Novel asymmetric copper-catalysed transformations

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In this chapter a spectroscopic study is reported of an asymmetric Mannich reaction, described in 2007 by Mauksch and Tsogoeva, which was reported to be autocatalytic. The combined spectroscopic data indicate that this Mannich reaction is not catalyzed by the product. Several control experiments were performed, demonstrating that addition of the product does not accelerate product formation.

* Parts of this chapter will be submitted for publication: Bos, P. H.; Teichert, J. F.; Feringa, B. L. 2012.
7.1 Introduction

Homochirality of essential molecules is a ‘signature of life’ but the origin of homochirality of biomolecules remains an unsolved mystery. Multiple hypotheses have been proposed including the concept of autocatalysis introduced by Frank in 1953. In this concept the reaction of two achiral compounds leads to two enantiomeric products that each catalyze their own formation. At the same time, each enantiomer reduces the activity of the other (mutual inhibition) which results in asymmetric amplification. Calculations based on such a model system show that it can evolve into a chirally asymmetric state.

In short, asymmetric autocatalysis is the process by which the chiral product of a reaction acts as a chiral catalyst for its own formation. In recent decades self-replicating systems and autocatalysis have received widespread attention and are among the most fascinating areas in chemistry. The introduction of this chapter will focus on asymmetric autoinduction and asymmetric autocatalysis. For an excellent overview of self-replicating systems see the recent review by Vidonne and Philp.

7.1.1 Asymmetric autoinduction

In 1989, Alberts and Wynberg reported on the role of the product in asymmetric C-C bond formation. The stereochemical effect of the product acting as a ligand in intermediate complexes in the reaction was investigated. In the first example, the effect of the addition of a stoichiometric amount of optically enriched \((+)-(R)-1\)-phenyl-1-propanol-\(d_2\), \(2-d_1\), on the addition of ethyllithium to benzaldehyde 1 was studied (Scheme 1).

![Scheme 1](image)

The use of deuterated \(2-d_1\) allowed for the determination of the enantiomeric excess of 2 separately in the mixture. The enantiomeric excess of the product \((+)-2\) was determined to be 17% ee. This value was reproducible and confirmed using both optical rotation as well as shift reagents in combination with \(^1\)H-NMR. This effect was defined as the principle of enantioselective autoinduction. Furthermore, it was demonstrated that the same effect could also be obtained using catalytic amounts of the optically enriched \(2-d_1\) (Scheme 2).
Asymmetric Autocatalysis in Organic Reactions: A Spectroscopic Study

Scheme 2  Catalytic asymmetric autoinduction in the reaction of Et₂Zn with benzaldehyde.

In this case, one mmol of the preformed titanate of 2-d₁ was added to 12 mmol of benzaldehyde 1 in the presence of diethylzinc. After hydrolytic workup the enantiomeric excess of (+)-2 was determined to be 32% ee. These important findings set the stage for tremendous efforts in the field of asymmetric autocatalysis.

7.1.2 Asymmetric autocatalysis: The Soai system.
An important breakthrough, in which a chiral product acts as a catalyst for its own formation with significant amplification of the enantiomeric excess was reported in 1995. Soai et al. proved that autocatalysis in a chemical reaction can indeed enhance a small initial enantiomeric excess of a chiral molecule (Scheme 3).

Scheme 3  Proposed reaction scheme of asymmetric autocatalysis of (S)-5. Addition of 5-pyrimidyl alcohol 5, with a small enantiomeric excess, to a mixture of diisopropylzinc and 5-pyrimidine carboxaldehyde 3, generates more of the alkoxide intermediate 4 in an autocatalytic reaction. After hydrolysis, product 5 is isolated with high enantiomeric excess. Because the reaction involves a chiral catalyst generated from the initial alcohol and because the catalytic step is enantioselective, the enantiomeric excess of
the product is enhanced. This process of automultiplication of a chiral product has been applied to the enantioselective addition of diorganozinc reagents to heteroaromatic carbaldehydes. Addition of trace amounts of a chiral heteroaromatic alcohol (an analog of (S)-5 substituted at the 2-position) with very low enantiomeric excess (0.8 mol% with ≈ 0.00005% ee) led to an amplification of the enantiomeric excess of the corresponding product to 57% ee. In further studies it was observed that not only the product itself, but also other chiral sources could induce very high selectivities. These chiral sources include: chiral alcohols, amines, epoxides, esters, and amino acids, [5]- and [6]-helicenes, and also crystals with enaniomorphous faces (e.g. sodium chlorate and quartz). Another impressive example is the use of α-deuterobenzyl alcohol (0.05 mol%, >95% ee) as a chirality inducing agent. Despite the enormous number of chiral sources that can be used to induce high enantioselectivity, the Soai reaction is limited to the use of heteroaromatic aldehydes together with diorganozinc reagents. Although kinetic models were reported in literature, the exact mechanism of this reaction is still under investigation. The best-supported hypothesis implicates that the active catalyst is a dimeric species consisting of two alkoxide molecules. Furthermore, kinetic studies implicate a tetrameric species as the transition state for the reaction; that is, composed of four aldehyde/alkoxide molecules. The exact structure of these species are not known.

