Cross-Catalysis between Self-Replicators of Different Handedness

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Enantioselective auto- and cross catalytic reactions

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CHAPTER 1

Introduction

1.1 Asymmetric Autocatalysis and self-replication

An understanding of how life began remains a formidable challenge for the whole scientific community thus driving considerable experimental research efforts in mimicking biological systems.[1–4] Replication is the fundamental driving force in all living organisms and emerges from complex molecular networks of self-organized and dynamically interacting biomolecules. Several mechanisms have been proposed for the transition from relatively simple self-replicative molecular systems to the complex biochemistry of life to explain prebiotic chemical evolution, such as the emergence of the pre-"RNA world", "hypercyclic systems", "systems chemistry" and so on, with self-replication centered as a key process. [1–7]

In addition to self-replicating capability, a vital characteristic of the biomolecules is homochirality (L-amino acids and D-sugars). The origin of homochirality is directly associated with the 'origin of life' question.[8] In the synthetic self-replicating systems developed over the last twenty years, homochirality has been predefined with the precursors employed being homochiral, i.e. no asymmetric centre is formed during the reaction. When considering the earliest stages of biomolecular evolution, it is improbable that the development of life began from complex homochiral biomolecules. Thus, many hypotheses were proposed in an attempt to explain possible prebiotic chemical pathways towards the asymmetric formation of the smallest chiral biomolecules.[9] From the chemical perspective, molecular self-replication processes function via autocatalytic, cross catalytic or collectively catalytic pathways with an additional information transfer (templating) from the product to the precursors (Figure 1).

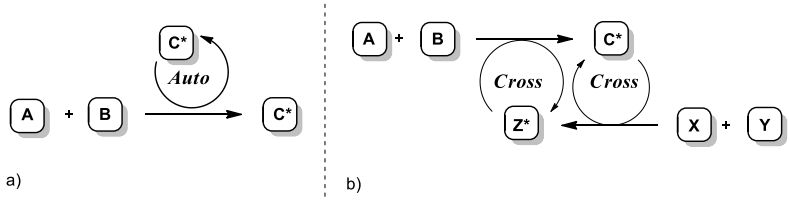
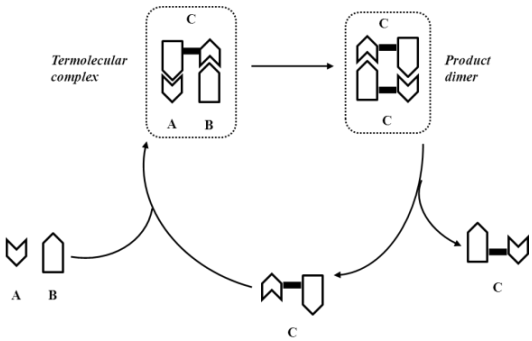


Figure 1 *- a) Autocatalytic reaction, b) Cross catalytic reaction.*

It has been proposed that, in the earliest stages of life, if small prebiotic molecules were catalytically active then small chiral imbalances would be amplified via auto or cross catalytic processes.[10] Over the last two decades, only two asymmetric autocatalytic reactions have been developed.[10–14]

1. 2 Design of a self-replicating system

The design of a non-natural compound, capable of a self-replication, represents a great challenge for chemists. In order to achieve self-replication, the designed system must satisfy at least two conditions: 1) The recognition site should be separated enough to prevent the template from binding to itself, but sufficiently close to allow for efficient ligation of reaction partners to occur; 2) the template should bind strongly to the fragments in order to enable catalysis, but weakly to itself to prevent product inhibition. These are demanding restraints on the design of self-replicating systems. For a minimal self-replicating system (Scheme 1), during the initial stage of the reaction, the product **C** is formed slowly through a bimolecular channel, resulting in an induction or lag period at the start of the reaction.



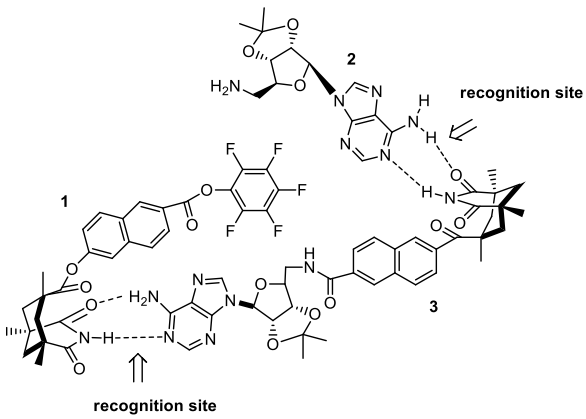
Scheme 1 *- General scheme for template replicators.*

Once the concentration of **C** is sufficient to form the ternary complex [**A**·**C**·**B**], the autocatalytic cycle starts to operate. After each turn of the cycle, a double amount of template is present in solution and the product concentration will increase exponentially, before reaching a plateau corresponding to the complete conversion of the reagents. The concentration time profile of a self-replicating system will show an "S" or sigmoidal shaped curve. In order to prove that a system is self-replicating, some control experiment are required. At first, it is necessary to select a control compound that has the same chemical functionality as the replicator, but does not participate in any recognition mediated process (i.e. whereby the recognition site is obstructed or removed). Secondly, it is important to demonstrate the reliance of the reaction on molecular recognition: The use of an unreactive compound, which is capable of binding to a competitive inhibitor, will interfere with the autocatalytic cycle and, as a result, the rate of the reaction will decrease and a sigmoidal profile will not be observed.

