Improving the design of pyrrolidine aminocatalysts for complete diastereoselectivity in cascade reactions

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Abstract

In recent years, organocatalysts have been increasingly popular in organic synthesis due to their excellent stereoselectivity, availability, and low toxicity. Among organocatalysts, proline-derived pyrrolidine aminocatalysts are effective catalysts in a wide range of carbonyl reactions. Their versatility is capitalised in cascade reactions, where multiple reactions occur in sequence. Cascade reactions are advantageous as they increase the atom economy and require less time and resources to carry out. However, they often suffer from incomplete diastereoselectivity and require additional purification steps to obtain a diastereopure product. Due to the increased time and resources spent in synthesis due to the purification steps, its application to fields that require a specific absolute stereochemistry of the compounds, such as drug synthesis, is limited. We propose to solve this problem by increasing the catalyst's stereoselectivity towards a wider range of substrates. To do this, we propose the design of a novel pyrrolidine aminocatalyst combining the carboxyl group of proline and the bulky substituent of the Jørgensen–Hayashi catalyst. The proposed catalyst will thus be able to employ two different modes of stereoinduction, attractive hydrogen bonding and repulsive steric shielding. With this combined stereocontrol, the proposed catalyst is expected to be more stereoselective over a wider range of substrates and reactions than existing pyrrolidine aminocatalysts. This will allow the proposed catalyst to be more diastereoselective and thus more effective in cascade reactions than existing pyrrolidine aminocatalysts. To assess the proposed catalyst, we have proposed a synthesis route and experimental procedures adapting existing individual and cascade reactions. The diastereoselectivity of the proposed catalyst will be measured and compared to existing catalysts.

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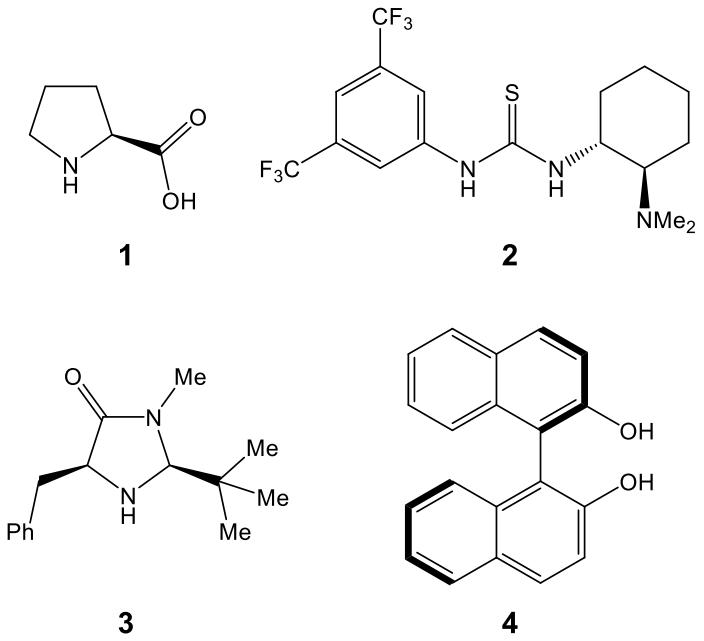
1. Introduction and significance

1.1 Asymmetric organocatalysis

A catalyst is a substance that increases the rate of a reaction by providing an alternate reaction pathway with a lower activation energy. As catalysts can be regenerated after the reaction, typically only a small amount of catalyst is required. In the past, chemists have primarily utilised organometallic catalysts in organic synthesis. However, in the past two decades, there has been rapid growth in the development of small metal-free organic catalysts (Figure 1),[1] now more commonly known as organocatalysts.



1 **2**

3 **4**

Figure 1. Examples of organocatalysts from different classes. ***1****: (S)-Proline (a pyrrolidine aminocatalyst);* ***2****: Takemoto's thiourea catalyst;* ***3****: MacMillan's 'second-generation' imidazolidinone catalyst;* ***4****: (R)-BINOL (a binaphthyl catalyst).*

The use of organocatalysts is advantageous for several reasons. They are reactive towards a wide range of substrates, allowing them to catalyse many different types of reactions.[2] In addition, they are easy to handle and store,[3] and are inexpensive and readily available.[2] As organocatalysts are metal-free organic compounds, they are generally less toxic and more environmentally-friendly,[4] making them more sustainable than organometallic catalysts. Hence, organocatalysts serve as cheap and green alternatives to organometallic catalysts.

A particularly important feature of organocatalysts is their ability to catalyse asymmetric reactions. Asymmetric organocatalysis occurs when a chiral organocatalyst favours the formation of one stereoisomer over another in a reaction. This results in an unequal amount of stereoisomers formed instead of a racemic mixture. Organocatalysts have been used to catalyse a wide range of asymmetric reactions with excellent stereoselectivities.[3] Since different stereoisomers can affect biological systems differently, stereoselective reactions are especially relevant in medicinal chemistry and biochemistry.[5] Given its applicability, the advancement of asymmetric organocatalysis continues to be an important field of study.

1.2 Proline

One of the earliest organocatalysts is the chiral amino acid proline. In the 1970s, Hajos *et al.*[6] and Eder *et al.*[7] first used proline to catalyse an intramolecular asymmetric aldol reaction. In 2000, List *et al.* expanded the scope of proline catalysis to include intermolecular asymmetric aldol reactions.[8] In the same year, Bui *et al.* used proline to catalyse both steps of a Robinson annulation.[9] These reports pioneered the field of organocatalysis in the early 2000s.