Recently, Carreira et al. published an improved synthesis of Efavirenz (S)-10, a key drug for the treatment of HIV, using an autocatalytic formation of the key intermediate (S)-8 based on the Soai system (Scheme 4). In this autocatalytic reaction, 18 mol % of product (S)-8 was added to the reaction of aldehyde 6 and alkyne 7 with Et2Zn, n-HexLi and ligand (1R,2S)-9. The combination of the addition of the product together with chiral alcohol 9 gave the best results and key intermediate (S)-8 could be isolated in 67% yield with 99.5% ee (79% yield and 99.6% ee including the initially added product (S)-8). When product 8 was added without ligand 9, (S)-8 was isolated with 88% ee. Ligand 9, without product 8 added, provided the product 176
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7.1.3 Evidence for autocatalysis in organocatalytic reactions

In 2007 Mauksch and Tsogoeva reported evidence of asymmetric autocatalysis in the formation of chiral ester 13 from acetone and α-imino ester 12 where optically enriched 13 was reported to act as a catalyst (Scheme 5).42, 43

![Scheme 5](image)

First, product 13 was prepared with L-proline as external catalyst in 98% ee (S) and with D-proline in 99% ee (R) following a literature procedure.44 The authors carried out experiments under various conditions (different concentrations of α-imino ester 12; in acetone or DMSO as solvent; different temperatures and reaction times). In all cases the product that was added as a catalyst was obtained via proline catalysis. Addition of 15 mol% of (S)-13 with 98% ee to 12 in acetone (0.25 M) at room temperature (4 days) afforded the product (S)-13 in 48% yield, after subtraction of the initial amount of product added, with an enantiomeric excess of the newly formed product of 79% ee. Higher ee values could be obtained at very high catalyst loadings (up to 50 mol%) and upon longer reaction times (6 days) the enantiomeric excess of the products decreased.

The authors propose a catalytic cycle that involves the hydrogen-bonded pre-complex of the substrate and the product which could be attacked by the enol tautomer of acetone (Scheme 6).
Scheme 6  Proposed general catalytic cycle for the autocatalytic Mannich reaction and schematic representation of the transition state leading to the enantiomer of the product formed in the reaction.42

Based on this proposed mechanism density functional theory (DFT) calculations were carried out using the B3LYP functional and the 6-31G basis set with the Gaussian03 quantum chemistry package. Mauksch and Tsogoeva42 found that, based on these calculations, both the hetero- and homochiral product dimers ((R)-13•(S)-13 and (S)-13•(S)-13) are less stable than the monomers with almost equal energies. Furthermore, the transition state (Scheme 6, TS-A) for the formation of (S)-13•(S)-13 from the substrate-product complex 12•(S)-13 is 1.8 kcal mol\(^{-1}\) lower in energy than the formation of the other enantiomer of the product (R)-13•(S)-13 leading to the observed preference for the formation of the (S)-enantiomer. The regeneration of substrate-product dimer 12•(S)-13 from free substrate molecules and product dimer (S)-13•(S)-13 is disfavored by 3.4 kcal mol\(^{-1}\). Recently, related observations of autocatalysis in Mannich reactions have also been reported.45

In 2009, Blackmond reported that the computational modeling studies for the autocatalytic Mannich reaction and the resulting proposed mechanism do not agree with the fundamental chemical principle of microscopic reversibility and do not represent a physically and chemically realistic reaction network.46 The main argument is that Mauksch and Tsogoeva42 include a recycling mechanism in their proposal in which a combination of (S)-13 and (R)-13 does not give an inactive dimer but converts to two molecules of the prochiral substrate 12. The kinetics of such a ‘recycling’ system violate the principle of microscopic reversibility, because in order to work the reverse pathway should go via an intermediate that is higher in energy than the intermediate in the forward pathway.46

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These results pose challenging questions about the mechanism of this reaction and the role of the product. Furthermore, the discovery of an asymmetric autocatalytic reaction without the use of organometallic reagents would be a very important breakthrough that has a big impact on the chemical society.

7.2 Goal

The aim of this research project was to investigate the evidence of the autocatalytic asymmetric Mannich reaction, reported in 2007 by Mauksch and Tsogoeva, using a combination of spectroscopy and control experiments. In the context of our program on chemically enhanced amplification and propagation of chirality and the tremendous impact of such a reaction on the mechanistic understanding of the amplification of homochirality in nature, we embarked on a study of this Mannich reaction in more detail and shed light on the origin of asymmetric autocatalysis in this transformation.

7.3 Results and Discussion

7.3.1 Synthesis of the products and product stability

In order to study the autocatalytic Mannich reaction depicted in Scheme 5 (vide supra), α-iminoester 12 and the Mannich products rac-13, (S)-13 and (R)-13 had to be synthesized. The α-iminoester 12 was synthesized in 85% yield as a bright yellow oil by condensation of ethyl glyoxalate 14 (~50 wt% in toluene) with p-anisidine 15 (recrystallized from water) (Scheme 7). To prevent degradation, α-iminoester 12 was stored under inert atmosphere in a glovebox.