The final and critical experiment is the "seeding" or "doping" experiment. The addition of a pre-synthesized product/template at the beginning of the reaction should result in a loss of the initial lag period in the rate profile of the reaction.

1.2.1 Non enzymatic self-replicating systems

Several self-replicating systems have been developed mainly based on biomolecules taking the advantage of their properties already. Design of self-replicating systems based on purely synthetic molecules is far more challenging. The concept of a non-enzymatic self-replicating system was established by von Kiedrowski in 1986.[15] However, the first example of a self-replicating system, using small organic molecules, was described by Rebek *et al*. [16,17] They developed a system based on the formation of the amide bond in the ligation step,[18–25] and found that the reaction between the ester **1** and the amine **2** exhibited autocatalytic behavior towards the formation of product **3** (Scheme 2). They also demonstrated the importance of the size of the spacer in the product, between the ester building blocks, whereby the naphthyl spacer was preferred over the phenyl spacer, to produce a more efficient self-replicating system.

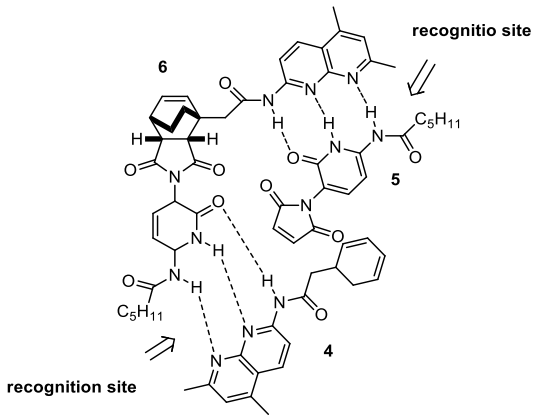


Scheme 2 *- Rebek system: termolecular complex; reactants and template.*

The seeding experiment showed acceleration in the initial rate of the reaction, but a sigmoidal profile was not observed. The addition of a competitive inhibitor was also tested: One equivalent of 2,6-bis(acylamino)pyridine was added to the reaction mixture and the reaction slowed down dramatically, showing the necessity for the free NH to coordinate to the recognition site in order to enhance the rate of the reaction (Scheme 2).

In the 1990s, Rebek's system was subject to many controversies. Studies carried out by the group of Manger[26] showed that a simple amide can also catalyze the reaction between **1** and **2**. They also demonstrated that **3**[27] can accelerate the reaction of **2** with other esters which are not capable of hydrogen bonding. Further kinetic studies[28] showed that all of the species formed during the reaction contribute to the product formation and they are concentration dependent. From these studies they concluded that the reaction between **1** and **2**, in presence of the template **3**, can operate through a self-replication pathway.

In 1997, the group of Sutherland and Wang[29] reported a Diels-Alder reaction, template directed between the diene **4** and maleimide **5** (Scheme 3).



Scheme 3 *- Wang and Sutherland system: termolecular complex; reactants and template.*

The recognition sites in this system are provided by the naphthyridine moiety present in **4** and the 2-piridone present in **5**. This system satisfies the requirements for a self-replicating system. Some aspects concerning the stereochemistry were not addressed in the work of 1997,[29] since the use of a racemic diene **4** could give rise to many diastereoisomeric reactions and the cycloadduct **6** was assumed to be *endo*. In 2005, studies carried by von Kiedrowski[5] demonstrated that the approximations reported by Sutherland are reasonable, since experiments carried out on similar substrates did not show the formation of any *exo* cycloadduct. A common limitation present in all of these systems is that, when the concentration of the template is too high, the template itself does not recognize the molecules of the reactants, and instead, begins to interact with other molecules of the template. This results in product inhibition, which is observed by a parabolic rate of the reaction instead of the expected exponential product growth.[29,30]

Another point to mention is that, in all of these synthetic self-replicating systems developed over the last twenty years, homochirality has been predefined with the precursors employed being homochiral, i.e. no asymmetric centre is formed during the reaction.