Proline's success as a catalyst is largely due to the versatility of its carbonyl substrates. Carbonyl compounds exhibit keto-enol tautomerism, which allows them to act as either electrophiles or nucleophiles respectively.[10] As such, carbonyl compounds are able to participate in several general reaction mechanisms such as α-substitution and direct or conjugate nucleophilic addition. While these carbonyl compounds are usually activated by acid or base catalysis, organocatalysts such as proline can also be used.[11]

Proline's catalytic activity arises from its pyrrolidine ring, allowing it to act as an aminocatalyst. Aminocatalysts react with carbonyl compounds such as ketones and aldehydes to form enamines, which are more nucleophilic than their corresponding enols (Figure 2).[11] Aminocatalysts are also able to react with α,β-unsaturated carbonyl compounds such as enones and enals to form iminium ions, which are more electrophilic than the initial enones or enals. The ability to activate both nucleophilic and electrophilic forms of carbonyl compounds allows proline and other aminocatalysts to effectively catalyse a wide range of carbonyl reactions[11] including the aldol condensation[8], Michael reaction[12], and Mannich reaction[13].

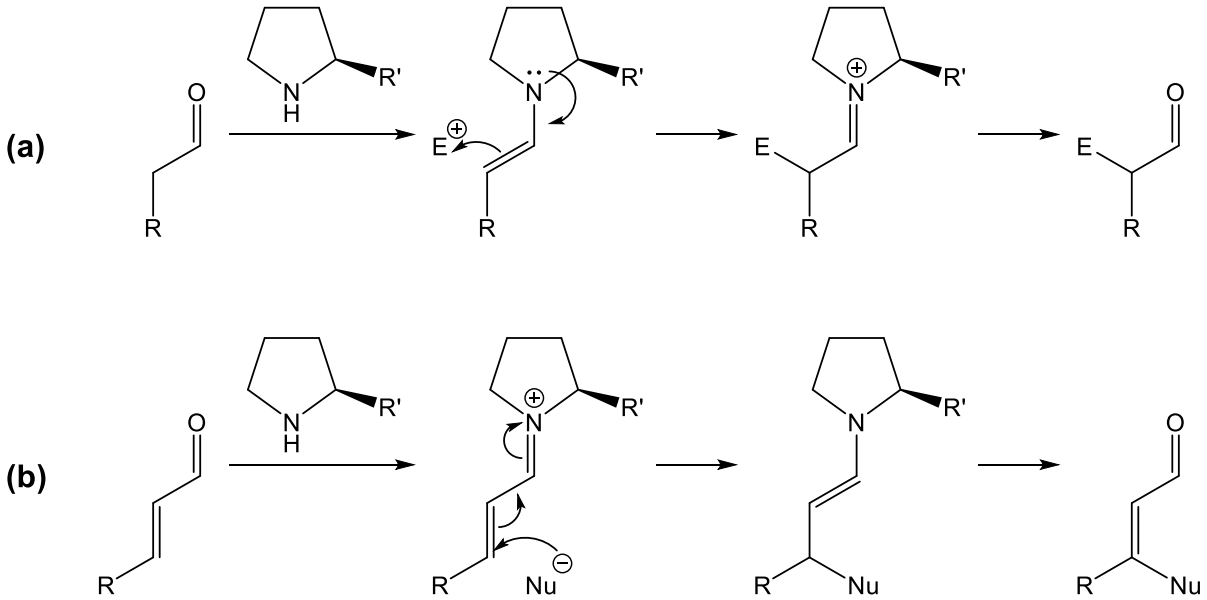


Figure 2. Reaction scheme of activation of carbonyl compounds by a pyrrolidine aminocatalyst. *E = electrophile, Nu = nucleophile, R, R' = substituents. (a) Nucleophilic activation: an aldehyde reacts with the catalyst to form a nucleophilic enamine. The enamine then reacts with an electrophile, followed by release of the catalyst from the product. (b) Electrophilic activation: an enal reacts with the catalyst to form an electrophilic iminium ion. The iminium ion then reacts with a nucleophile, followed by release of the catalyst from the product.*

Proline is a chiral catalyst, allowing it to selectively favour the formation of one stereoisomer. In a proline-catalysed α-substitution reaction, the carboxyl proton forms

attractive hydrogen bonds with incoming electrophiles, thereby stabilising the transition state (Figure 3). However, these hydrogen bonds can only be formed with electrophiles that approach from the same face of the enamine as the carboxyl group. Electrophiles approaching from the opposite face are unable to form these stabilising hydrogen bonds, making the 'opposite-face' approach energetically unfavourable. This results in the preferential formation of the stereoisomer that arises from the favoured 'same-face' approach.[14]

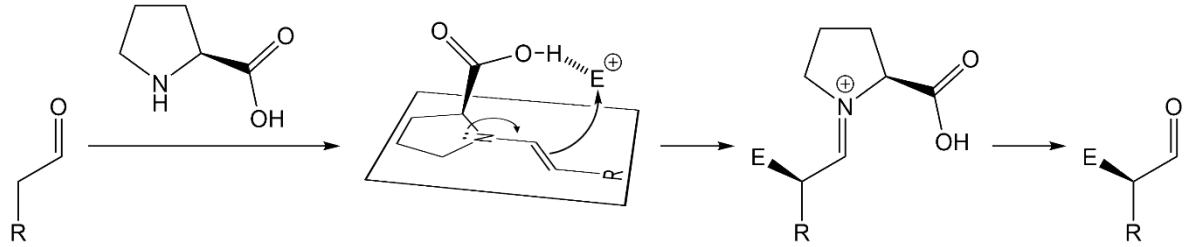
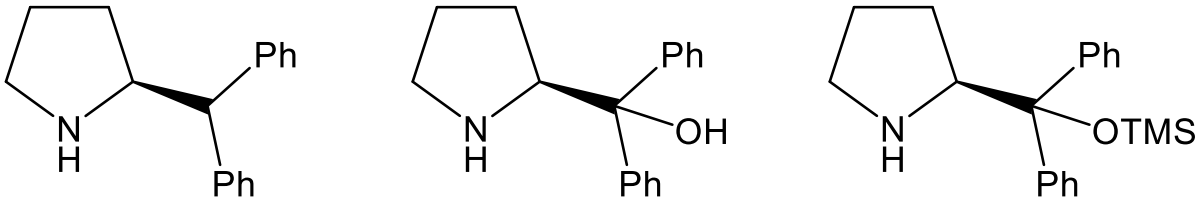