![Scheme 7](image)

In the next step, a Mannich reaction of α-iminoester 12 and acetone, catalyzed by 20 mol% of D-, L- or DL-proline, afforded the products rac-13, (S)-13 and (R)-13 in good yield and enantiomeric excess ((S)-13 and (R)-13) as light yellow oils that were analytically pure (Scheme 7 and Experimental Section). The products were stored under inert atmosphere in a glovebox to prevent degradation.
It should be noted that both the α-iminoester 12 as well as the Mannich products rac-13, (S)-13 and (R)-13 are not stable when they are stored in the refrigerator, probably due to presence of traces of moisture. In the case of 12, the color changes from bright yellow to brown and a complex mixture of products was observed by 1H-NMR after 5 days. The Mannich products also degrade over time if they are not stored under inert atmosphere, changing color from light yellow to dark brown. Furthermore, (S)- and (R)-13 show significant racemization after 4 days. These problems could be prevented by storing all compounds under inert atmosphere in a glovebox and as a result the compounds could be stored for months without degradation (12 and 13) or deterioration in ee (13).

7.3.2 Reaction monitoring by Raman spectroscopy

Initial attempts to reproduce the autocatalytic Mannich reaction as published by Mauksch and Tsogoeva et al. provided inconclusive evidence on the autocatalytic aspect of the reaction. Therefore, we decided to follow the conversion of α-iminoester 12 in time using Raman spectroscopy (Figure 1).

![Raman spectra of 12 and 13 in acetone.](image)

Figure 1 Raman spectra of 12 and 13 in acetone.

The conversion was followed by measuring the decrease of starting material 12 in time. During the reaction, we did not observe the expected significant change in reaction rate in the presence of 15 mol% of the product 13 as a catalyst in either racemic form or with 99% enantiomeric excess (see Figure 2). Furthermore, a sigmoid curve, associated with an autocatalytic reaction, was not observed.

Enantiomerically pure Mannich product 13, applied as a catalyst in this reaction, was synthesized in a separate reaction using a D- or L-proline catalyzed reaction of 12 in acetone in the same fashion as reported by Mauksch and Tsogoeva. We therefore
hypothesized that due to incomplete purification the possibility of trace amounts of proline in product 13 could not be excluded. These impurities (e.g. proline) could in principle catalyze the reaction of α-iminoester 12 towards Mannich product 13 in an enantioselective manner. Furthermore, it is puzzling that by performing the reaction in dimethyl sulfoxide, which is capable of reducing product-substrate interactions, similar results were obtained compared to acetone.42

To investigate this hypothesis, catalyst 13 was synthesized in a racemic fashion using two alternative pathways, not involving proline, to exclude any trace of proline. Reaction of α-ketoester 16 with p-anisidine 15 under Dean-Stark conditions in toluene afforded enamine 17 in 73% yield. After subsequent hydrogenation with catalytic palladium on activated charcoal (Pd/C), rac-13a was isolated in 41% yield (Scheme 8).

Scheme 8 Alternative synthetic route to product rac-13a.

Alternatively, commercially available ketoester 18 was transformed into α,β-unsaturated ketoester 19 via a bromination-elimination sequence in 35% yield. Subsequent Michael addition of p-anisidine 15, afforded rac-13b in 71% yield (Scheme 9).

Scheme 9 Second alternative synthetic route to product rac-13b.

Next, the Mannich reaction of 12 with acetone in the presence of 15 mol% of rac-13a and rac-13b, obtained from these alternative syntheses, was monitored by Raman spectroscopy. The conversion of the reaction was measured by the disappearance of the absorption of the starting material (12) at 1163 cm⁻¹ in the Raman spectrum. These reactions were compared to the Mannich reaction without any product added, the reaction with 15 mol% of (S)-13 (99% ee) and the reaction in the presence of 15 mol% of rac-13 (synthesized with DL-proline, see Scheme 7). All of these reactions displayed the same time profile and in all cases addition of the product did not give any rate acceleration compared to the blank reaction, in which no product was added to the reaction mixture (Figure 2).
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Figure 2 The effect of the addition of 15 mol\% of rac-13, (S)-13, rac-13a and rac-13b at t=0 on the conversion of 12 (Scheme 7) monitored by the decrease of the absorbance at 1163 cm\(^{-1}\) in the Raman spectrum (see Figure 1).