1.3 Small molecule replication with symmetry breaking-asymmetric autocatalysis

L-Amino acids and D-sugars are the main carriers of homochirality in living organisms.[31] One of the widely accepted hypotheses for the origin of homochirality is astrochemically relevant and based on the fact that only an excess of left-handed L-amino acids have been found in carbonaceous meteorites.[32–35] Intriguingly, enantiomeric excess was found only for non-proteinogenic quaternary amino acids and racemic of L- and D-forms for proteinogenic ternary amino acids. This is indeed not surprising, taking into account that proteinogenic amino acids are prone to rapid racemization under aqueous or radiogenic conditions. It is important to note that quaternary amino acids are free of this problem. Preferential excess of L-amino acid found in carbonaceous meteorites may arguably indicate that the origin of life on the earth has an extraterrestrial input. But to get homochirality in life there would need to be some mechanism of transferring the single-handedness between different types of amino acids. An important question is how this initial preference was further amplified.

Several mechanisms have been proposed to explain the emergence of homochirality in the absence of the asymmetric influence such as stochastic fluctuations, circularly polarized light or chiral surfaces such as quartz.

In 1953 Franck[36] developed a model to explain the amplification of a small initial asymmetry and noted that the autocatalytic process has to be operative in such a system. According to this model, in order to achieve asymmetric amplification, the process of self-replication of a catalyst must be accompanied by the suppression of the activity of its enantiomer, referred to by Frank as mutual antagonism (Figure 2).[36]

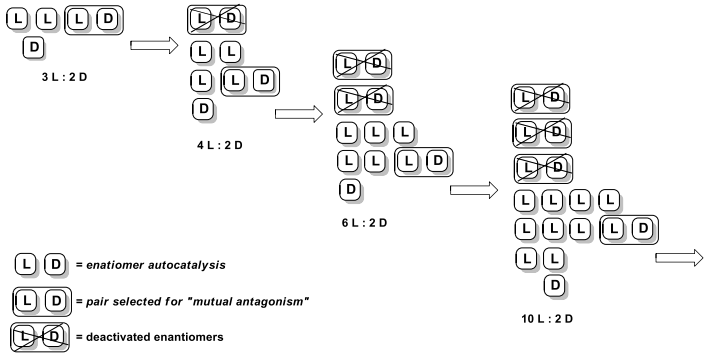


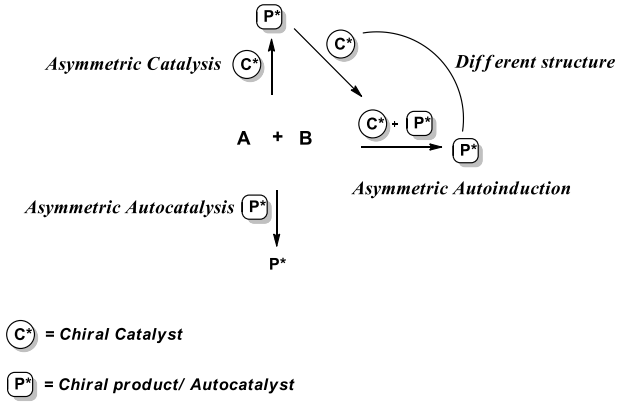
Figure 2 *- Schematic representation of Frank's model based on the autocatalysis and mutual antagonism.*

L and D are the enantiomers which can act as autocatalysts for their own formation, by reacting with molecules of substrate.[37] Together with this autocatalytic process, there is a mutual antagonism between L and D such that, when they react together, they deactivate and lose their self-replicating property. As shown in Figure 2, the self-replication of the enantiomers cause a change in the D:L ratio, which grows as long as there was a small initial imbalance at the beginning of the process. The cooperation of the autocatalysis and mutual antagonism propagate and amplify the imbalance of the enantiomers. If the substrate pool is large enough, the process can be sustained and the selectivity towards the self-production of one enantiomer will dominate.

The actual term of *asymmetric autocatalysis* was coined by Wynberg, who very early acknowledged the great potential of a system where the chiral product catalyzes its own asymmetric synthesis.[38] Already in 1989 he was postulating the question if asymmetric autocatalysis would represent the next generation in asymmetric catalysis.[38,39]

1.4 Asymmetric autoinduction

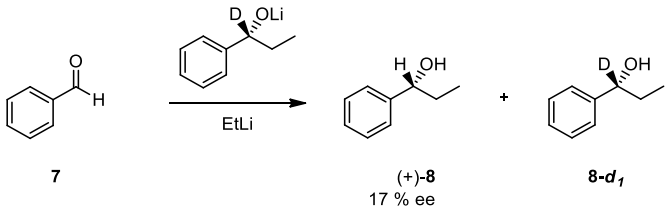
Asymmetric autoinduction (Scheme 4): a chiral product that does not possess catalytic activity participates in the formation of a chiral complex with the enantioselective catalyst to effect the asymmetric amplification.[38,40]



Scheme 4 *- Differences between asymmetric catalysis, asymmetric autoinduction and asymmetric autocatalysis.*

In asymmetric autoinduction, the product of the reaction modifies the further course of the reaction, by changing the nature of the reagent or the catalyst. The autoinduction can involve the formation of a product different from, or identical to, the catalyst. Asymmetric autocatalysis involves only the latest.