Figure 3. Reactants, transition state, and product of a proline-catalysed α-substitution reaction between an aldehyde and an electrophile. *E = electrophile, R = substituent. In this α-substitution reaction, an electrophile is substituted onto the α-carbon of the nucleophilic enamine, which was generated from proline and the aldehyde. The wedged bond in proline indicates that the carboxyl group is pointed out of the plane (forwards). The hashed bond represents a hydrogen bond between the carboxyl proton and the electrophile in the transition state. The hydrogen bond can only be formed when the electrophile approaches from the same face as the carboxyl group. After the substitution of the electrophile, the catalyst is released from the product. The wedged bond in the product indicates that the electrophile substituent is pointed out of the plane (forwards).*

1.3 Jørgensen–Hayashi catalyst

Since proline's stereoinduction relies on hydrogen bonding, it generally only performs well when the incoming reactants are good hydrogen bond acceptors.[14-16] In the years following the initial reports of proline's organocatalytic utility, many other similar compounds were also investigated as organocatalysts (Figure 4). These proline derivatives generally retained the catalytic pyrrolidine ring, with the addition or modification of substituents.



5 **6** **7**

Figure 4. Notable pyrrolidine aminocatalysts studied by Jørgensen and coworkers. ***5****: (S)-2-(diphenylmethyl)pyrrolidine;* ***6****: (S)-2-(diphenylhydroxymethyl)pyrrolidine;* ***7****: (S)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (Jørgensen–Hayashi catalyst).*

Jørgensen and coworkers[17-19] found that although **5** was an active catalyst in many reactions, it generally exhibited poor stereocontrol. To address this, the authors added a hydroxyl group to **5** to form **6**, which induced much better stereoselectivities. However, this

came at the cost of low turnover, causing reduced yields and longer reaction times. Attributing this to a parasitic side-reaction involving the hydroxyl group,[15,16] the authors added a trimethylsilyl (TMS) protecting group to **6** to form **7**. In the same year, **7** was also independently developed by Hayashi *et al.*[20] **7** was found to be a very efficient and versatile catalyst, promoting a wide range of reactions with excellent yields and stereoselectivities.[15,16] Many of these reactions did not have good hydrogen bond acceptors, and could not be effectively catalysed by proline. Since its introduction, **7** has established itself as the catalyst of choice across its reaction scope and is now commonly known as the Jørgensen–Hayashi catalyst.

As **7** lacks a labile proton, it is unable to induce stereoselectivity through hydrogen bonding. Instead, it uses a different mode of stereoinduction known as steric shielding. In an α-substitution reaction, **7**'s bulky phenyl and trimethylsiloxy (TMS) groups hinder incoming electrophiles that approach from the same face of the enamine (Figure 5). Electrophiles approaching from the opposite face are not hindered by the steric bulk of the substituent and are better able to access the nucleophilic enamine. This results in the preferential formation of the stereoisomer that arises from the favoured 'opposite-face' approach.[21]

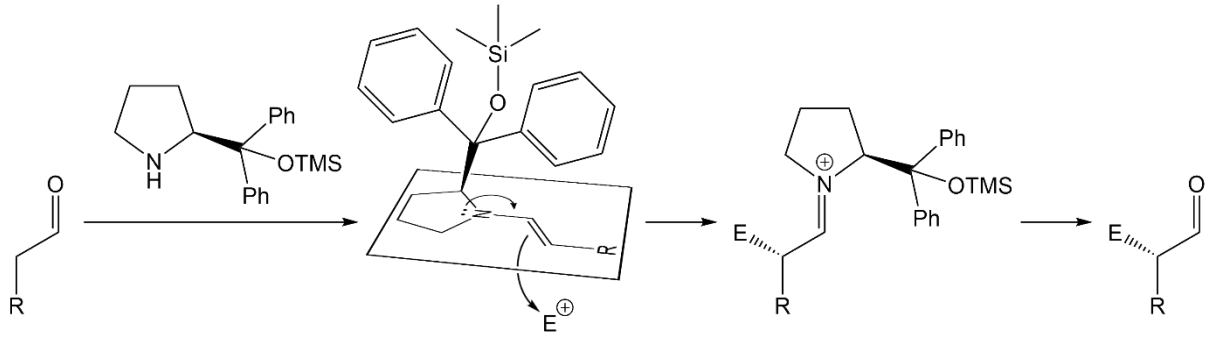


Figure 5. Reactants, transition state, and product of a 7-catalysed α-substitution reaction between an aldehyde and an electrophile. *E = electrophile, R = substituent. In this α-substitution reaction, an electrophile is substituted onto the α-carbon of the nucleophilic enamine, which was generated from* ***7*** *and the aldehyde. The wedged bond in* ***7*** *indicates that the bulky substituent is pointed out of the plane (forwards). Since the enamine is shielded from electrophiles approaching from the same face as the bulky substituent, the electrophile can only approach from the opposite face. After the substitution of the electrophile, the catalyst is released from the product. The dashed bond in the product indicates that the electrophile substituent is pointed into the plane (backwards).*

1.4 Cascade reactions

7's versatility, combined with its ability to activate both nucleophilic and electrophilic forms of carbonyl compounds, makes it an especially effective catalyst in cascade reactions.[22,23] A cascade reaction is a sequence of individual reactions that occur consecutively in a single container, usually without any change to the reaction conditions. Cascade reactions eliminate the need for intermediate purification and protection-deprotection steps, increasing the atom economy while reducing the consumption of time and resources. In doing so, cascade reactions are able to efficiently construct complex structures from simple precursors.