Based on these initial findings we decided to perform additional control experiments using the original reaction conditions, reported by Mauksch and Tsogoeva, as well as reactions in which trace amounts of either L- or D-proline (1 mol\%) were added at the start of the reaction together with the Mannich product (R)-13 (15 mol\%, 95\% ee) (Table 1). If no proline is added to the reaction, product 13 was isolated in 40\% yield with 36\% ee. After correction for the initially added amount of (R)-13, using the formula depicted in equation 1,\(^{42}\) it can be concluded that the product that is formed during the reaction is racemic (Table 1, entry 1).

\[
\text{ee}_p = \frac{n_1}{(n_1-n_0)} (\text{ee}_p' - \frac{n_0 \cdot \text{ee}_0}{n_1})
\]

**Equation 1** To assess the effect of the asymmetric induction, the corrected ee value of the product (ee\(_p\)) after deduction of the effect of the initially added product on the ee values of the isolated product was calculated using this formula in which \(\text{ee}_0\) = ee value of the initially added product, \(\text{ee}_p'\) = observed ee value of the isolated product, \(n_0\) = product initially added [mol] and \(n_1\) = total isolated product [mol].\(^{42}\)
Addition of L-proline (1 mol%) to the reaction mixture afforded the product with 14% ee of the opposite enantiomer than expected for the product catalyzed reaction reported by Mauksch and Tsogoeva (Table 1, entry 2). In this case the small amount of L-proline that is present in the reaction mixture controls the outcome of the reaction completely. Addition of only 1 mol% of D-proline in conjuction with \( (R)-13 \) (15 mol%, 95% ee) to the reaction mixture afforded the chiral product with high ee, likely as a result of proline catalysis (Table 1, entry 3). To summarize, these experiments show that trace amounts of proline have a profound effect on the enantiomeric excess of the reaction and determine the outcome of the reaction completely. Furthermore, addition of only \( (R)-13 \) (15 mol%, 95% ee) to the reaction mixture, in our hands, seems to have no effect on the product formation.

Table 1  Effect of the addition of trace amounts of L- or D-proline on the reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>Product 13 ee (%)</th>
<th>Corrected ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R)-13)</td>
<td>40</td>
<td>36 (R)</td>
<td>0.6 (R)</td>
</tr>
<tr>
<td>2</td>
<td>((R)-13) + L-proline</td>
<td>40</td>
<td>14 (S)</td>
<td>79 (S)</td>
</tr>
<tr>
<td>3</td>
<td>((R)-13) + D-proline</td>
<td>39</td>
<td>90 (R)</td>
<td>87 (R)</td>
</tr>
</tbody>
</table>

* Conditions: 12 (0.188 mmol) in dry acetone (0.78 mL), \((R)-13\) (15 mol%, 95% ee), 25 °C, 4 days. Entry 2-3, L- or D-proline (1 mol%) was added at t=0. Isolated yield including initially added product. Enantiomeric excess determined by chiral HPLC analysis (See Experimental Section). Absolute configuration determined by comparison with literature data (See Experimental Section). Corrected ee values were determined using equation 1.

Intrigued by these findings, we decide to follow the reaction in time using different amounts of D-proline (Figure 3). In general, proline catalyzed reactions are carried out with relatively high catalyst loading (>15 mol%). Surprisingly, there was only a small difference in reaction rate using 5 mol% compared to 10 mol% of D-proline. In these cases the conversion of the starting material was almost complete after only 12 h. Lowering the catalyst loading even further (1 mol% of D-proline) gave ~80% conversion of \( \alpha \)-iminoester 12 after 3 days. It is interesting to note that the initial conversion of starting material is very fast and then levels off. The resulting curve can be explained by a combination of proline-catalyzed product formation and degradation of the starting material. Furthermore, even a substrate to catalyst ratio of 1000:1 provided almost 60% conversion of the starting...
material in 4 days similar to the conversion observed by Mauksch and Tsogoeva.\textsuperscript{42} These experiments show that even minute quantities of residual proline can catalyze the Mannich reaction in an impressive manner.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{conversion_plot.png}
\caption{D-proline catalyzed Mannich reaction of 12 with acetone to product 13. The conversion of $\alpha$-iminoester 12 was monitored by the decrease of the absorbance at 1163 cm\textsuperscript{-1} in the Raman spectrum (see Figure 1).}
\end{figure}

Amedjkouh and Brandberg reported that water has an influence on product formation in similar systems.\textsuperscript{55} So far, all the reactions were carried out using dry acetone and both the starting material, $\alpha$-iminoester 12, as well as product 13 added to the reaction were stored under inert atmosphere in the glovebox (see section 7.3.1). Addition of water (0.15 – 2.0 eq) showed a slight increase in the rate of conversion of the starting material, $\alpha$-iminoester 12, in both the blank reaction (without additional 13 added) as well as the reaction in which 15 mol\% of 13 was added. Analysis using high performance liquid chromatography (HPLC) and thin layer chromatography (TLC) revealed however that this increase in conversion was caused by an increase of hydrolysis of $\alpha$-iminoester 12 leading to higher quantities of $p$-anisidine 15 and not to an increase in the formation of Mannich product 13.
7.3.3 Influence of work-up procedure on the purity of product 13

Mauksch and Tsogoeva et al. reported a slightly different work-up procedure for the proline-catalyzed synthesis of enantiopure 13 compared to the original procedure reported by Barbas III et al. in 2002. As another control experiment we decided to perform the proline-catalyzed Mannich reaction as described by Barbas III et al., split the reaction mixture in two equal portions and perform both work-up procedures and analyze the purity of the products by elemental analysis (Table 2).