The first example of a reaction, where the product was found to influence the stereochemical outcome of the reaction, was reported by Wynberg *et al*. in 1989.[38,39] They showed that the product acted as a ligand for the intermediate complex that is formed during the reaction (Scheme 5).[39]

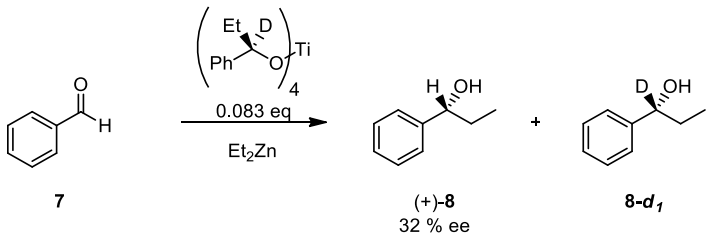


Scheme 5 *- Evidence of asymmetric autoinduction in the addition of EtLi to benzaldehyde using stoichiometric amount of product.*

In the first instance, they demonstrated the effect of adding the enriched (+)-(*R*)-1-phenyl-1-propanol-d_1 (**8-*d*$_1$**) (used in a stoichiometric amount) to the reaction of ethyllithium to benzaldehyde **6** (Scheme 5).

The deuterium labelled compound **8-*d*$_1$** was employed due to the fact that the *ee* was determined using ^{1}H-NMR spectroscopy, and in this way the *ee* of **8** could be determined separately in the mixture. The enantiomeric excess of (+)-**8** was found to be 17%. The effect of the product acting as a ligand on the stereochemical outcome of the reaction has been defined as "*the principle of the enantioselective autoinduction*",[38] and shows that aggregates containing both product and starting material influence the stereochemistry of the C-C bond formation.

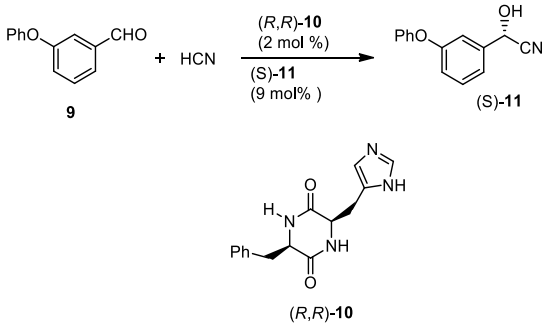
Subsequently, Wynberg *et al.* demonstrated that this autoinductive effect was also a factor in the addition of diethyl zinc to benzaldehyde, using a catalytic amount of compound **8-*d*$_1$** (Scheme 6).



Scheme 6 *- Asymmetric autoinduction in the addition of Et_2Zn to benzaldehyde using catalytic amount of product.*

A solution containing 1 mmol of **8-*d*$_1$** titanate intermediate was prepared by treating compound **8-*d*$_1$** and $TiCl_4$ in ether with Et_3N. This compound was added to a mixture containing 12 mmol of benzaldehyde **7**, in presence of 16 mmol of diethylzinc in toluene, and was left to react overnight. Following aqueous workup, the enantiomeric excess of compound (+)-**8** was found to be 32%. This significant discovery provided the foundation for the emergent field of asymmetric autocatalysis.

A few years later, another example of asymmetric autoinduction was reported by the group of Danda *et al*., in the asymmetric hydrocyanation of 3-phenoxybenzaldehyde **9**, in the presence of diketopiperazine (*R*,*R*)-**10**.[41] They established that the diketopiperazine is modified by the addition of the product (*S*)-**11**, forming the catalytically active species (Scheme 7).



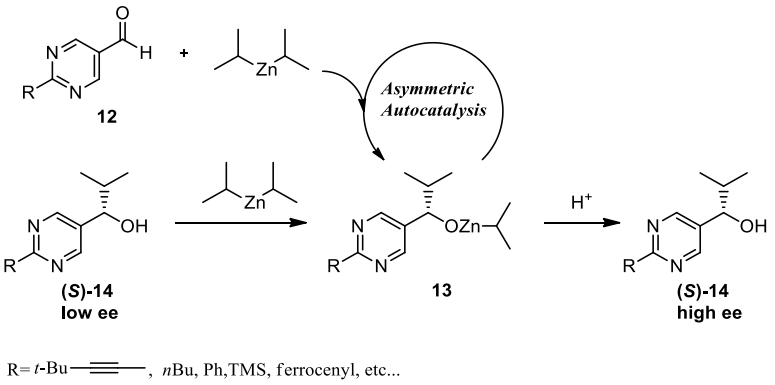
***Scheme 7** - Asymmetric autoinduction in the hydrocyanation of 3-phenoxybenzaldehyde **8** in the presence of diketopiperazine (R,R)-**10**.*