The key mechanism behind aminocatalysed cascade reactions is iminium-enamine activation (Figure 6).[22,23] In this mechanism, an α,β-unsaturated carbonyl compound reacts with a nucleophile followed by an electrophile. As such, two new bonds and up to four new chiral centres can be formed within a single catalytic cycle. This highly efficient mechanism has been employed in most aminocatalysed cascade reactions.[2,22,23]

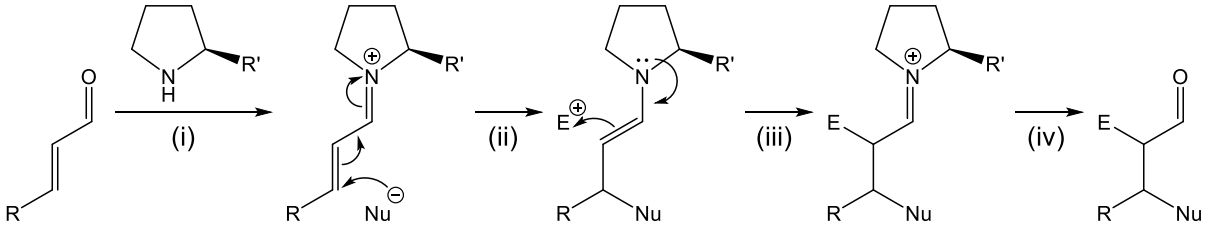


Figure 6. Iminium-enamine activation catalysed by a pyrrolidine aminocatalyst. *E = electrophile, Nu = nucleophile, R, R' = substituents. (i) An enal reacts with the catalyst to form an electrophilic iminium ion. (ii) The iminium ion then reacts with a nucleophile, forming a nucleophilic enamine intermediate. (iii) The enamine intermediate proceeds to react with an electrophile. (iv) The catalyst is then released from the product.*

A notable cascade reaction catalysed by **7** (Figure 7) was reported by Enders *et al.* in 2006.[24] The reaction followed a Michael/Michael/aldol sequence, making it the first asymmetric organocatalytic triple cascade to be developed. Starting from achiral reactants, the reaction formed three new bonds and four new chiral centres. Three of those chiral centres were generated with complete stereocontrol. Out of sixteen possible diastereomers of the final product, only two diastereomers were formed, with the lowest diastereomeric ratio (dr) reported at 6.8:3.2. Following this work, many **7**-catalysed cascade reactions using various protocols have been investigated, including more recent reports of quadruple cascade reactions.[2]

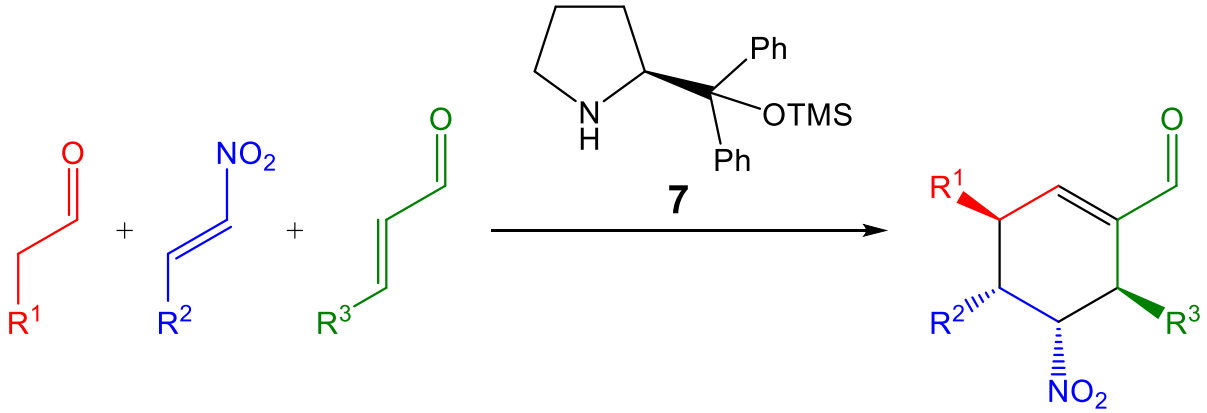


Figure 7. Triple cascade protocol as reported by Enders et al. *R^1, R^2, R^3 = substituents. An aldehyde (red), a nitroalkene (blue), and an enal (green) react in a **7**-catalysed Michael/Michael/aldol sequence to form a cyclohexenecarbaldehyde. Three new bonds (black) and four new chiral centres are formed. Enantioselectivity: (ee ≥ 99%); diastereoselectivity: (dr = 6.8:3.2 to 9.9:0.1).*

1.5 Evaluation

Since the initial breakthroughs of proline catalysis, the design of pyrrolidine aminocatalysts has been iteratively improved to address various limitations. Earlier catalysts were largely tailored to meet the needs of specific reactions,[16] and a general organocatalyst remained elusive until the development of **7** in 2005.[15,16,19,20] The use of **7** has since become ubiquitous in organocatalysis, especially in cascade reactions, with its design largely untouched aside from minor modifications.

