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Dynamic control of chiral space

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Summary

Responsive molecular systems are systems, which upon external stimuli; produce observable changes of physical or chemical properties. Those changes are typically the result of configurational or conformational changes. They have recently gained a lot of interest in the scientific community in attempts to mimick dynamic functions in biological systems. One of the fascinating potential applications of responsive systems lies in catalysis. Inspired by Nature, novel responsive catalytic systems are built, which show analogy with allosteric regulation of enzymes. The design of responsive catalytic systems allows control of catalytic activity and selectivity. A major part of the research presented in this thesis deals with the design, synthesis and properties of novel responsive systems capable of dynamic control over catalytic functions. Apart from that, exploring the dynamic control of chiral space was pushed even further, by investigating the possibility of dynamic chiral anion binding.

In the first chapter, the advances in the field of responsive catalysis over the last four decades are discussed. A comparison of dynamic responsive systems based on the principles underlying their catalysis mechanism is presented. The catalyst systems are sorted by the trigger used to achieve control of the catalytic activity and their applications in various catalytic reactions are illustrated.

In chapter 2, the design of a novel motor-based organocatalyst is presented, with which dual stereocontrol of the Henry reaction was achieved (Figure 1). The research in this chapter was based on the breakthrough previously reported by group, where the three distinct states of a molecular motor (stable *trans*, unstable *cis* and stable *cis*) were employed in catalysis and showed significantly different activities and selectivities in the Michael addition of 2-methoxythiophenol to 2-cyclohexen-1-one. The structure of the originally published catalyst was modified, by bringing catalytically active moieties, thiourea and DMAP, into greater proximity and the new catalyst was shown to be more active and selective than the original catalyst, in the Henry reaction. Using external triggers, light and heat respectively, distinct enantiomers of the Henry reaction product could be obtained with very good yields and enantioselectivities.

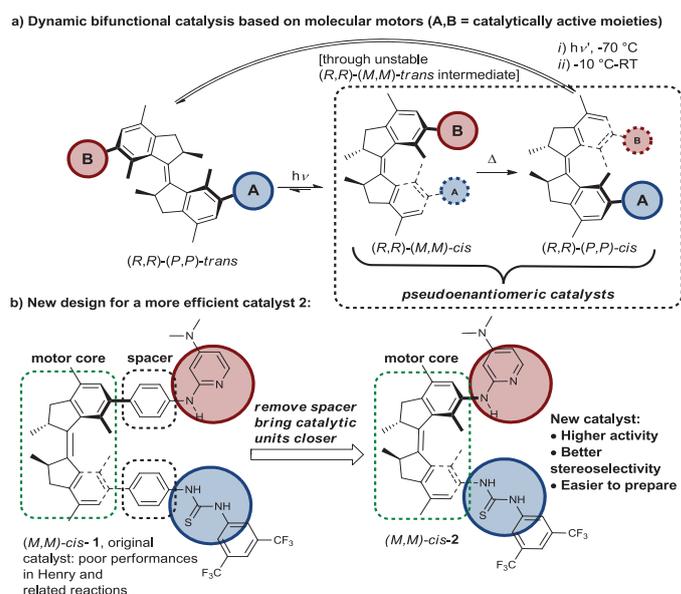


Figure 1 Responsive asymmetric organocatalyst: molecular motor based catalyst for dual stereoselective synthesis and original and new catalyst design.

Chapter 3 deals with the process of ‘unclicking’ thioureas which was encountered as a side process happening during the thermal step of the unidirectional rotary cycle of the novel DMAP thiourea catalyst described in chapter 2. Apart from the characterization of the aniline and isothiocyanate products eliminated during the rotary cycle it was shown with model thiourea compounds that such elimination of anilines and isothiocyanate compounds is a general phenomenon, which takes place under elevated temperatures and in the presence of a base.

In Chapter 4 two novel bithiourea motor-based catalysts are described and tested in the Henry reaction. It has been shown that the base component of the catalytic system, such as DMAP, does not need to be covalently bound to the catalyst in order to achieve high activity of the catalyst and enantioselectivity in this C-C bond transformation. The results obtained with the DMAP thiourea catalyst described in chapter 2 were comparable with those achieved using aromatic bithiourea catalyst. In contrast to the precedences in literature, where it is claimed that aliphatic thioureas as part of catalyst are more active and selective, it was shown that in our case the aromatic bithiourea demonstrates more potent and selective catalysis than its aliphatic analogue.

Chapter 5 describes a bisurea receptor, derived from the first generation molecular motor, which has shown to be very selective for binding dihydrogen phosphate. The receptor could be switched photochemically and thermally between three isomers with distinct anion binding affinities. Using the chiral version of the bisurea receptor it has been shown that the stable *cis* and unstable *cis* form of receptor exhibit enantioselectivity for the binding of chiral binol phosphate (Figure 2).

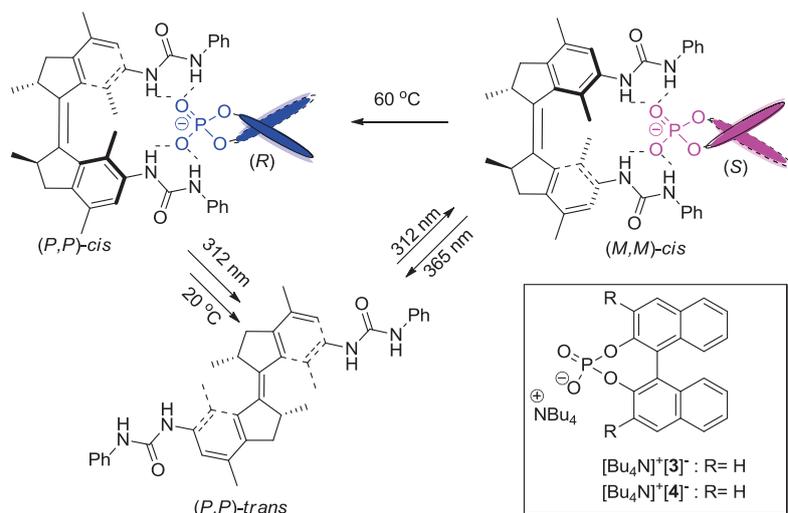


Figure 2 Isomerization and coordination behavior of the chiral bisurea receptor.

In Chapter 6 synthetic efforts towards a new photoswitchable phosphoric acid are described. Unfortunately even though we came very close to the final target molecule, the overall synthesis was extremely low yielding, which did not allow for the synthesis of larger amounts of material, necessary to perform catalytic studies. Nevertheless a series of novel overcrowded alkenes has been synthesized in attempts towards the synthesis of a chiral photoswitchable phosphoric acid. Significant progress has been made towards the final molecule using a novel lithium based homocoupling (which was recently described in our group). Novel overcrowded alkenes were studied in depth. It has been found that the size-difference of the substituent on the naphthyl ring of the upper half of overcrowded alkene significantly affects the half-life of thermal relaxation.

Overall, the research presented in this thesis contributes to the better understanding of how space restricted by chiral boundaries, can create a chiral environment at the molecular scale, and how this environment can be controlled in a dynamic fashion. Dynamic switching of such “chiral space” can *e.g.*, be used to control the basic parameters of a catalytic function: activity and selectivity. Also, it could be used to switch the affinity towards anions, and even control the enantioselectivity in binding chiral anions. The insight and knowledge gained whilst studying those fascinating molecular systems may bring new opportunities for future research in the field of responsive systems, enantioselective catalysis and anion receptors, as well as pave the way for potential practical applications.