Synthesis of a chiral artificial receptor with catalytic activity in Michael additions and its chiral resolution by a new methodology†

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Xanthone derivatives were tested as organocatalysts for the Michael addition of pyrrolidine to an α,β-unsaturated lactam. The receptors combine a double H-bond donor pattern that resembles the oxyanion hole in natural enzymes, with a sulfone or sulfoxide that acts as a proton-transfer group. Since these compounds cannot be obtained enantiomerically pure from natural sources, chiral resolution was necessary to study their enantioselectivity. For the most promising receptor, this was accomplished using a new methodology that exploits its supramolecular interactions with a chiral guest and that is inspired in dynamic combinatorial chemistry. The success in the resolution of the racemic mixture indicates that this new method offers an alternative to kinetic resolution.

Introduction

The feasibility of chiral catalysis in asymmetric synthesis is conditioned by the accessibility of the catalyst as a single enantiomer. In many cases, the catalyst can be obtained enantiomerically pure from a natural source. A good and well documented example is the use of proline or proline derivatives in organocatalysis.[1–6] Nevertheless, some synthetic catalysts cannot be derived from natural *enantio*-pure sources, so their application in asymmetric synthesis requires an effective and simple method for isolating the required enantiomer. This can be accomplished by either asymmetric synthesis of the catalyst or by chiral supramolecular recognition.

In recent works,[7–9] we have designed and synthesized xanthone-derived receptors with catalytic activity in the Michael addition of amines to the α,β unsaturated lactam **1** (Fig. 1). Like many other organocatalysts containing double H-bond donors,[10–44] these catalysts are inspired by the oxyanion hole structure[45–60] present in many enzymes (such as hydrolases, lipases, proteases, esterases, etc). The role of H-bond donors is to stabilize the electron density

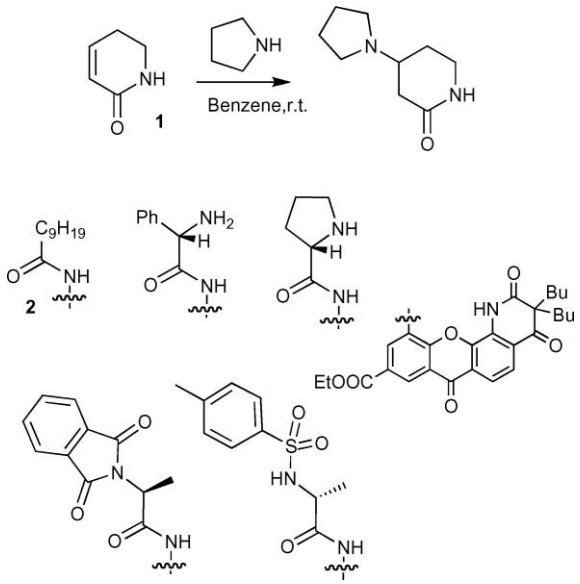

Fig. 1 Michael addition of pyrrolidine to lactam **1** and structures of the lactam and chiral catalysts studied in previous works and prepared from chiral natural sources.

that is accumulated during the transition state, but recently it has been observed that the geometry of xanthone receptors better fits the geometric parameters in oxyanion hole enzymes.[61,62] In addition to H-bond donors, these catalysts include groups that assist the proton transfer of the amine nucleophile to the α,β-unsaturated lactam. When the xanthone scaffold was functionalized with chiral amines (derived from α-amino acids), moderate degrees of chiral assistance were observed, but the self-aggregation derived from the basicity of these groups is detrimental for the association of the substrate. Moreover, Bruice[63,64] has pointed out that H-bond acceptors can act as proton transport groups in the proton slide mechanism, where the basicity of the heteroatom is not as important as its ability to act as a good hydrogen bond acceptor. Accordingly, receptors with amide carbonyl oxygen and sulfonamide oxygen atoms were prepared.[8] As these receptors were obtained from chiral natural products, it was possible to observe moderate degrees of chiral assistance.