Using the enantiopure diketopiperazine *(R,R)-**10*** (2 mol%), the product (*S*)-**11** was obtained with 92% *ee*. Instead, using nearly racemic diketopiperazine *(R,R)-**10*** (2% *ee*) in the presence of 4 mol equivalents of (*S*)-**11** with 92 % *ee*, the new formed compound compound *(S)-**11*** was isolated with 81% *ee*. However, in the presence of 4 mol equivalents of (*R*)-**11** with 85 % *ee*, the (*R*)-**11** product was generated with 74% *ee*. This shows that the cyanohydrine (*R)*-**11** is the stereocontrolling factor in the reaction. Furthermore, they observed that the diketopiperazine with 2 % *ee* is almost inactive by itself, which could be due to the formation of a conglomerate in the *meso* inactive form. The addition of (*S*)-**11** gives the formation of a new species (*R,R*)-**10-**(S)-**11**, which is more catalytically active then (*R,R*)-**10** alone. In this way, the active catalyst is generated by the combination of the diketopiperazine and one enantiomer. They proved that both the complexes (*R,R*)-**10** (S)-**11** and (*S,S*)-**10** (*R*)-**11** are catalytically active. The results also suggest that asymmetric amplification can operate in this system since the *ee* of the product is higher than the *ee* of the two added compounds. Further mechanistic studies are required to prove the existence of this phenomena.

1.5 A unique example of Asymmetric Autocatalysis: Soai system

In Frank's model no actual compounds or reactions are mentioned but in 1995 Soai and coworkers experimentally demonstrated its feasibility by finding a reaction that satisfied the conditions of Frank's theoretical kinetic scheme. [42]

The reaction consisted of the addition of dialkyl zinc to 5-pirimidine carboxialdehyde **12** to form the intermediate alkoxide **13**. Upon hydrolysis, the chiral pyrimidyl alkanol **14** was obtained (Scheme 8).



Scheme 8 *- Soai system, asymmetric autocatalysis of (S)-**14** with amplification of ee.*

This reaction demonstrates autocatalytic behavior. The generated chiral intermediate **13** acts as a chiral ligand for the zinc reagent, which is consequently then activated and accelerates the nucleophilic attack. This phenomenon has been shown for the addition of dialkylzinc to different heteroaromatic aldehydes. Remarkably, when an aromatic aldehyde, substituted at the 2-position, was employed as a substrate, and nearly racemic heteroaromatic alcohol **14** as a catalyst (0.8 mol%, 0.00005 % *ee*), the newly formed product (*S*)-**14** was isolated with 57 % *ee*.[43] The effect of the substituent on the aromatic aldehyde is still not clear.[44]

Many efforts have been made to understand the exact mechanism of this reaction but no a clear explanation has been found thus far.[45–48]

The group of Blackmond and Brown[47,48] proposed a theoretical model, supported by kinetic studies, which shows a dynamic system where many species can be present (Figure 3). A tetrameric species **B** was hypothesized to be the transition state for the reaction, composed of four aldehyde/alkoxide molecules, and the catalytic active dimeric species **C** is a dimer consisting of two alkoxide molecules **13**.

During the enantioslective reaction, the association of these species with the aldehyde **12** forms a trimeric complex **A**. The exact structure of these species are not known.[47]