Despite its many advantages, **7** still has several shortcomings. The first is high catalyst loading, which is a common problem among organocatalysts. Catalyst loadings in organocatalysed reactions typically range between 10–40 mol%, which is orders of magnitude more than that of organometallic or enzyme catalysts.[25] The main reason for this is that organocatalysts typically have low turnover numbers (TON) and turnover frequencies (TOF). For example, side-reactions such as the formation of oxazolidine and oxazolidinone species deactivate aminocatalysts, decreasing their TON.[11,15,26] This makes high catalyst loadings necessary to obtain good yields. Although organocatalysts are relatively inexpensive, the need for high loading limits their applicability on an industrial scale,[27] and eliminating this problem could establish them as choice catalysts in organic synthesis.[25]

Another shortcoming of pyrrolidine aminocatalysts is their relatively poor diastereoselectivity. Although reactions with complete enantiocontrol are frequently reported, their diastereoselectivities are often worse. This problem is compounded in cascade reactions, where multiple new bonds and chiral centres are formed. For complete diastereoselectivity, each new chiral centre must be formed with complete enantiocontrol. Even a single step with incomplete stereoselectivity can result in a pair of epimers.[24,28] Thus, a general catalyst for cascade reactions must promote excellent stereoselectivity over a wide range of reactions and substrates. Although **7** is sufficiently versatile for widespread use in cascade reactions, several **7**-catalysed cascade reactions still suffer from diastereomeric impurities.[24,29] Ultimately, if purification steps have to be performed to obtain diastereopure compounds, the advantages of using cascade reactions will be diminished.

Efforts have been made to address the shortcomings of pyrrolidine aminocatalysts and organocatalysts in general. Various methods were employed to successfully lower catalyst loadings to under 3 mol%.[25] In aqueous aldol reactions, the loading of pyrrolidine aminocatalysts with hydrophobic substituents could even be reduced to 0.5 mol%.[25,30] On the other hand, there has been less effort put into addressing the problem of incomplete diastereoselectivity. While **7** is excellent as a general enantioselective catalyst for single-step reactions and adequate in many cascade reactions, a truly general diastereoselective catalyst for cascade reactions has yet to be found. Our research problem is thus to improve the design of pyrrolidine aminocatalysts to achieve complete diastereoselectivity in cascade reactions.

2. Research gap and research directions

2.1 Research gap

The design of pyrrolidine aminocatalysts has evolved over the years to overcome the various challenges that arose. At present, we have identified two shortcomings of existing pyrrolidine aminocatalysts: high catalyst loading and incomplete diastereoselectivity in cascade reactions. While many design modifications have been explored to lower catalyst loading,[25] the problem of diastereoselectivity has been largely unaddressed. In light of this, we have chosen to focus our research problem on improving diastereoselectivity in cascade reactions.

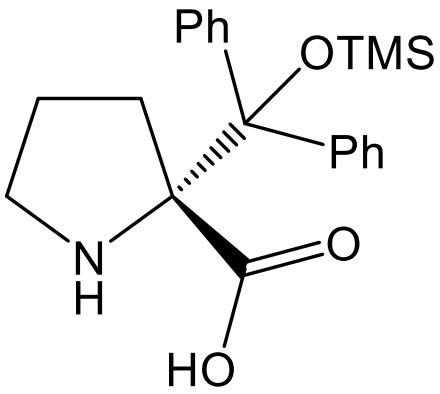
Poor diastereoselectivity is most apparent in cascade reactions. A reaction that forms *n* new chiral centres will yield a product with 2^n possible diastereomers. Since cascade reactions inherently form multiple new bonds and chiral centres, the number of possible diastereomers increases exponentially. This is a problem as often, only one diastereomer is desired with the rest being impurities that require further separation. This is the case in medicinal chemistry, where two diastereomers can have markedly different effects in the human body and other biological systems. As an increasing number of organocatalytic cascade protocols are being incorporated into synthesis of drugs,[31] it is essential to be able to reliably achieve complete diastereocontrol in cascade reactions.

In order to find solutions to our research problem, it is important to first identify the causes of incomplete diastereoselectivity. Complete diastereocontrol is only achieved with complete enantiocontrol of each new chiral centre formed. Therefore, the effect of even slightly imperfect stereoselectivities of individual steps will be compounded, potentially resulting in a significant amount of diastereomeric impurities. The solution is to improve the enantioinduction of the catalyst used in the reaction, thereby eliminating the diastereomers formed in each step. Another source of incomplete diastereoselectivity is when all but one chiral centre is formed with complete stereoselectivities. The single chiral centre formed with moderate stereocontrol results in a significant proportion of the minor diastereomer. Since the individual steps in cascade reaction can be entirely different reactions using unrelated mechanisms, maintaining complete stereocontrol throughout the cascade requires a general catalyst with a wide substrate and reaction scope.

Existing pyrrolidine aminocatalysts use one of two modes of stereoinduction: hydrogen bonding and steric shielding. Proline uses hydrogen bonding, and is an effective catalyst in reactions with good hydrogen bond acceptors.[8,9,12,13] However, it does not perform as well in reactions with poor hydrogen bond acceptors.[14-16] On the other hand, the Jørgensen–Hayashi catalyst **7** uses steric shielding, allowing it to promote good stereoselectivity regardless of the reactants' ability to accept hydrogen bonds.[15,16] Despite this, in reactions where hydrogen bonding is especially effective such as aldol condensations, **7** is outperformed by hydrogen bonding catalysts.[32,33] Consequently, we hypothesise that combining both modes of stereoinduction into a single catalyst will grant it the best stereoselectivities achieved by both proline and **7**.