Continuing with this research, in the present work we explore the possibilities of xanthone receptors containing sulfone and sulfoxide oxygens as proton-transport groups, since both groups are strong H-bond acceptors[65–67] and can assist the proton transfer process.[8,68] Cyclic compounds were also included in the study with the aim of reducing the flexibility of the catalysts, which could increase the chiral assistance by reducing the conformational space

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Table 1 Catalytic activities of the receptors studied in this work

Receptor	$t_{1/2}$ (min)[a]	K_{rel}[b]
—	2385	—
2	84	1.00
3	17	0.11
4	37	—
5	34	0.058
6	22	1.1
7*u*	6.5	—
7*l*	8	—

[a] Half life times of the catalyzed reactions ([pyrrolidine] = 3.0 M; [lactam] = 0.80 M; [receptor] = 0.04 M; solvent: benzene; T = 298 K. [b] Relative association constants referred to receptor **2**.

of the catalyst (and therefore the probability that different catalyst conformers might generate opposite enantiomers). A drawback of the catalysts included in this work is that they cannot be obtained enantiomerically pure starting from affordable chiral compounds. Therefore, in order to test the chiral assistance of the new catalysts it was necessary either to prepare or to isolate a single enantiomer. This was accomplished by means of a new technique based on the supramolecular properties of the catalyst and its interactions with a chiral analogue of the transition state.

Results and discussion

The sulfone and sulfoxide-based receptors shown in Fig. 2 (see ESI for synthetic procedures†) were prepared and their performance as catalysts in the Michael addition of pyrrolidine to lactam **1** was evaluated. The half-life times of the reaction (catalyzed by 5% mol of the receptors) are shown in Table 1. Receptor **2** (Fig. 1) was also included in the study, since it allows the effect of the oxyanion hole structure alone to be established because it lacks the proton transport group. The half-life time of sulfone derivative **3** was decreased by a factor of 5 relative to the above-mentioned receptor **2**. Even though higher rigidity is desirable to develop more efficient catalysts, receptors **4** and **5** (which have cyclic structures) did not improve the catalytic properties of receptor **3**. This is probably because they cannot match the ideal geometry for proton transport. Receptor **6** afforded similar results to the acyclic receptor **3**. The better catalytic activity of receptors 7*u* and 7*l* is logical because sulfoxides are better hydrogen-bond acceptors

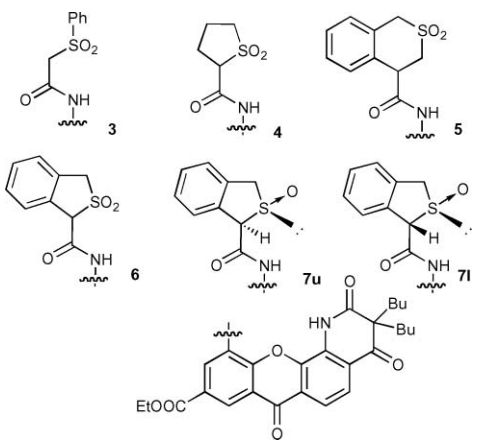


Fig. 2 Structures of the catalysts studied in this work.

than sulfones[65] (the relative stereochemistry of these receptors was assigned comparing with the reactivity of other cyclic thioeters described in the literature,[69] modelling studies and ^{1}H NMR chemical shifts; see electronic supplementary information for details†).

The similar catalytic activity obtained for receptors ***7u*** and ***7l*** is a striking result considering the different geometries of both compounds. In fact, CPK models and modelling studies have suggested that only the ***7u*** sulfoxide could assist the proton transfer. Inspection of ^{1}H NMR spectra revealed that both receptors, ***7u*** and ***7l***, were in equilibrium in benzene or chloroform solutions in the presence of a base. Under these conditions, the carbon stereogenic center underwent a fast epimerization as a result of its acidity (the carbanion is stabilized by amide, sulfoxide groups and the aromatic ring). When traces of base such as imidazole were added to a chloroform or benzene solution of ***7u*** and ***7l***, receptor ***7u*** isomerized completely to ***7l***, and hence ***7u*** could no longer be detected in the ^{1}H NMR spectra (Fig. 3). Modelling studies using the ONIOM[70–72] hybrid method with the Gaussian 98W[73] program revealed that the sulfoxide oxygen can establish two strong H-bonds with receptor NHs that stabilize the formation of the *l* epimer (Fig. 4). As the chemical shifts were insensitive to dilution, it is very likely that the formation of

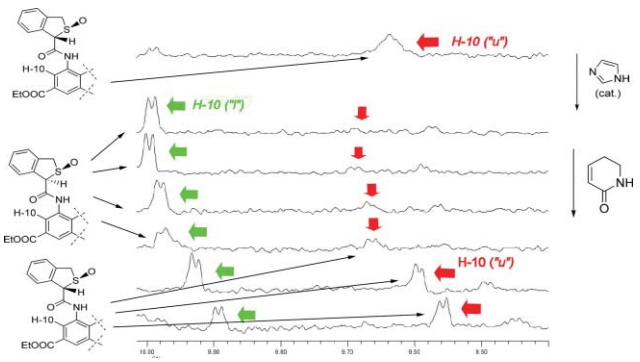


Fig. 3 ^{1}H NMR spectra of ***7u*** and ***7l*** receptor equilibrium mixtures as lactam **1** is added to the benzene solution. Proton H-10 is compared.