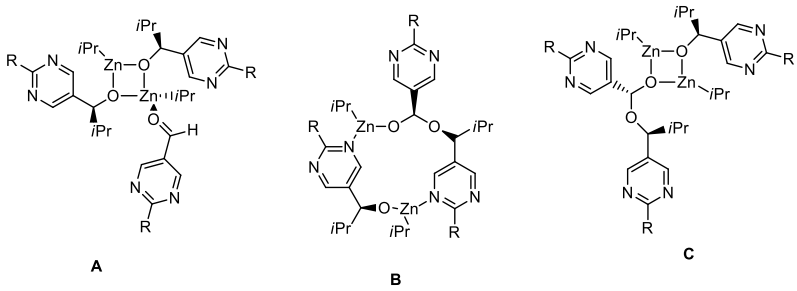
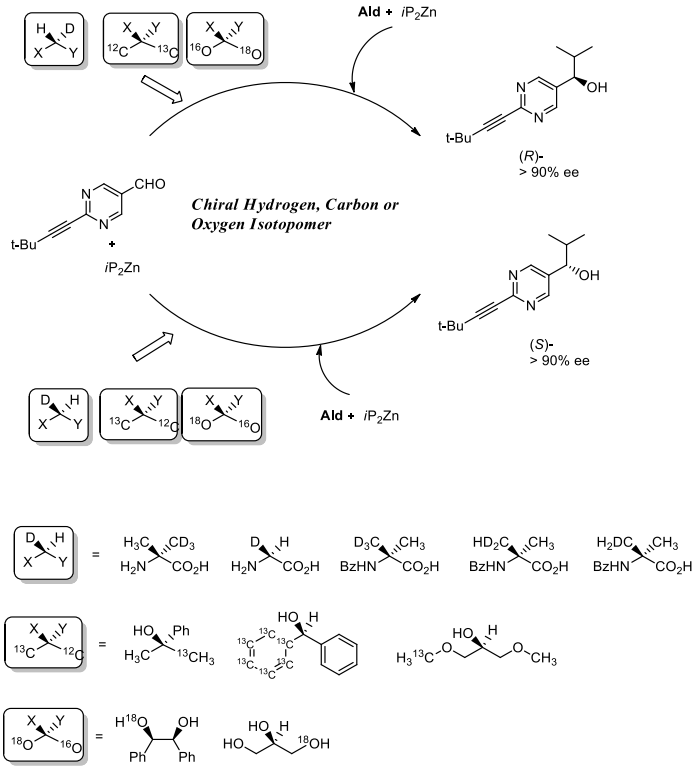


Figure 3 *- Possible active dimeric catalyst for the Soai system and probable trimeric complex precursor of the square core dimer* ***C****.*

Further studies showed that many chiral sources could trigger selectivity in this reaction:[43,49,50] Circular polarized light, chiral inorganic crystals of quartz, sodium chlorate, sodium bromate and cinnabar, chiral alcohols, amine, epoxides, esters, amino acids, [5]-[6]-helicenes and crystals with enantiomorphous faces.

Amongst the many different trigger sources that can induce chirality in the Soai system, an impressive example is the use of isotopically chiral compounds, such as; α-deuterobenzyl alcohol (0.05 mol%, >95% *ee*),[51] ^{13}C-labeled alcohol,[12] ^{18}O-labeled glycerin (Scheme 9).[52,53]

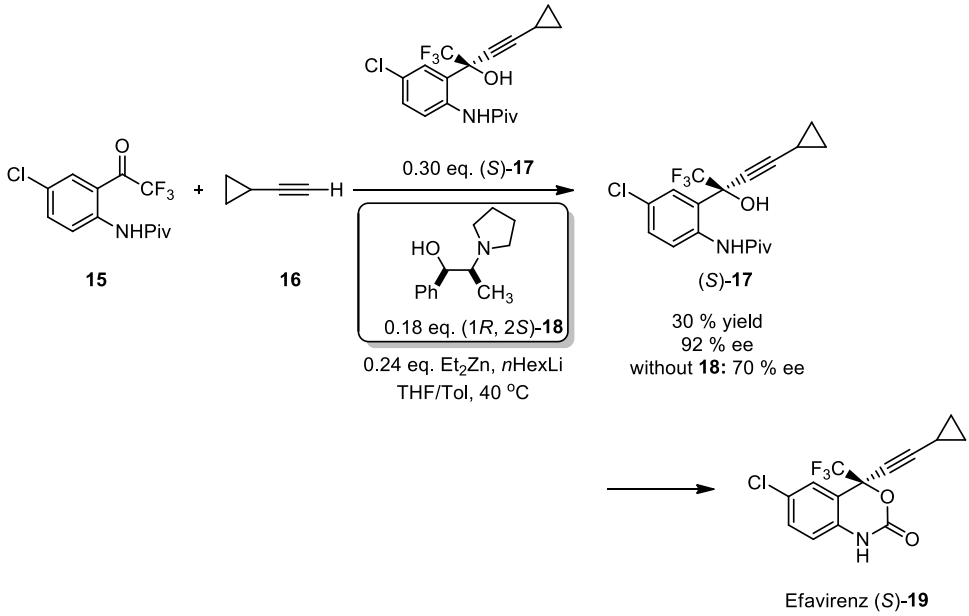


Scheme 9 *- Asymmetric autocatalysis triggered by chiral compounds arising from hydrogen, carbon and oxygen isotope substitution.*

One of the latest tools used to trigger selectivity is the use of single wall carbon nanotubes, with helical chirality as a chiral initiator for asymmetric autocatalysis.[54] Although there are a large variety of chiral triggers which can be used as a source of chirality, the Soai reaction is very specific, as only heteroaromatic aldehydes, together with diorganozinc, can be employed as reagents.

