124.04, 115.57, 115.26, 114.94, 114.63, 112.98, 39.72. HRMS ( $\text{ESI}^+$ ,  $m/z$ ); calcd for  $\text{C}_{15}\text{H}_{11}\text{F}_3\text{NO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 294.0590, found 294.0578.

### 2-fluorobenzenaminium 2-oxo-2-phenylacetate (40)



Compound **40** was obtained following the general procedure, as a white solid in 85% yield.  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.94 (d,  $J = 7.1$  Hz, 2H), 7.87 (d, 1H), 7.77 (t, 1H), 7.63 (t,  $J = 8.1$  Hz, 2H), 7.57 (t, 1H), 7.32 – 7.22 (m,  $J = 10.8$  Hz, 1H), 7.22 – 7.13 (m,  $J = 5.2$  Hz, 2H), 7.02 – 6.90 (m, 1H), 6.86 (t,  $J = 6.9$  Hz, 1H), 6.75 (t,  $J = 8.6$  Hz, 1H), 6.55 – 6.44 (m,  $J = 12.5, 5.9$  Hz, 1H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{DMSO-d}_6$ )  $\delta$  188.77, 166.14, 151.85, 149.50, 136.25, 136.13, 135.12, 131.87, 129.43, 129.28, 124.46, 124.43, 116.32, 116.28, 116.03, 115.97, 114.86, 114.68, 39.72. HRMS ( $\text{ESI}^+$ ,  $m/z$ ); calcd for  $\text{C}_{14}\text{H}_{11}\text{FNO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 244.0775, found 244.0763.

### 4-fluorobenzenaminium 2-oxo-2-phenylacetate (41)



Compound **41** was obtained following the general procedure, as a white solid in 88% yield.  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.93 (d,  $J = 7.1$  Hz, 2H), 7.77 (t,  $J = 7.4$  Hz, 1H), 7.62 (t,  $J = 7.8$  Hz, 2H), 6.85 (t,  $J = 8.9$  Hz, 2H), 6.58 (dd,  $J = 8.9, 4.7$  Hz, 2H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ )  $\delta$  192.30, 169.35, 165.07, 163.60, 161.69, 149.29, 147.08, 138.15, 136.47, 135.16, 132.55, 132.39, 132.15, 130.79, 124.63, 118.77, 118.37. HRMS ( $\text{ESI}^+$ ,  $m/z$ ); calcd for  $\text{C}_{14}\text{H}_{11}\text{FNO}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 244.0771, found 244.0768.

### 2.4.3 Kinetic studies of imino acid based reactions

For the kinetic studies several reactions were carried out, using 10 or 30 equivalents of acetone, 10, 25 and 50 mol% of product as catalyst and DCE as internal standard for the integration. The general procedure for the Mannich reaction: 1.1 mmol (250 mg) of imino acid **36** was solubilized in a solution of DMSO- $d_6$  containing 10 mol% of DCE (7  $\mu$ L), then acetone was added (10 or 30 eq.). In the case of the catalytic reaction, the appropriate amount of catalyst was added, taking into account that by adding the solution of catalyst also more acetone and DMSO were added, so all the solutions were prepared in such a way that the overall final concentration was kept at 1 M.

**Stock solution of catalyst (crude reaction mixture):** The solution of product/catalyst was obtained from a blank reaction of imino acid **36** (2.2 mmol; 500 mg) in DMSO- $d_6$  (20 mL) and acetone 10 eq. (1.5 mL).

**Blank reaction and 10 eq. of acetone:** 1.1 mmol of imino acid **36** (250 mg), 10 equivalents of acetone (0.8 mL), in DMSO- $d_6$  (9.2 mL) total concentration 0.1M, reaction time 73 hours.

**Blank reaction and 30 eq. acetone:** 1.1 mmol of imino acid **36** (250 mg), 30 equivalents of acetone (1.9 mL), in DMSO- $d_6$  (7.6 mL) total concentration 0.1M, reaction time 50 hours.