<table>
<thead>
<tr>
<th>Work-up procedure:</th>
<th>Barbas III et al.44</th>
<th>Mauksch and Tsogoeva et al.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Quench with aq. NH₄Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Extract with EtOAc (3x)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dry organic layer (MgSO₄)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Filter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Concentrate in vacuo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Column chromatography (n-pentane:Et₂O, 3:1 – 1:1)</td>
<td>- Concentrate in vacuo</td>
<td></td>
</tr>
<tr>
<td>- Column chromatography (n-pentane:EtOAc:DCM, 1:1:1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcd:</th>
<th>Found:</th>
<th>Found:</th>
</tr>
</thead>
<tbody>
<tr>
<td>%C 63.38</td>
<td>63.57</td>
<td>64.01</td>
</tr>
<tr>
<td>%H 7.22</td>
<td>7.29</td>
<td>7.25</td>
</tr>
<tr>
<td>%N 5.28</td>
<td>5.39</td>
<td>5.54</td>
</tr>
<tr>
<td>%C 63.59</td>
<td>64.05</td>
<td>64.05</td>
</tr>
<tr>
<td>%H 7.19</td>
<td>7.32</td>
<td>7.33</td>
</tr>
<tr>
<td>%N 5.40</td>
<td>5.56</td>
<td>5.56</td>
</tr>
</tbody>
</table>

Although the product isolated after both work-up procedures is pure by ¹H-NMR spectroscopy, the elemental analysis shows that the product obtained after the work-up procedure by Barbas III et al. has a higher purity than the product obtained using the work-up procedure described by Mauksch and Tsogoeva et al. (Table 2).

Furthermore, a clear difference in color was observed for product 13 after the two different work-up procedures. Using the original procedure described by Barbas III et al., product 13 was isolated as a pale yellow oil whereas the other work-up procedure provided the product as a brown oil. These observations indicate that the work-up procedure has an influence on the purity of the product and it also proves that the product 13 that was used in our attempts to reproduce the autocatalytic Mannich reaction reported by Mauksch and Tsogoeva et al. is analytically pure.
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7.3.4 Monitoring the reaction in time using $^1$H-NMR spectroscopy

In order to explain the initial lag period observed in the conversion in the absence of proline (Figure 2) and to gain further insight into the course of the reaction, we decided to follow the reaction in time using $^1$H-NMR spectroscopy and isotopic labeling (Table 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>Solvent</th>
<th>Acetone</th>
<th>Expected product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>acetone-$d_6$</td>
<td>-</td>
<td>13-$d_5$</td>
</tr>
<tr>
<td>2</td>
<td>(S)-13</td>
<td>15 mol%</td>
<td>acetone-$d_6$</td>
<td>-</td>
<td>13-$d_5$</td>
</tr>
<tr>
<td>3</td>
<td>13-$d_5$</td>
<td>15 mol%</td>
<td>acetone-$d_6$</td>
<td>-</td>
<td>13-$d_5$</td>
</tr>
<tr>
<td>4</td>
<td>13-$d_5$</td>
<td>50 mol%</td>
<td>DMSO-$d_6$</td>
<td>5 eq</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>(S)-13</td>
<td>15 mol%</td>
<td>DMSO-$d_6$</td>
<td>3 eq</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 3 Study of the Mannich reaction in time using $^1$H-NMR spectroscopy.$^a$

Initially, the Mannich reaction without additional product 13 was studied in acetone-$d_6$ in an NMR tube fitted with a capillary tube containing tetramethylsilane in acetone-$d_6$ as an internal standard. The expected product from this reaction would be deuterated product 13-$d_5$. The spectrum at $t = 0$ days shows $\alpha$-iminoester 12 in acetone-$d_6$ (Figure 4). Following the reaction between $\alpha$-iminoester 12 and acetone-$d_6$ in time by $^1$H-NMR showed that in the initial three days no reaction takes place. Between three to nine days an increase in the amount of a complex mixture of degradation products, originating from the starting material, was observed in the $^1$H-NMR spectra. It is possible that the product that was isolated in earlier experiments (i.e. Table 1, entry 1) is formed in the work-up following Mauksch and Tsogoeva’s protocol, which consists of evaporation of the solvent in vacuo at elevated temperature using rotatory evaporation (see work-up procedure, Table 2).
Figure 4 $^1$H-NMR study of the reaction of $\alpha$-iminoester 12 (0.188 mmol) with acetone-\textit{d}6 (0.8 mL) monitored for 9 d (one spectrum per day was taken) at room temperature in an NMR tube fitted with a capillary containing tetramethylsilane in acetone-\textit{d}6 serving as internal standard. See Table 2, entry 1. A spectrum of the expected product 13-\textit{d}5 in CDCl$_3$ is added for comparison.

Addition of 15 mol % of (S)-13 to the reaction of $\alpha$-iminoester 12 with acetone-\textit{d}6 gave a similar result compared to the reaction in which no additional product 13 was added (Table 2, entry 2). After three to four days a decrease in 12 was observed in the $^1$H-NMR. At the same time the appearance of a complex mixture of degradation products was observed. The formation of the product was not observed under these conditions (Figure 5).
Figure 5 1H-NMR study of the reaction of \( \alpha \)-iminoester 12 (0.188 mmol) with acetone-d₆ (0.8 mL) in the presence of 15 mol% of (S)-13 monitored for 6 d (one spectrum per day was taken) at room temperature in an NMR tube. See Table 2, entry 2. A spectrum of the expected product 13-d5 in CDCl₃ is added for comparison.