1.6 Carreira's example of enantioselective synthesis of Efavirenz by means of the autocatalytic formation of the key intermediate

A recent example of autocatalysis has been reported by Carreira.[55] The importance of this reaction is not only strictly related to asymmetric autocatalysis, but also because the product of this reaction relates to the synthesis of a key intermediate of the HIV treatment drug Efavirenz (*S*)-**19**,[56] (Scheme 10). In terms of asymmetric autocatalysis, this reaction does not show strong asymmetric amplification in comparison to that observed in Soai's system.



Scheme 10 *- Catalytic enantioselective synthesis of Efavirenz (S)-**19**.*

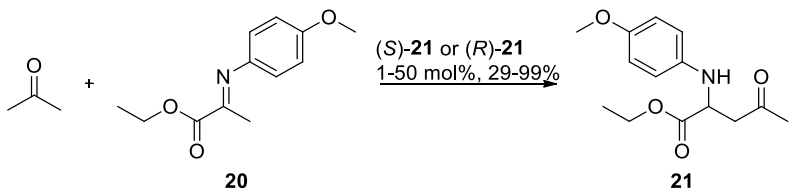
The formal synthesis of Efavirenz includes the use of stoichiometric amounts of reagents. From the work reported from Carreira *et al.*, the system has been optimized to work catalytically.[55] The reaction consist of the addition of a zinc acetylide to a ketone (Scheme 10), in order to obtain compound (*S*)-**17** in good yields and enantioselectivity (30 % yield, 92 % *ee*). To obtain this result, a combination of the product (*S*)-**17** (30 mol %) with the ligand (1*R*, 2S)-**18** (18 mol %) was necessary.

This is a clear example of autoinduction. When only the enantiopure compound (*S*)-**17** (24 mol %) was used as a catalyst, product **19** was obtained with an enantiomeric excess of 70 %. On the other hand, when the ligand (1*R*, 2S)-**18** (24 mol %) was employed, only 20% *ee* was obtained. Due to these results, the authors proposed that the product plays an important role in the catalytic cycle of the reaction. In fact, the addition of a small amount of product increased the selectivity of the reaction. However, according to the definition of autocatalysis,[38] such a reaction cannot be described as a purely asymmetric autocatalytic reaction due to the fact that it involves the use of an additive in order to achieve higher enantioselectivity. In this case, the concept of autoinduction introduced by Wynberg is more suitable,[38] in which he defines "Asymmetric *Autoinduction*: the process in which a chiral product, that does not possess catalytic activity, participates in the formation of a chiral complex with the enantioselective catalyst to effect asymmetric induction".[38,39]

So far, the only example of an autocatalytic reaction is the one reported by Soai,[42] despite the fact that this reaction cannot be related to the origin of homochirality of biomolecules, since organometallic reagents are used. As such, the design of an organocatalytic version of such reactions became a new focus in this area.

1.7 The organo-"Auto"-catalytic asymmetric Mannich reaction: Tsogoeva

While Soai reaction is within the field of organometallic reactions, in the field of organocatalytic reactions, an arguable example of asymmetric auto-organocatalysis was reported in 2007 from Mauksch and Tsogoeva.[14,57] The reaction consists of the Mannich addition of acetone to α-iminoester **20** to form a chiral amino keto ester **21** (Scheme 11).

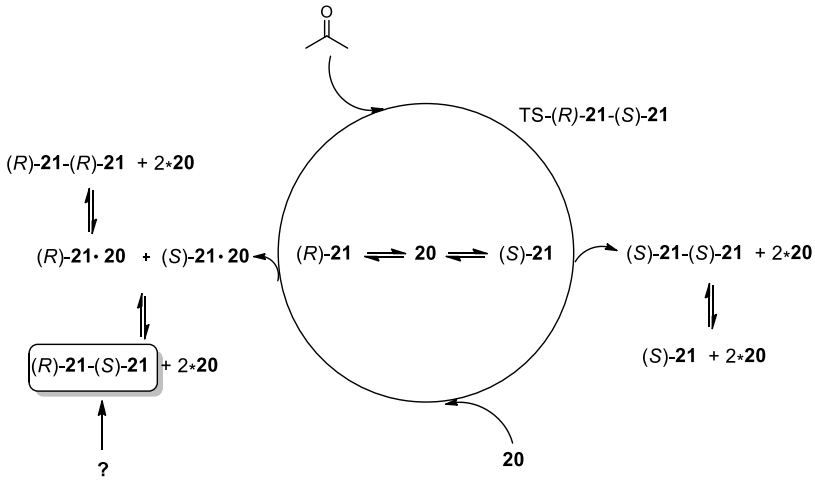


Scheme 11 *- Asymmetric organocatalytic Mannich reaction.*

Initially, L-proline was used as a catalyst to obtain the compound (*S*)-**21** with 98% *ee* and the D-Proline was used to obtain the corresponding enantiomer (*R*)-**21** with 99% *ee*.[58]

The chiral product obtained was then used as a catalyst for its own formation. The reaction was performed in different solvents, at different temperatures and using different catalyst loadings for both the enantiomers of **21**. The reaction was performed with 15 mol% of enantiopure (*S*)-**21**, using acetone as the solvent, and after four days the newly formed product **21** was isolated in 48% yield and with 81% *ee*.[57] Lowering the catalyst loading to 5 mol% gave poor yields (38%) and enantioselectivity (11%), and carrying out the reaction with a higher catalyst loading (50 mol% of (*S*)-**21**) gave higher *ee* (91%) but comparable yields (41%).