**10 mol% of catalyst and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 10 equivalents of acetone (0.64 mL), in DMSO- $d_6$  (6.5 mL) 10 mol% of solution containing the product/catalyst (0.88 mL from the stock solution) were added, concentration 0.1M, reaction time 40 hours.

**25 mol% of catalyst and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 10 equivalents of acetone (0.46 mL), in DMSO- $d_6$  (5.3 mL) 25 mol% of solution containing the product/catalyst (2.2 mL from the stock solution) were added, concentration 0.1M, reaction time 40 hours.

**50 mol% of catalyst and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 10 equivalents of acetone (0.29 mL), in DMSO- $d_6$  (3.3 mL) 50 mol% of solution containing the product/catalyst (4.4 mL from the stock solution) were added, concentration 0.1M, reaction time 40 hours.

**10 mol% of catalyst and 30 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 30 equivalents of acetone (1.9 mL), in DMSO- $d_6$  (5.2 mL) 10 mol% of solution containing the product/catalyst (0.88 mL from the stock solution) were added, concentration 0.1M, reaction time 37 hours.

From an autocatalytic design to a system with slow release of a catalyst and catalytic enantioselective synthesis of  $\alpha$ -hydroxy acids

**25 mol% of catalyst and 30 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 30 equivalents of acetone (1.7 mL), in DMSO- $d_6$  (4.0 mL) 10 mol% of solution containing the product/catalyst (2.2 mL from the stock solution) were added, concentration 0.1M, reaction time 37 hours.

**50 mol% of catalyst and 30 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg), 30 equivalents of acetone (1.5 mL), in DMSO- $d_6$  (2.0 mL) 10 mol% of solution containing the product/catalyst (4.4 mL from the stock solution) were added, concentration 0.1M, reaction time 37 hours.

**Blank reaction and 10 eq. of acetone 0.5M:** 5.5 mmol of imino acid **36** with 10 equivalents of acetone (4.0 mL), in DMSO- $d_6$  (6.0 mL), reaction time 73 hours.

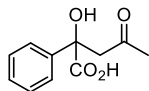
**10 mol% of DL-proline and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg) with 10 equivalents of acetone (0.8 mL), in DMSO- $d_6$  (7.2 mL) 10 mol% of DL -proline (10 mg) were added, concentration 0.1M, reaction time ~60 hours.

**30 mol% of propanoic acid and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg) with 10 equivalents of acetone (0.8 mL), in DMSO- $d_6$  (7.2 mL) 30 mol% of propanoic acid (19  $\mu$ L) were added, concentration 0.1M, reaction time ~60 hours.

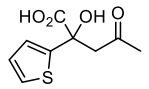
**10 mol% of H<sub>2</sub>O and 10 eq. acetone:** 0.88 mmol of imino acid **36** (200 mg) with 10 equivalents of acetone (0.8 mL), in DMSO- $d_6$  (7.2 mL) 10 mol% of H<sub>2</sub>O (1.6  $\mu$ L) were added, concentration 0.1M, reaction time ~60 hours.

#### **2.4.4 General procedure for aldol reaction**

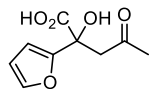
To a mixture of anhydrous acetone (1 mL) and toluene (3 mL) were added the corresponding  $\alpha$ -keto acid (0.5 mmol) and catalyst (20 mol %), the resulting mixture was stirred at room temperature till full conversion was reached. The conversion was monitored by taking an aliquot of the reaction mixture, diluted in CDCl<sub>3</sub> and analyzed by <sup>1</sup>H-NMR spectroscopy. After complete conversion, H<sub>2</sub>O was added to the reaction mixture and the product extracted with EtOAc. The organic phase was dried using Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. If necessary further purification was performed by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>: EtOH, 90:10) to yield the desired hydroxy acid. The *ee* was determined using <sup>1</sup>H-NMR and chiral solvating agent **61**.