2.2 Proposed solution

As a solution to our research problem, we propose the design of pyrrolidine aminocatalyst **8** (Figure 8). Its structure contains both a carboxyl group and the bulky substituent of **7**, allowing **8** to use both hydrogen bonding and steric shielding as modes of stereoinduction. As hydrogen bonding favours 'same-face' approach and steric shielding favours 'opposite-face' approach, the two groups are placed on opposite faces of the pyrrolidine ring so as to synchronise their stereoinduction (Figure 9). Furthermore, the two groups are bonded to the same carbon atom such that the s-trans enamine or iminium ion is preferentially formed.[11]



8

Figure 8. Proposed design of pyrrolidine aminocatalyst 8. *(R)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine-2-carboxylic acid.*

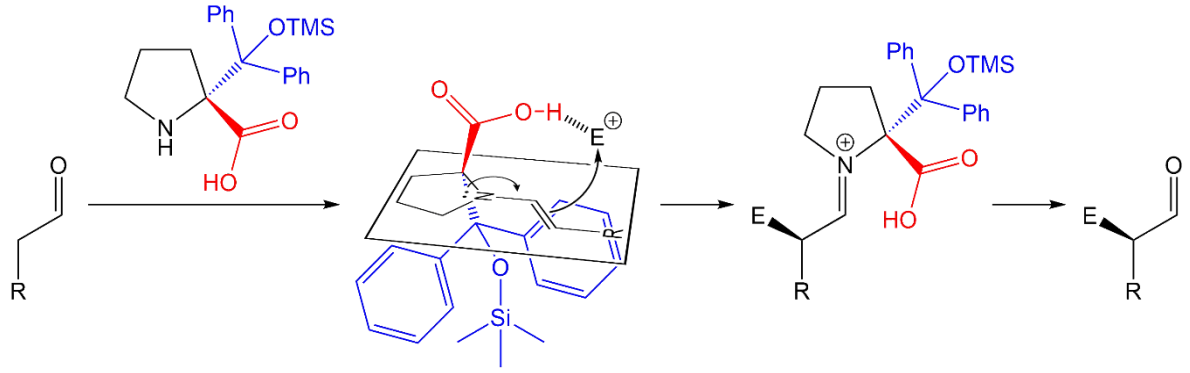


Figure 9. Reactants, transition state, and product of a general 8-catalysed α-substitution reaction between an aldehyde and an electrophile. *E = electrophile, R = substituent. In this α-substitution reaction, an electrophile is substituted onto the α-carbon of the nucleophilic enamine, which was generated from **8** and the aldehyde. The wedged bond in **8** indicates that the carboxyl group (red) is pointed out of the plane (forwards). The dashed bond in **8** indicates that the bulky substituent (blue) is pointed into the plane (backwards). The hashed bond represents a hydrogen bond formed between the carboxyl proton and the electrophile approaching from the front. The hydrogen bond can only be formed when the electrophile approaches from the same face as the carboxyl group. Concurrently, the enamine is shielded from electrophiles approaching from the same face as the bulky substituent. After the substitution of the electrophile, the catalyst is released from the product. The wedged bond in the product indicates that the electrophile substituent is pointed out of the plane (forwards).*

We hypothesise that the design of **8** will address both sources of incomplete diastereoselectivity. Firstly, the combined effect of both groups will direct incoming reactants more strongly to the carboxyl face of the catalyst and away from the bulky face. Compared to proline, the additional bulky group in **8** will repel incoming reactants approaching from the 'opposite-face' that may have still reacted with proline's substrate. This would allow **8** to achieve better enantioinduction than both proline and **7**, thereby addressing the first source. Secondly, the presence of both groups will optimise the stereocontrol over both proline's and **7**'s reaction scope. Poor hydrogen bond acceptors will still be repelled by the bulky group and good hydrogen bond acceptors will still form stabilising hydrogen bonds with the carboxyl group. This allows **8** to achieve the best stereocontrol achieved by both **7** and proline, thereby addressing the second source. As such, we hypothesise that **8** will be able to achieve complete diastereocontrol over a wide range of cascade reactions.

To test our hypothesis, we will adapt an existing cascade reaction, substituting the original catalyst with **8**, and assess its diastereoselectivity. The cascade reaction we have chosen is the previously mentioned triple cascade reported by Enders *et al.*[24] This reaction was chosen as it has a significant minor diastereomer, the 5-epimer of the final product, that we expect can be eliminated through the use of **8**. The cascade uses a nitroalkene Michael reaction followed by a Michael/aldol iminium-enamine activation, which are both commonly found in cascade reactions.[2] Additionally, it is a well-known cascade reaction, being the first triple organocatalytic cascade developed, and its mechanism has been studied in depth.[28] The minor diastereomer is a result of incomplete stereocontrol during the formation of the third chiral centre. According to a mechanistic study,[28] this chiral centre is determined by the face of the nitronate used to attack the iminium ion. Using **8**, only attacks from one of those faces will be stabilised by hydrogen bonding with the carboxyl group of **8** (Figure 10). As such, the chiral centre will be formed with potentially complete stereocontrol, which will result in complete diastereoselectivity of the final product.