The same effect was also observed when deuterated product 13-d5 (15 mol%) was added to \( \alpha \)-iminoester 12 in deuterated acetone (Table 2, entry 3). Product 13-d5 was synthesized in an L-proline catalyzed reaction of 12 with acetone-d₆ and the product was isolated in 72% yield with 90% ee and >95 atom% D (Scheme 10). After four days a decrease in the amount of \( \alpha \)-iminoester 12 was observed together with the appearance of degradation products (Figure 6). These observations can explain the initial lag phase that was observed in the Raman experiments (Figure 2, section 7.3.2). Initially, no reaction takes place and after approximately four days the starting material starts to degrade leading to the time profile seen in Figure 2.
Scheme 10  Synthesis of 13-d5 in a L-proline catalyzed reaction with acetone-d6.

Figure 6  \(^1\text{H-NMR}\) study of the reaction of \(\alpha\)-iminoester 12 (0.188 mmol) with acetone-d6 (0.8 mL) in the presence of 15 mol% of 13-d5 monitored for 6 d (one spectrum per day was taken) at room temperature in an NMR tube. See Table 2, entry 3. A spectrum of the expected product 13-d5 in CDCl\(_3\) is added for comparison.
Because a kinetic isotope effect on the reaction could not be excluded, the Mannich reaction was also carried out adding five equivalents of acetone to α-iminoester 12 with a very high loading of 13-d5 (50 mol%) in DMSO-d6 and followed by 1H-NMR over 8 days (Figure 7). In the original article, Maucksch and Tsogoeva reported that the Mannich reaction also works well in DMSO. If product 13 would be formed in this experiment it is clearly distinguishable from the deuterated product 13-d5 by the appearance of a doublet at 2.86 ppm (J = 8 Hz) originating from 13 (see also Figure 8). Although the starting material 12 appears to be much more stable in DMSO-d6 compared to acetone-d6, no traces of product formation were observed.

**Figure 7** 1H-NMR study of the reaction of α-iminoester 12 (0.188 mmol) with acetone (5 eq) in the presence of 50 mol% of 13-d5 in DMSO-d6 (0.8 mL) monitored for 8 d (one spectrum per day was taken) at room temperature in an NMR tube. See Table 2, entry 4. A spectrum of α-iminoester 12 in DMSO-d6 is added for clarity.

To exclude the influence of using deuterated product 13-d5 as catalyst, non-deuterated Mannich product (S)-13 (15 mol%) was added to α-iminoester 12 together with three equivalents of acetone in DMSO-d6 in the final 1H-NMR experiment that was carried out (Figure 8). A similar result was observed; even after seven days there were no signs of additional Mannich product formation.
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7.4 Conclusion

In conclusion, the combined spectroscopic data from the Raman studies and the $^{1}$H-NMR spectra, presented in this chapter, indicate that the Mannich reaction of $\alpha$-iminoester 12 and acetone is not catalyzed by the Mannich product 13. Several control experiments were performed demonstrating that addition of various amounts of product 13, which was also synthesized via two alternative synthetic routes, does not accelerate the formation of the product. Elemental analysis showed that product 13 was analytically pure and that the workup procedure has an influence on product purity. Moreover, it was established that trace amounts of proline as low as 0.1 mol% were able to catalyze the Mannich reaction of acetone and $\alpha$-iminoester 12 to product 13 in a satisfactory manner indicating that potential contamination of 13 cannot be excluded as a possible origin of the reported autocatalytic effect observed in the original communication by Mauksch and Tsogoeva.42

Figure 8 $^{1}$H-NMR study of the reaction of $\alpha$-iminoester 12 (0.188 mmol) with acetone (3 eq) in the presence of 15 mol% of (S)-13 in DMSO-d$_{6}$ (0.8 mL) monitored for 7 d (one spectrum per day was taken) at room temperature in an NMR tube. See Table 2, entry 5. A spectrum of $\alpha$-iminoester 12 in DMSO-d$_{6}$ is added for clarity.
7.5 Experimental Section

General Experimental

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and cerium/molybdenum or potassium permanganate staining. Raman spectra were recorded using a fibre optic equipped dispersive Raman spectrometer (785 nm, Perkin Elmer RamanFlex). Mass spectra were recorded on an AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). $^1$H- and $^{13}$C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian VXR300 (300 and 75 MHz, respectively) using either CDCl$_3$, DMSO-$d_6$ or acetone-$d_6$ as a solvent. Chemical shifts are denoted relative to the residual solvent absorption ($^1$H: CDCl$_3$ 7.26 ppm, DMSO-$d_6$ 2.50 ppm, acetone-$d_6$ 2.05 ppm; $^{13}$C: CDCl$_3$ 77.0 ppm DMSO-$d_6$ 39.52 ppm, acetone-$d_6$ 29.84 ppm). 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 HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10A VP diode array detector. Elemental analysis was performed on an EuroVector Euro EA-3000 Elemental Analyzer.