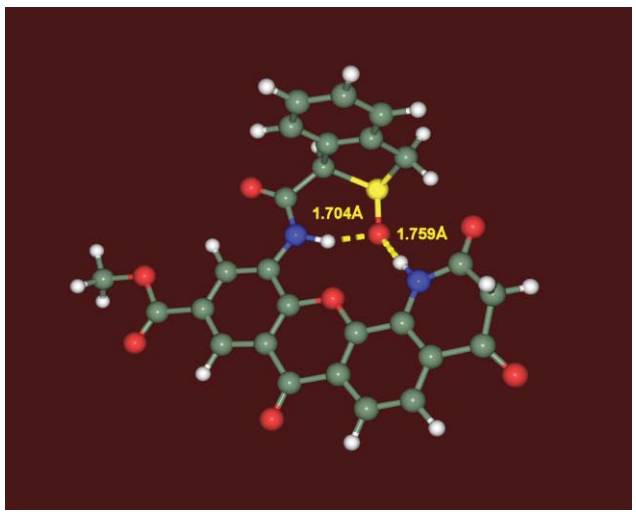


Fig. 4 Optimized geometry (ONIOM B3LYP/3-21G**::PM3MM) of the model of receptor ***7l*** establishing intramolecular H-bonds between the NH groups and the sulfoxide oxygen atom.

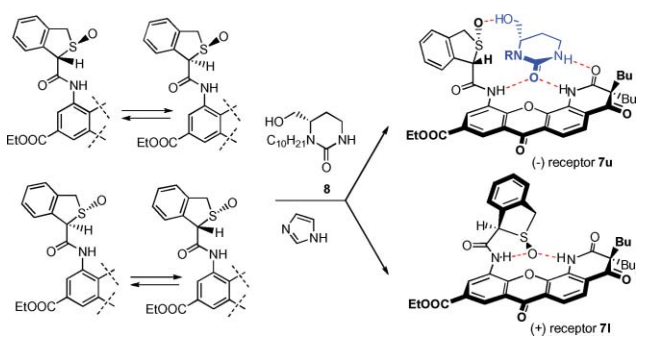
intermolecular complexes is not relevant, so the only interaction is the intermolecular H-bonds in the *l* form. The additional stability of these H-bonds shifts the position of the equilibrium to this diastereoisomer.

This hypothesis was confirmed after the addition of increasing amounts of a guest to the receptors, such as the lactam **1** used as substrate in the reaction. The guests are able to compensate the effect of the intramolecular H-bonds, since the formation of the complex competes with the intramolecular interactions. Therefore, the preference for the *l* epimer disappears and the ^{1}H NMR spectrum reveals a 1/1 mixture of *u* and *l* forms when enough guest has been added. Interestingly, under the reaction conditions, the amount of active *u* form should have been less than 50%, regardless of which isomer was initially used. This explains the similar catalytic activity of both receptors and indicates that the catalytic activity of the active *u* form can be calculated to be at least $(2385/6.5) \times (1/0.05) \simeq 7300$, considering that only 5% of mol of catalyst is used. Moreover, if the *l* form is not as effective catalyzing the reaction and only one half of the catalyst is in the *u* form, the real catalytic activity could be as high as $7300 \times 2 = 14600$.

Receptor **7*u*** (or **7*l***) is a good candidate for study of its asymmetric induction, since the chiral sulfoxide should support proton transfer through a single face of the lactam. Instead of designing its asymmetric synthesis, we considered that the epimerization equilibrium between the *u* and *l* forms would offer a possibility to resolve the racemic mixture using a strategy similar to dynamic combinatorial chemistry, by means of the supramolecular properties of the receptor and its interaction with a template analogue to the transition state of the reaction.

Dynamic combinatorial chemistry[74–79] is based on the reversible formation of covalent or non-covalent bonds in the presence of a template, such that when equilibrium is reached, a prevalence of the compound(s) that can establish supramolecular interactions with the template is favored. The driving force that displaces the equilibrium is the formation of the supramolecular complex with this template. In the case of receptors **7*u*** and **7*l***, traces of a base made the equilibrium possible. This epimerization changes the geometry of the receptor dramatically, which affects its ability to interact with the template. Thus, although no additional bonds are formed, the methodology of dynamic combinatorial chemistry can be used to select a particular enantiomer of the receptors, provided that the appropriate chiral template is used.