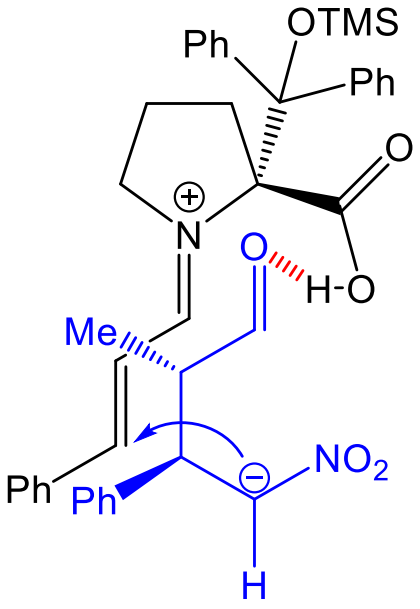


Figure 10. Transition state of the second step (Michael addition) of an 8-catalysed triple cascade reaction adapted from Enders et al. *In this transition state, the nucleophilic nitronate ion (blue) attacks the electrophilic iminium ion (black). The hashed bond (red) represents a hydrogen bond between the carboxyl proton of the iminium ion and the carbonyl oxygen of the nitronate ion. This transition state is stabilised by hydrogen bonding and will be energetically favourable compared to other unstabilised transition states.*

2.3 Procedure

A five-step synthesis of **8** from (S)-proline is proposed (Figure 11). Firstly, the protocol developed by Seebach *et al.*[34] will be used to obtain the α-substituted proline derivative with retention of chirality. The TMS protecting group will then be added according to the literature procedure outlined by Jørgensen and coworkers[19]. Finally, an improved method reported by Genin *et al.*[35] will be used to hydrolyse the oxazolidinone ring, yielding the final product **8** (expected yield ≈ 60%). After purification, the product will be characterised as described by Hayashi *et al.*[20]

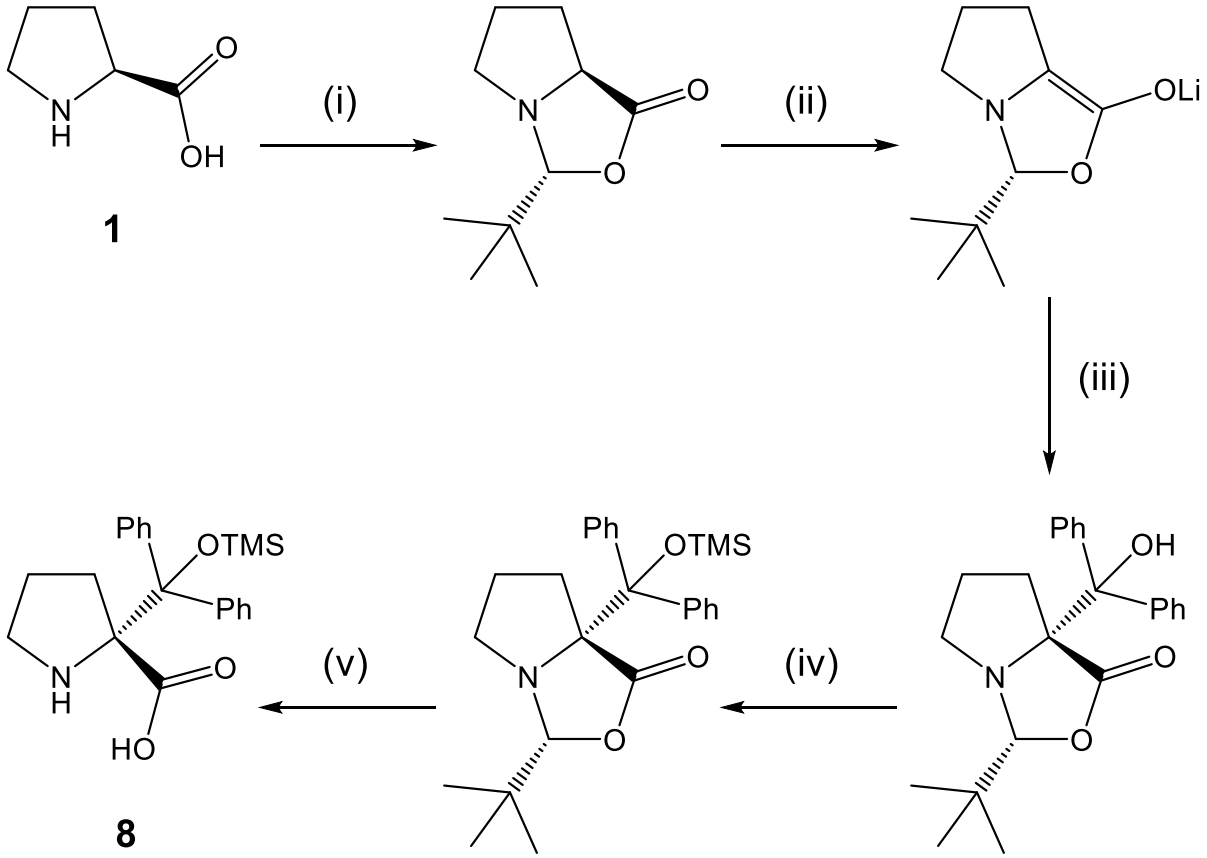


Figure 11. Proposed synthetic route for 8. *Reagents and conditions: (i) t-BuCHO, TFA (cat.), pentane, reflux, 48 h;[34] (ii) LDA, THF, -78°C, 30 min;[34] (iii) Ph_2CO, -78°C to -30°C, 2 h;[34] (iv) TMSOTf, NEt_3, CH_2Cl_2, 0°C to RT, 1 h;[19] (v) Silica gel, MeOH/H_2O (6:1), RT, 12 h.*[35]

Before testing **8** in a cascade reaction, we will first assess its stereoselectivity in previously reported individual reactions, namely a cross-aldol reaction by Northrup *et al.*,[36] a nitroalkene Michael reaction by Hayashi *et al.*,[20] a Michael reaction by Gotoh *et al.*,[37] and a Michael/aldol reaction by Enders *et al.*[38] These reactions are similar to the steps of the triple cascade reaction reported by Enders *et al.*,[24] allowing for indirect investigation of the individual steps. Afterwards, **8** will be used in the triple cascade reaction by Enders *et al.*[24] All reaction procedures and product characterisation will be directly adapted from their respective reports. The diastereoselectivities (dr) of the reactions, along with the enantioselectivities (ee) and product yields, will then be compared to determine if **8** is indeed a more diastereoselective catalyst.