Acetone was dried and distilled over potassium carbonate. Ethyl glyoxalate (~50 wt% in toluene) was purchased from Sigma-Aldrich, and used without further purification. $p$-Anisidine (99%) was purchased from Fluka and recrystallized from water and isolated as white needles. $^{53}$ D-proline (99%), L-proline (99%) and DL-proline (99%) were purchased from Sigma-Aldrich.
Synthesis of ethyl 2-((4-methoxyphenyl)imino)acetate 12

Ethyl glyoxalate 14 (8.38 g, 40 mmol, ~50 wt% in toluene) was dissolved in freshly distilled dichloromethane (150 mL). A solution of p-anisidine 15 (1 eq, 4.92 g, 40 mmol) in dichloromethane (50 mL) was added dropwise and the mixture was stirred for 30 min followed by addition of molecular sieves (4 Å). After stirring overnight the reaction mixture was filtered, the solvent evaporated and the crude product purified by column chromatography on silica using dichloromethane as the eluent to give the 12 as a bright yellow oil (7.07 g, 34.1 mmol, 85% yield). The product was stored under nitrogen atmosphere in the glovebox to prevent degradation. The physical data were identical in all respects to those previously reported.44

General procedure for the synthesis of 13 catalyzed by proline44

In a typical experiment, ethyl 2-((4-methoxyphenyl)imino)acetate 12 (207 mg, 1 mmol) was dissolved in anhydrous acetone (10 mL). Proline (D-, L-, or DL-; 0.2 mmol, 23 mg, 20 mol%) was added and the mixture was stirred for 24h at room temperature. After aqueous work-up with a half-saturated aqueous ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried with magnesium sulfate, filtered, concentrated and the residue purified by column chromatography on silica (n-pentane/diethyl ether, 3:1-1:1) to afford ethyl 2-((4-methoxyphenyl)amino)-4-oxopentanoate 13 as a light yellow oil (72-
78% yield). The enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD column, 1.0 mL/min, \( n \)-heptane/propan-2-ol 95:5, 40 °C, 240 nm retention times (min): 17.0 (R) and 19.8 (S). The product was stored under inert atmosphere in the glovebox to prevent degradation. The physical data were identical in all aspects to those previously reported.\(^{44}\) Anal. Calcd for \( \text{C}_\text{14}\text{H}_{19}\text{NO}_4 \): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.57; H, 7.19; N, 5.39.

**General procedure for the Mannich reaction of 12 with acetone in the absence of proline**

In a typical experiment, ethyl 2-((4-methoxyphenyl)imino)acetate 12 (39 mg, 0.188 mmol) was dissolved in anhydrous acetone (0.78 mL). Product 3 (15 mol%, 0.028 mmol, 7.49 mg) was added and the mixture was stirred for 4 d at room temperature. The progress of the reaction was monitored *in situ* by Raman spectroscopy to follow the conversion of starting material. The reaction mixture was concentrated and the residue purified by column chromatography on silica (\( n \)-pentane:diethyl ether 3:1-1:1) and the enantiomeric excess of 13 was determined by chiral HPLC analysis, Chiralcel OD column, 1.0 mL/min, \( n \)-heptane/propan-2-ol 95:5, 40 °C, 240 nm retention times (min): 17.0 (R) and 19.8 (S). The product was stored under inert atmosphere in the glovebox to prevent degradation. The physical data were identical in all aspects to those previously reported.\(^{42, 44}\)

**Alternative proline-free synthetic routes for the synthesis of ethyl (2-((4-methoxyphenyl)amino)-4-oxopentanoate 13**

a) **Synthesis of rac-13a starting from 16**

![Diagram](attachment:image.png)

Ethyl 2,4-dioxopentanoate 16 (2.06 g, 12.65 mmol) and \( p \)-anisidine 15 (1.56 g, 12.65 mmol, 1 eq) were dissolved in toluene (50 mL) and the reaction mixture was heated at reflux for 60 h using a dean-stark trap to remove water. The solvent was evaporated and the crude product purified by column chromatography on silica (3:1 \( n \)-pentane:diethyl ether) to give pure (Z)-ethyl 2-((4-methoxyphenyl)amino)-4-oxopent-2-enoate 17 (2.44 g, 9.27 mmol, 73 % yield) as a yellow crystalline solid, mp = 70 °C. \(^1\)H NMR 400 MHz, CDCl\(_3\) \( \delta \) 11.39 (s, 1H), 6.93 (d, \( J \) = 8.8 Hz, 2H), 6.82 (d, \( J \) = 8.8 Hz, 2H), 5.61 (s, 1H), 4.12 (q, \( J \) = 7.1 Hz,
2H), 3.78 (s, 3H), 2.20 (s, 3H), 1.07 (t, J = 7.1 Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.9, 163.4, 157.3, 149.2, 132.7, 123.7, 114.3, 98.8, 62.0, 55.4, 30.0, 13.7 ppm. HRMS (ESI+, m/z): calcd for C\(_{14}\)H\(_{18}\)NO\(_4\) [M+H]\(^+\): 264.12303; found: 264.12250. (Z)-ethyl 2-(4-methoxyphenylamino)-4-oxopent-2-enoate 17 (263 mg, 1.0 mmol) was dissolved in ethanol (4.0 ml) and ethyl acetate (4.0 ml) under nitrogen in a dry flask and palladium on carbon 10 wt% (21.26 mg, 0.02 mmol, 2 mol%) was added. The reaction mixture was put under a hydrogen atmosphere (1 bar) using a balloon and stirred overnight. The reaction mixture was filtered over Celite and the Celite was washed with ethyl acetate. The solvent was evaporated and the crude product was purified by column chromatography on silica (\(n\)-pentane/diethyl ether, 4:1-1:1) to yield ethyl 2-((4-methoxyphenyl)amino)-4-oxopentanoate rac-13a as a pale yellow oil (108 mg, 0.41 mmol, 41% yield). The product was stored under inert atmosphere in the glovebox to prevent degradation. The physical data were identical in all aspects to those previously reported by Barbas III et al.\(^44\)

