Summary

Chirality is a fundamental aspect of modern organic chemistry. Many biologically active compounds, ranging from pharmaceuticals to agrochemicals, flavor, fragrances and nutrients are chiral. During the last century, scientists have jointly built a strong and multifaceted knowledge of stereochemistry, which led to the development of a plethora of stereoselective synthetic methodologies and analytical techniques. While static stereochemistry deals with the spatial arrangement of atoms in molecules and the corresponding chemical and physical properties, dynamic stereochemistry emphasizes structural change and comprises asymmetric reactions as well as interconversion of configurational and conformational isomers. Dynamic stereochemistry plays a fundamental role across the chemical sciences, ranging from asymmetric synthesis to drug discovery and nanomaterials. The unique stereodynamics of chiral compounds have paved the way to artificial machines and other molecular devices that lie at the interface of chemistry, engineering, physics, and molecular biology. The stereospecific interaction between fixed and dynamic chirality of molecular and supramolecular systems has given access to a playground full of remarkable nanomachines capable of displaying controllable transfer and amplification of chirality. Among the several approaches exploited to achieve control over responsive molecular systems, the use of light as an external stimulus is characterized by its non-invasive nature, high spatio-temporal resolution, and selectable wavelength – hence energy – of radiation, which provides asymmetric responses by photoisomerization of chiral molecular switches or motors. Most remarkable examples for application of light-driven systems are based on sterically overcrowded alkenes, azobenzenes and dithienylethenes derivatives (Scheme 1), which confer helix inversion and motion capabilities to nanovehicles, liquid crystals, polymers, gelators, catalysts, and biological derivatives.

Scheme 1. Most popular light-responsive molecular switches: a) azobenzenes; b) dithienylethenes; c) molecular motors.

The work described in this thesis explores how of second generation molecular motors/switches can be tuned, modified and applied in photoswitchable catalysis. The final aim is to develop alternative designs of switchable catalysts which could display improved thermal stability and more advanced catalytic performance when compared with previously described systems based on first generation molecular motors. We envisioned these novel responsive scaffolds to be tailored for applications via multiple modes of catalytic activity (e.g. metal-catalysis, organocatalysis, activity control, dual stereocontrol) and in wider range of reaction conditions (e.g. temperature, reaction time).
Summary

Chapter 1 provides an introduction to the concept of photo-controlled dynamic transfer of chirality. The most popular types of photoresponsive switches and related isomerization mechanisms are presented. Subsequently, relevant examples of applications of molecular switches and motors to achieve dynamic transfer of chirality are discussed. Main fields of application include: molecular motion, control over supramolecular, liquid crystal or polymer morphology, stereoselective catalysis, chiral recognition, and control of biological derivatives. The aim is hereby to draw the attention on how the light-responsive dynamic chirality of such systems is used to selectively induce a reversible and reproducible asymmetrical response for smart applications in functional materials.

Chapter 2 describes the synthesis and experimental and computational investigation of four overcrowded alkenes 2.1-2.4 featuring scaffolds analogous to second generation molecular motors (Scheme 2). Irradiation with UV light allowed for high yielding E-Z isomerizations providing metastable diastereoisomers. Kinetic studies on metastable isomers using CD and HPLC identified two pathways at high temperatures for thermal isomerization. All the metastable isomers displayed unprecedented high energy barriers for thermal helix inversion, thus making the alternative thermal E-Z isomerization the predominant relaxation process. In order to show the value of these overcrowded alkenes as bistable switches, photochemical switching cycles were performed which proved the alkenes to be excellent switches displaying good reversible selectivity and fatigue-resistance. The switch featuring a phenanthrenyl upper-half 2.1 showed the best performance as reversible photochromic selector, while the benzo[f]thiochromene derivative 2.4 excelled in thermal stability, both exhibiting highly selective isomerizations. These favorable switching properties offer attractive prospects towards the design of novel photoresponsive bistable catalysts.

Scheme 2. Schematic representation and isomerization pathways of overcrowded alkenes 2.1-2.4 discussed in Chapter 2.