**2-hydroxy-4-oxo-2-phenylpentanoic acid (44).**

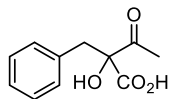
Isolated as a white solid in 85% yield and 70% *ee*.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (d,  $J = 7.5$  Hz, 1H), 7.36 (t,  $J = 7.3$  Hz, 2H), 7.32 (m, 1H), 3.58 (d,  $J = 17.9$  Hz, 2H), 2.99 (d,  $J = 17.8$  Hz, 2H), 2.22 (s, 3H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  209.48, 176.88, 139.27, 135.67, 131.26, 129.14, 128.86, 128.67, 76.75, 52.26, 30.94. HRMS (ESI<sup>+</sup>,  $m/z$ ) calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_4$  [ $\text{M}+\text{H}^+$ ]: 209.0808, found: 209.0813. The spectroscopic data matched those reported in literature.<sup>61</sup>

**2-hydroxy-4-oxo-2-(thiophen-2-yl)pentanoic acid (60).**

Isolated as yellow solid in 70% yield and 38% *ee*.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.24 (d, 2H), 7.08 (d,  $J = 3.7$  Hz, 1H), 7.01 – 6.90 (m, 1H), 3.55 (d,  $J = 18.0$  Hz, 1H), 3.18 (d,  $J = 17.8$  Hz, 1H), 2.23 (s, 3H).  $^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  207.87, 176.27, 144.30, 127.42, 125.95, 124.49, 75.26, 53.16, 30.76. HRMS (ESI<sup>+</sup>,  $m/z$ ) calcd for  $\text{C}_9\text{H}_{11}\text{O}_4\text{S}$  [ $\text{M}+\text{H}^+$ ]: 214.0302, found: 214.0310.

**2-(furan-2-yl)-2-hydroxy-4-oxopentanoic acid (61).**

Isolated as brown solid in 74% and 50% *ee*.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 – 7.09 (m, 1H), 6.42 – 6.21 (m, 2H), 3.44 (m, 2H), 3.22 (d,  $J = 17.8$  Hz, 1H), 2.17 (d,  $J = 3.2$  Hz, 3H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  207.58, 180.58, 144.58, 143.48, 111.80, 99.55, 73.64, 47.09, 31.69. HRMS (ESI<sup>+</sup>,  $m/z$ ) calcd for  $\text{C}_9\text{H}_{11}\text{O}_5$  [ $\text{M}+\text{H}^+$ ]: 198.0506, found: 198.0511.

**2-benzyl-2-hydroxy-4-oxopentanoic acid (62).**

Isolated as white solid in 75% yield and 34% *ee*.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (m, 3H), 7.21 (m, 2H), 3.20 (d,  $J = 17.9$  Hz, 1H), 3.01 (d,  $J = 13.7$  Hz, 1H), 2.91 (d,  $J = 13.7$  Hz, 1H), 2.73 (d,  $J = 17.8$  Hz, 1H), 2.16 (s, 3H).  $^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  209.27, 177.52, 134.59, 130.67, 128.55, 127.57, 76.22, 49.82, 44.95, 31.04. HRMS (ESI<sup>+</sup>,  $m/z$ ) calcd for  $\text{C}_{12}\text{H}_{13}\text{O}_4$  [ $\text{M}+\text{H}^+$ ]: 223.09649, found: 223.09556.

**2.4.5 General procedure for the *ee* determination using  $^1\text{H}$  NMR and CSA**

To 0.02 mmol of keto acid in 0.6 mL of  $\text{CDCl}_3$  4 equivalents of (*R*)-1-(naphthalen-1-yl)ethanamine **59**, then the solution was transferred into the NMR tube. The NMR tube was shaken for a few seconds and a  $^1\text{H-NMR}$  spectrum was obtained immediately (16 scans). The NMR *ee* values were obtained by integration of the peaks corresponding to the splitting of the  $\text{CH}_3$  groups.

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