**b) Synthesis of rac-13b starting from 18**

![Reaction diagram]

Ethyl levulinate 18 (0.2 mol, 28.8 g) was dissolved in chloroform (150 mL) under nitrogen at room temperature. A solution of bromine (1.11 eq, 0.222 mol, 35.5 g, 11.4 mL) in chloroform (25 mL) was added dropwise over 1 h. The reaction mixture was cooled to 0 °C and triethylamine (3.2 eq, 0.65 mol, 65.5 g, 90 mL) was added dropwise over 1 h. After stirring for another hour at 0 °C, the reaction mixture was subsequently washed with water, aqueous HCL (1.0 M) and brine and the organic layer dried with Na\(_2\)SO\(_4\) and filtered. Chloroform was removed by rotatory evaporation and the concentrate was distilled under reduced pressure (bp = 55 °C at 1.5 mbar) to give the product which was purified further by column chromatography on silica (\(n\)-pentane/diethyl ether, 96:4) to give (E)-ethyl 4-oxopent-2-enoate 19 as a colorless liquid (35% yield, 0.07 mol, 9.95 g). The physical data were identical in all aspects to those previously reported.\(^57\) (E)-ethyl 4-oxopent-2-enoate 19 (284 mg, 2.0 mmol) was dissolved in dry acetone (8 ml) in a Schlenck vessel. Upon addition of \(p\)-anisidine 15 (246 mg, 2.0 mmol, 1 eq) the color changed from colorless to yellow. Thin layer chromatography showed complete conversion after 60 min (\(n\)-pentane:diethyl ether, 1:1). The reaction was quenched with a half-saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3x10 mL). The organic layers were dried with sodium sulfate and the solvent was evaporated. The crude
product was purified by column chromatography on silica (n-pentane:diethyl ether, 3:1-1:1). After column chromatography residual p-anisidine was removed by dissolving in an aqueous HCl solution (pH=1) extraction with ethyl acetate (3x10 mL). The organic layer was dried with sodium sulfate and the solvent evaporated to yield pure ethyl 2-((4-methoxyphenyl)amino)-4-oxopentanoate rac-13b (386.6 mg, 1.46 mmol, 73 % yield) as a pale yellow oil. The product was stored under inert atmosphere in the glovebox to prevent degradation. The physical data were identical in all aspects to those previously reported.44

Synthesis of 13-d5

Ethyl 2-((4-methoxyphenyl)imino)acetate 12 (80 mg, 0.39 mmol) was dissolved in acetone-d6 (4 mL). L-proline (8.9 mg, 0.077 mmol, 20 mol%) was added and the mixture was stirred for 24h at room temperature. After aqueous work-up with a half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried with magnesium sulfate, filtered, concentrated and the residue purified by column chromatography on silica (n-pentane:diethyl ether 3:1-1:1) to afford ethyl 2-((4-methoxyphenyl)amino)-4-oxopentanoate-d5 13-d5 (76 mg, 0.28 mmol, 72% yield, 90% ee, >95 atom% D) as a light yellow oil. 1H NMR (400 MHz, CDCl3) δ 6.75 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 8.9 Hz, 2H), 4.31 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H) ppm. 1H NMR (400 MHz, DMSO-d6) δ. 13C NMR (100 MHz, CDCl3) δ 206.0, 172.9, 153.0, 140.5, 115.7, 114.8, 61.4, 55.6, 54.1, 45.8-44.7 (m), 30.4-28.9 (m), 14.1 ppm. HRMS (ESI+, m/z): calcd for C14H15D5NO4 [M+H]+: 271.1691; found: 271.1700. The enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD column, 1.0 mL/min, n-heptane/ propan-2-ol 95:5, 40 °C, 250 nm retention times (min): 14.6 (minor) and 16.9 (major).
7.6 References

(48) Feringa, B. L. *Chemia* **2006**, *60*, 90.
(56) Formation of trace amounts of product 13 (<5%) can not be excluded.