Chapter 3 describes the design and synthesis of two photoresponsive bifunctionalized catalysts 3.1 and 3.2 (Scheme 3a) based on corresponding overcrowded alkene cores 2.1 and 2.2 investigated in Chapter 2. Each motor half is equipped with a catalytically active group, with the aim of obtaining bifunctional switches whose catalytic activity could be turned ON and OFF by light-induced configurational isomerization (Scheme 3b). The compounds show switching upon irradiation with 312 nm light, forming the corresponding metastable states with high photostationary state ratios. Interestingly, they do not exhibit reversible switching upon irradiation at longer wavelength. Based on comparative results with differently functionalized derivatives, the dimethylamine group was hypothesized to have a detrimental influence on the reversibility of the switching processes. Switches St-(E)-3.1 and St-(Z)-3.2 display properties of photoswitchable catalytic activity control in the Michael addition reaction between (E)-3-bromo-β-nitrostyrene and 2,4-pentanedione (Scheme 3c). From the experimental results, both isomers displayed a decrease in catalytic activity upon irradiation to the metastable state. As opposed to our initial assumption
of controlling the activity of the thiourea moiety by steric hindrance or hydrogen bonding interactions, both \( E \)- and \( Z \)-isomers behave comparably as ON/OFF catalytic switches upon photoisomerization with clear changes in reaction rate and turnover frequency, regardless of the catalyst geometry. Therefore, such behavior does not seem predominantly regulated by the steric hindrance exerted by the amine substituent around the thiourea moiety.

\[ \text{Scheme 3. a) Schematic representation of catalytically active bifunctionalized overcrowded alkenes discussed in Chapter 3. b) Proposed designs of bifunctionalized overcrowded alkenes for light-assisted control of catalytic activity. c) Light-assisted control of catalytic activity in organocatalyzed Michael addition.} \]

Chapter 4 describes the study towards a trifunctionalized molecular photoswitch based on an overcrowded alken for light–assisted tandem catalytic processes (Scheme 4a). We proposed a two-step sequence of Morita–Baylis–Hillman (MBH) reaction and enamine catalyzed aldol reaction catalyzed by merging two pairs of orthogonal bifunctional catalytic groups. Preliminary tests on the catalytic performance in MBH reaction of bifunctional molecular switches 3.1 and 3.2 described in Chapter 3 were discouraging. Alternative designs, featuring thiourea and tertiary amine or phosphines groups and aimed to improve the catalytic activity in the MBH reaction, and respective attempted syntheses are presented (Scheme 4b).

Lastly, we explored other organocatalyzed reactions that could be mediated by the initially proposed photoswitchable catalysts design (e.g. conjugated addition; alkylation via benzyl transfer; decarboxylative protonation; alcoholysis). In all instances, the screening tests described herein were performed by using compound 4.5 as a model catalyst, due to its inherent similarity with the \( Z \)-isomers of 3.1 and 3.2. As opposed to our initial assumption, no activity was observed in any case. As demonstrated in this work, an aromatic amine substituent was shown to be a poorly active catalytic moiety.
Summary

Scheme 4. a) Proposed design of a trifunctionalized light-responsive organocatalyst for ‘one-pot’ assisted tandem catalysis. b) Proposed alternative designs of bifunctionalized overcrowded alkenes derivatives 4.1-4.4 and binaphthyl-derivative 4.5 used as model catalyst discussed in Chapter 4.

Chapter 5 describes the synthesis and study of a photoresponsive molecular switch 5.1, featuring a versatile 2,2'-biphenol motif in which chirality is transferred across three stereochemical elements has been designed and successfully executed. The design of 5.1 was based on parent compound 2.3 described in Chapter 2 to achieved good photoresponsive properties and thermal stability. The comparison of experimental and computational data confirmed the proposed model of coupled central-to-helical-to-axial transfer of chirality, demonstrating the most favored conformation of the lower aryl substituent to be parallel to the fluorenyl lower half of the switch core. Investigation with CD and UV-vis absorption spectroscopy, $^1$H NMR spectroscopy and chiral HPLC analysis proved the reversible photoswitchability of 1. However, compared with the forward photoisomerization at 365 nm, the reverse process induced by irradiation at 420 nm was shown be less selective, yielding an equimolar mixture of isomers of 5.1 with opposite helicities. The dynamic central-to-helical-to-axial-to-central transfer of chirality was successfully applied to creation of another stereogenic element, as demonstrated by using $(R)$-5.1 as photoswitchable stereoselective catalyst in the enantioselective addition of diethylzinc to benzaldehydes. Clear reversal of enantioselectivity was accomplished for each substrate, with ee’s of secondary alcohols up to 68% and $\Delta$ee’s up to 113%.
Scheme 5. a) Schematic representation of photoswitchable 2,2'-biphenol-substituted overcrowded alkene 5.1 and relative photochemical isomerization described in Chapter 5. b) Light-assisted control of stereoselectivity in enantioselective addition of organozinc to aromatic aldehydes.