Based on the above ideas, we designed chiral urea **8** (Scheme 1) as a good candidate to assist in this resolution. This structure



Scheme 1 Chiral resolution of receptor **7** using urea **8**.

resembles a possible transition state for the reaction of lactam **1** and pyrrolidine. Considering the good catalytic activity of the receptor **7*u***, this structural similarity might involve an H-bond interaction between the hydroxyl group in the urea and the sulfoxide in the catalysts. Additionally, this compound was obtained from asparagine (see ESI†), and therefore can readily be prepared enantiomerically pure. Competitive titration in chloroform (see ESI†) revealed that urea **8** was associated with one of the *u* sulfoxide stereoisomers 7.14 times more strongly than with the other *u* stereoisomer, and more than 264 times more strongly than with either of the two *l* stereoisomers.

Under conditions that facilitate the equilibrium, the intramolecular H-bonds favored the 7*l* form, but when an excess of urea **8** was added, the thermodynamic advantage of the **7*l*** form was lost since the complex formation broke the intramolecular H-bonds. Since any of the **7*u*** receptor enantiomers can make stronger complexes than the **7*l*** receptors, it was indeed expected that the epimerization equilibrium would be displaced to the *u* form. When only 0.5 equivalents of chiral urea **8** were added, the amount of guest was insufficient to make the complex with the receptor, and accordingly only one enantiomer of the receptor (the one involved in the stronger diastereomeric complex) would interact with the guest under thermodynamic control. Since the formation of the strongest complex exhausts the guest added, the other enantiomer would remain in the *l* form, because in this way the stabilization of the intramolecular H-bonds can be exploited. When equilibrium was reached, the racemic mixture of receptor **7*l*** was transformed into a mixture of two diastereoisomers. One of them was involved in the formation of the strongest complex with the chiral guest **8** (and therefore corresponded to the *u* form). The other was present in the equilibrium in the most stable form when no guest was present, the *l* form, since this geometry is compatible with the intramolecular H-bonds. It is important to note that this methodology does not correspond either to kinetic resolution[80–82] or to dynamic kinetic resolution,[80,81,83–87] since in this case the resolution was performed under thermodynamic control (and therefore time-independent) conditions.

The mixture of diastereoisomers obtained by this thermodynamic control was resolved by column chromatography using silica gel impregnated with L-tartaric acid (TLC analysis revealed two spots corresponding to the diastereoisomers, but in the preparative scale the acid in the stationary phase was needed to prevent further epimerization, as it freezes the equilibrium for the mixture of receptors). The complex with the urea was broken, and owing to the intramolecular H-bonds the *l* sulfoxide was more easily eluted than the *u* form (see ESI†). This procedure afforded two fractions corresponding to 70% e.e. and 66% e.e. of each enantiomer, but it could be repeated on the enriched mixtures to obtain a product with e.e. >95%. An advantage of this procedure is that unlike other methods based on supramolecular recognition that use differential elution on TLC plates impregnated with a chiral guest[88] it can be scaled up to several grams of product.

The absolute configuration of chiral centers was studied in this *l* form since intramolecular H-bonds allow easier interpretation of the circular dichroism spectrum. This spectrum was simulated with theoretical methods (time dependent-DFT), following the procedures described in the literature[89,90] (see ESI†). After comparing the theoretical and experimental CD spectra (Fig. 5), it was observed that the *l* isomer obtained as indicated above when

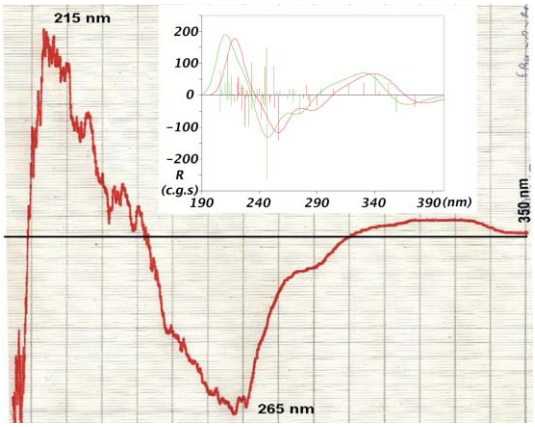


Fig. 5 Comparison between the experimental ($\Delta\varepsilon$ (*265 nm*)= *-25.36*; $\Delta\varepsilon$ (*215 nm*)= *+29.26*) and TD-DFT simulated CD spectra (in red: B3LYP/3-21G**; in green: MPW1PW91/3-21G**).