These results suggest that maybe there is decomposition of the catalyst during the reaction. Some density functional theory (DFT) calculations were performed[57] in order to support a proposed catalytic cycle (Scheme 12), where the formation of homo- and heterochiral dimeric complexes of (*S*)-**21**·(*S*)-**21** and (*S*)-**21**·(*R*)-**21** are less stable with respect to the monomers. The formation of these dimers competes with the coordination of the product with the starting material **36**, which is disfavored by only 3.4 kcal mol^{-1}. According to the DFT calculations, the expected product formation is favored, due to the lower energy calculated for the transition-state structure corresponding to the product (*S*)-**21**.



Scheme 12 *- Proposed catalytic cycle for the Mannich reaction.*

Blackmond *et al*. [59] performed some computational studies on Tsogoeva's autocatalytic Mannich reaction. The results that Tsogoeva *et al* reported for their system are not in agreement with the principle of microscopic reversibility and do not represent a physically and chemically realistic reaction network.

The IUPAC definition of the principle of microscopic reversibility states that in a system at equilibrium, any molecular process, and the reverse of that process, occur, on average, at the same rate.[60]

With regard to Tsogoeva's system, the main cause of concern is the recycling step, where the heterochiral complex (*S*)-**21**·(*R*)-**21** (Scheme 12) does not give any inactive dimer but converts to two molecules of the prochiral substrate. Conversely, according to the principle of microscopic reversibility, in order for the reaction to undergo the reverse process, the reverse pathway should go through an intermediate with higher energy, compared to the intermediate formed in the forward pathway. The unclear explanation provided by Tsogoeva's group, along with some divergence in their results, raised some doubts about the autocatalytic nature of this reaction. Furthermore, some reproducibility issues have been encountered for this reaction.[61]

The group of Feringa *et al*.[61] attempted to analyze the mechanism of this reaction in order to understand the role of the product as the catalyst for its own formation. A common way to prove an autocatalytic nature of a reaction is to use the enantiopure product as a catalyst. In Tsogoeva's report, the enantiopure product (*S*)-**21** was synthesized using an L-proline catalyzed enantioselective Mannich reaction and, after purification, used as a catalyst for its own formation. In contrast, Feringa's group synthesized the chiral racemic product **21** and enantiopure (*S*)-**21** was isolated by preparative chiral HPLC, thus excluding any traces of possible chiral catalyst present in the product. Using this enantiopure (*S*)-**21**, Feringa's group repeated the autocatalytic reaction reported by Tsogoeva, however, the previously reported results were not reproducible. Such a result indicates that in the catalytic system, reported by Tsogoeva, traces of L-proline (0.01%) were most likely still present in the product (*S*)-**21**, which was the actual catalyst of the reaction.[61]

All of these inconsistent results put a question mark on the autocatalytic nature of this reaction. So far, the only uncontestable example of an autocatalytic reaction is the one reported from Soai.

1.8 Thesis outline

In this thesis the efforts towards the development of an auto organocatalytic reactions, using structurally different autocatalysts are described. Furthermore, we have developed an organocatalytic synthesis of C-1 substituted tetrahydroisoquinolines. Next to this main topic, we studied the origin of the asymmetric amplification in the 1,2-addition of Grignard reagents to α,β-unsaturated ketones.

In **Chapter 2**, a design of an autocatalytic system based on amino acids and experimental efforts 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.

In **Chapter 3**, the design of an asymmetric autocatalytic system and experimental efforts towards the synthesis of a proline analogue, to be used as a catalyst for its own formation in an asymmetric Mannich reaction, are reported.

In **Chapter 4**, the development of an organocatalytic approach towards the synthesis of C-1 substituted tetrahydroisoquinolines and of an enamine based autocatalysis using isoquinolines motives, are described.

In **Chapter 5**, an L-proline catalyzed cascade reaction for the synthesis of C-1 substituted polycyclic tetrahydroisoquinolines is described. Using this methodology, a variety of tricyclic *N*-heterocycles were synthetized.

In **Chapter 6**, studies towards the understanding of the large asymmetric amplification observed in copper catalyzed asymmetric addition of Grignard reagents to enones are described. This phenomenon is not reaction or catalyst specific, but can be observed for metal complexes of a variety of chiral diphosphine ligands extensively used in asymmetric catalysis.

1.9 References

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