Chapter 6 describes the synthesis and study of five photoresponsive chiral phosphoramidite-molecular switch derivatives L, obtained from parent compound 5.1, in which chirality is dynamically transferred across from five to seven stereoechemical elements (Scheme 6a). The unique combination of a light-triggered molecular switch featuring a bridged biaryl-derived monodentate ligand moiety allows reversible photo-switching between two stereochemical forms with distinct ligand properties. The ligands were used to alter the activity and invert the stereoselectivity of the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one (Scheme 6b). Catalysis results supported by kinetic experiments suggest that each diastereoisomer of the ligand provides a distinctive activity and opposite stereoselectivity in the asymmetric catalytic event. This results in an elegant balance of two competing diastereoisomeric catalysts (Scheme 6c), of which complementary catalytic performance is tunable upon photoisomerization due to the reversible matched-mismatched interaction between the dynamic chirality of the switch unit and the fixed chirality of the phosphoramidite ligand site.

Scheme 6. a) Schematic representation of chiral photoresponsive phosphoramidite ligands L and relative photochemical isomerization described in Chapter 6. b) Light-assisted control of activity and stereoselectivity in enantioselective copper-catalyzed addition of diethylzinc to 2-cyclohexen-1-one. c) Schematic top-down view of Cu-L complexes: for each (S,Sp)- or (S,Rp)-diastereoisomer two metal-ligand complexes with opposite coupled helicity (M or P) can be selectively addressed by irradiation with UV-light.

Chapter 7 describes the synthesis and study of a photosensitive chiral phosphoric acid 7.1, obtained from parent compound 5.1, in which chirality is dynamically transferred from the switch core to the biaryl motif (Scheme 7a). The established concept of coupled helical-to-axial transfer of chirality described in Chapters 5-6 is further extended to a non-P-stereogenic phosphoric acid functionality for application in...
organocatalysis. Experimental analysis by UV-vis absorption, CD and $^1$H NMR spectroscopy proved the reversible photoswitching properties of 7.2. Its applicability as a switchable stereoselective organocatalyst was investigated in a selection of previously reported Brønsted acid-catalyzed transformations. Unfortunately, slow reaction rates and no asymmetric induction were observed in each case. In attempt to increase catalytic efficiency and asymmetric induction, a more complex design of a 3,3'-biaryl substituted phosphoric acid switch derivative 7.2 was proposed (Scheme 7a) and an attempt towards its synthesis is described.

Scheme 7. a) Schematic representation of chiral photosensitive phosphoric acid derivative 7.1 and relative photochemical isomerization described in Chapter 7. b) Proposed alternative design of phosphoric acid 7.2 featuring a 3,3'-disubstituted-biaryl switch core.

Chapter 8 describes the study towards a bidentate biaryl bis(diphenylphosphine) ligand 8.1 based on an overcrowded alkene for photoswitchable asymmetric homogeneous metal-catalyzed transformation (Scheme 8a). Unlike the designs previously described in Chapters 5-6-7, hereby an efficient coupled motion with effective inversion of the local chirality surrounding the coordinated metal center is envisioned to occur only in the bidentate metal-ligand complex ML$_n$-8.1. The proposed synthetic route started with derivatization of 2,2'-bisphenol functionalized molecular switch 5.1 to provide the corresponding bis-triflate 8.2 (Scheme 8b). Palladium-catalyzed phosphorylation and phosphine oxide reduction yielded the monophosphine-derivative 8.3. Various procedures to synthesize the bis-phosphine derivative 8.1 failed, supposedly due to the high steric hindrance that impedes the metal-catalyzed phosphination mechanism. An attempt to redirect the goal of the project to the development of a chiral photoswitchable Brønsted acid catalyst 8.4, featuring diphenylphosphine and phenol functionalities on the biphenyl unit, is described.

Scheme 8. a) Schematic representation of proposed metal complexes ML$_n$-(S)-8.1 and relative photochemical isomerization described in Chapter 8. b) Attempted synthetic route stating from 5.1 towards bis(diphenylphosphine)-derivative 8.1 and hydroxy-diphenylphosphine-derivative 8.4.