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Glossary

Aldehyde	A carbonyl compound where the carbonyl carbon is bonded to a hydrogen atom (-C(=O)-H)
Amine	An organic compound where a carbon atom is bonded to a nitrogen atom (-C-N)
Aminocatalyst	An organocatalyst which is an amine
Atom economy	The efficiency of conversion of a chemical reaction in terms of the atoms involved and the desired products produced
Asymmetric	An asymmetric reaction favours the formation of one stereoisomer over another, resulting in an unequal amount of the stereoisomeric products instead of a racemic mixture *(see also* stereoselectivity*)*
Carbonyl	A functional group where a carbon atom has a double bond with an oxygen atom (-C=O)
Carboxyl	A functional group where a carbon atom has a double bond with an oxygen atom and a single bond with a hydroxyl group (-C(=O)-O-H)
Cascade reaction	A sequence of individual reactions that occur consecutively in a single container, usually without any change to the reaction conditions
Catalytic cycle	A cyclic sequence of reaction steps involving a catalyst (usually involves substrate binding, the catalysed reaction, and catalyst regeneration)
Chiral	A chiral compound is one that is non-superimposable on its mirror image
Chiral centre (*also* stereocentre *or* stereogenic centre)	A point in a molecule bearing different substituents, such that interchanging any two substituents leads to a stereoisomer
Diastereocontrol	Selective control of the formation of diastereomers in a reaction
Diastereomer	Stereoisomers that are not mirror images of one another, usually occurring when stereoisomers have different configurations at least one, but not all, of their chiral centres
Diastereomeric ratio (dr)	The ratio of the amount of a pair of diastereomers present in a mixture (a measure of diastereoselectivity)
Diastereopure	Containing only one diastereomer

Diastereoselectivity	The property of a reaction to form an unequal mixture of diastereomers
Electrophile	An electron-deficient species that is attracted to electron-rich regions and reacts with nucleophiles
Enal	An α,β-unsaturated carbonyl compound consisting of an alkene conjugated to aldehyde
Enamine	The nitrogen analogue of an enol, where a carbon atom has a single bond with a nitrogen atom and a double bond with a carbon atom
Enantiocontrol *(also* enantioinduction*)*	Selective control of the formation of enantiomers in a reaction
Enantiomer	Stereoisomers that are mirror images of one another, usually occurring when stereoisomers have different configurations at all of their chiral centres
Enantiomeric excess (ee)	Difference between the mole percentage of each enantiomer (a measure of enantioselectivity)
Enantiopure	Containing only one enantiomer
Enantioselectivity	The property of a reaction to form an unequal mixture of enantiomers instead of a racemic mixture
Enone	An α,β-unsaturated carbonyl compound consisting of an alkene conjugated to ketone
Epimer	Diastereomers that have different configurations at only one chiral centre
Functional group	A group of atoms in a molecule that exhibits similar chemical behaviour across different compounds
Hydrogen bond	A strong noncovalent interaction between an electronegative atom (such as nitrogen, oxygen, or fluorine) and a hydrogen atom bonded to another electronegative atom
Hydroxyl	A functional group where an oxygen atom has a single bond with a hydrogen atom (-O-H)
Iminium ion	An organic cation where a nitrogen atom with a formal positive charge has a double bond with a carbon atom
Intermediate	A molecule formed between steps of a reaction, having a relatively long lifetime compared to a transition state
Intermolecular	Between two or more molecules
Intramolecular	Within one molecule

Keto-enol tautomerism	A carbonyl reaction involving an intramolecular proton transfer, resulting in an equilibrium between a keto form and an enol form
Ketone	A carbonyl compound where the carbonyl carbon is bonded to two other carbon atoms (-C(=O)-C)
Nucleophile	An electron-rich species that is attracted to electron-deficient regions and reacts with electrophiles
Phenyl	A functional group containing a benzene ring with one fewer hydrogen atom (-C_6H_5) (frequently abbreviated as Ph)
Protecting group	A functional group that prevents certain parts of the molecule from participating in reactions
Pyrrolidine	A five-membered cyclic secondary amine (C_4H_9N)
Racemic mixture *(also* racemate*)*	A mixture that has equal amounts of a pair of enantiomers
Stereocontrol *(also* steroinduction*)*	The control of the stereochemistry of a reaction
Stereoisomer	Molecules that have the same chemical formula and sequence of bonded atoms, but different spatial arrangement of atoms
Stereoselectivity	The property of a reaction to form an unequal mixture of stereoisomers instead of a racemic mixture *(see also* asymmetric*)*
Steric shielding	Occurs when there is a large group on the molecule that physically hinders incoming reactants form reacting with the molecule
Substrate	A compound that reacts with the catalyst and is converted to the product
Transition state	A transient structure formed in the middle of a reaction step, where bonds are partially formed and broken, having a relatively short lifetime compared to an intermediate
Trimethylsiloxy (TMS)	A functional group consisting of three methyl groups bonded to a silicon atom ($-Si(CH_3)_3$)
Turnover frequency (TOF)	Amount of substrate converted (moles) per unit time (seconds)
Turnover number (TON)	Amount of substrate converted (moles) per amount of catalyst (moles)
Unsaturated compound	A compound that has at least one of either a double bond or a triple bond
Yield	Amount of product (moles) per amount of reactant (moles)