L-asparagine derived urea was used had an *R* absolute configuration on the sulfur and *R* on the carbon atom. Thus, the *u* stereoisomer with the strongest association constant with urea **8** derived from L-asparagine has an absolute configuration of *S* on the sulfur and *R* on the carbon atom.

The asymmetric induction obtained with this receptor was investigated under the same conditions as in previous experiments,[7–9] but the nucleophile concentration was reduced to 0.80 M. To determine the degree of chiral assistance, a xanthone-based chiral shift reagent was used, which splits α pyrrolidine ^{1}H NMR signals of enantiomeric amino lactams. Integration of these signals afforded a 5 : 1 enantiomeric ratio at the half-life time. The *R* absolute configuration of the major product was established by circular dichroism.[8] CPK models and modelling studies confirmed that this was indeed the expected configuration when the sulfoxide oxygen was involved in the proton transfer. In the case of modelling studies, two diastereomeric transition state structures were obtained, the one yielding the *R* compound being 6.14 kcal mol^{-1} more stable (Fig. 6). The energy difference obtained is large compared with the observed enantioselectivities, but it should be noted that the size of the system precludes to use of a higher level of theory, which would allow more reliable results to be obtained.

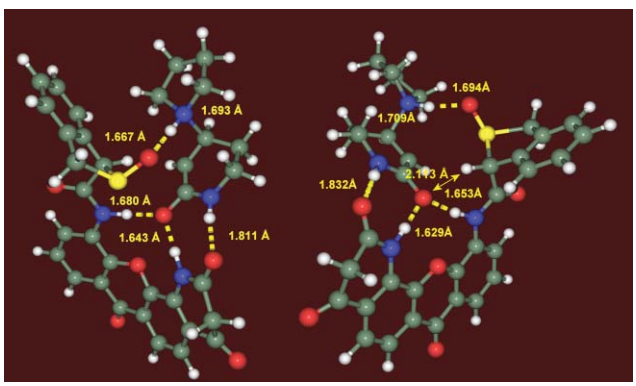


Fig. 6 Optimized transition state structures (ONIOM B3LYP/3-21G**:PM3MM, further details in ESI†) leading to *R* (left) and *S* (right) enantiomers for the addition of pyrrolidine to lactam **1** catalyzed by (-) receptor ***7l*** (model).

Conclusions

As in previous studies,[8] this work confirms that non basic groups can assist proton transfer mechanisms if they are able to act as H-bond acceptors. This was not only confirmed by the increase in the catalytic activities, but also by the enantioselectivity observed in the reaction when the chiral catalyst was used. Nevertheless the chiral enrichment should be improved to consider the synthetic usefulness of the catalysts, although the confirmation of the catalytic role of sulfones and sulfoxides might inspire the design of new catalysts able to improve the e.e. and reaction rates.

In a precedent work,[91] we have observed that xanthone receptors containing amino groups showed k_{cat}/k_{uncat} values up to 10^4 for this reaction, but the half-life time was not reduced accordingly since self aggregation of these receptors precludes the association of the substrate. With these new receptors, which include groups different than amines for assisting the proton transfer, the catalytic activity is not improved significantly. Nevertheless, the increase of the association constant implies a considerable reduction in the half-life time of the reaction.

More interestingly, we have employed a new method used for the chiral resolution of the catalysts that offers an alternative to kinetic resolution. The method described is based on the supramolecular interactions of the catalyst with a chiral guest and on the reversible epimerization of the catalysts, in full agreement with the principles and ideas underlying dynamic combinatorial chemistry. This is not limited to the separation of catalyst enantiomers, but a similar methodology might be useful in the resolution of other compounds of interest with at least two stereogenic centers, provided that: i) an epimerization equilibrium is possible and ii) that the diastereoisomers are involved in the formation of supramolecular complexes with a chiral receptor such that the receptor shows a preference for association with one of the four possible diastereoisomers. The first condition is similar to the racemization required in dynamic kinetic resolution, and important advances have been obtained through the use of metal catalysts[92–98] or enzymes.[93,96] The second condition replaces the need for a selective chiral catalyst that will preferentially react with one enantiomer.[99–101] Considering the advances in supramolecular chemistry and chiral recognition, fulfilling this second condition might be possible in cases where no chiral catalyst exists, offering a new possibility for resolution.

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