Recent advances in molecular design have displayed striking examples of dynamic chirality transfer between various elements of chirality, e.g. from central to either helical or axial chirality and vice versa. While considerable progress in atroposelective synthesis has been made, it is intriguing to design chiral molecular switches able to provide selective and dynamic control of axial chirality with an external stimulus for functional application. This chapter describes the synthesis and characterization of a photoresponsive bis(2-phenol)-substituted molecular switch 1. The novel design exhibits a dynamic hybrid central-helical-axial transfer of chirality. The change of preferential axial chirality in the biaryl motif is coupled to the reversible switching of helicity of the overcrowded alkene core, dictated by the fixed stereogenic center. The potential for dynamic control of axial chirality was demonstrated by using (R)-1 as switchable catalyst to control the stereochemical outcome of the enantioselective addition of diethylzinc to aromatic aldehydes, with successful reversal of enantioselectivity for several substrates.

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The computational studies here reported were performed by J. C. M. K. and T. v. L. For more details, see also: J. C. M. Kistemaker, PhD thesis, University of Groningen.
5.1 Introduction

Chirality plays a fundamental role in a myriad of biological processes, including information storage and transmission, gene expression, energy production and cellular motion. For instance, life has developed on Earth by optimizing its biological functions using L-amino acids as polypeptide building blocks and D-glucose as chemical energy source. The chirality of D-deoxyribose is amplified to the (almost) exclusively right handed helices of DNA. The supreme control of directional movement showcased by biological machine structures like ATP synthase, proteasomes, ribosomes, myosin, kinesin and bacterial flagella are astonishing demonstrations of how transfer of chiral information leads to accurate control of metabolic functions and motion in cells. None of these processes could take place without precise propagation, amplification and coupling of movement, from the very bottom scale of single molecular chiral motifs to the fine interplay of large protein sub-units.

While early research on stereochemistry mainly focused on point chirality, other motifs that feature axial chirality, helical chirality, and planar chirality have been extensively investigated for their potential use in synthesis, in asymmetric catalysis, and as chiral dopants. Compared with molecules that feature fixed central chirality (i.e. point chirality), axially chiral compounds may not comprise stereogenic center(s) yet exist as enantiomers. Atropisomers belong to the class of axially chiral compounds: in this case the enantiomers exist due to the restricted rotation around a single bond. The stereodescriptor for distinctive axial chirality ($R_a, S_a$) is assigned according to the CIP rules (Figure 5.1a). Atropisomers also display axial helicity ($P_a, M_a$) similarly to overcrowded alkenes (Figure 5.1b).

![Schematic representation of biaryl atropisomers chirality](image)

**Figure 5.1.** Schematic representation of biaryl atropisomers chirality: a) axial chirality ($R_a/S_a$); b) axial helicity ($P_a/M_a$), where $0^\circ<\alpha<90^\circ$.

The phenomenon of equilibration of stereoisomers about a rotational axis - atropisomerization - has become a main topic of investigation in organic, materials, and medicinal chemistry. Despite a number of responsive molecular devices based on reversible cis-trans isomerization of double bonds, cyclizations, redox cycles and rotation around single bonds, only limited examples of stimuli responsive systems featuring elements of axial chirality have been reported. Focused efforts have produced elegant systems displaying unidirectional aryl–aryl bond rotation of biaryl structures via sequential addition of chemical stimuli, overcoming the atropisomerization energy barrier inherently featured by the open structures via more flexible macrocyclic or tricyclic intermediates. Among the atropisomeric chiral inductors, biaryl-type ligands have also played an undisputed central role in the field of catalytic asymmetric transformation. Crafting from the most common 1,1'-binaphthyl motif, a myriad of derivatives, e.g. BINOL, BINAP, BINAM, phosphoramidites, organic phosphoric acids, etc., have been developed, tuned and tested by chemists to fulfill nearly any possible stereochemical task. Hence,
atroposelective synthesis and selective functionalization of axially chiral biaryl compounds gained major attention during the last decades.\textsuperscript{12,13,37,38} Here we report the photochemical control of axial biaryl chirality by a light-responsive BINOL-type catalyst based on a chiral molecular switch, which displays dual stereocontrol in an asymmetric addition of organozinc reagents to aromatic aldehydes. Limited examples of reversible biaryl dihedral angle restriction based on molecular switching have been reported as a strategy for controlling the degree of extended conjugation.\textsuperscript{39–41} Despite interesting approaches to use external stimuli such as redox modulation of a disulfide bridge,\textsuperscript{42} pH-change\textsuperscript{43} and ion binding,\textsuperscript{44} stereocontrol of the atropisomerization was not achieved. Noticeably, an approach to develop an axial chirality switch for application as a responsive ligand was reported in a study by Breit and co-workers, showing solvent-dependent atropisomerism of a flexible 2,2'-biphenol core bridged tricyclic structure,\textsuperscript{45} however, catalytic application was not included. Therefore, the major challenge remains to design chiral molecular switches able to selectively and dynamically generate and exploit axial chirality with an external stimulus. Combining dynamic chirality, chirality transfer, and photoswitches,\textsuperscript{46–48} our group has achieved control of activity and stereoselectivity\textsuperscript{49} by switchable catalytically active first generation molecular motors (see Chapter 4 for further details).\textsuperscript{50–53} These catalysts harness the intra- and intermolecular transfer of chirality to ultimately control the stereochemical outcome of a catalytic transformation via photochemical and thermal induced isomerizations of a functionalized unidirectional four-stage rotary motor. We anticipate that the development of new molecular switches which harness the pairing of hybrid helical-axial chiralities within chiroptical switchable units could provide unprecedented levels of dual stereoselective induction with non-invasive control and high spatio-temporal resolution. By combining the fixed point chirality originating from the two stereocenters on either side of the overcrowded alkene with the dynamic alkene configuration and helical chirality, the configuration and enantiomeric excess of the catalysis product could be reversibly controlled.

5.2 Results and discussion

5.2.1 Design and modeling calculations
Molecular motors of the second generation are helical-shaped overcrowded alkenes consisting of a symmetric tricyclic lower half and an asymmetric upper half that features a single stereocenter.\textsuperscript{54–56} Harnessing the hybrid chirality generated by the stereogenic center and the helical structure, the photochemical E-Z isomerization (PEZI) and thermal helix inversion (THI) of the central alkene bond allow to achieve unidirectional rotary motion controlled by a light- and heat-driven four-stage cycle (Scheme 5.1). The combinations of an upper half containing a six-membered ring and a lower half featuring a five membered ring, are characterized by a high activation energy for the thermal relaxation process and have been recently reported as a new class of bi-stable photoswitches.\textsuperscript{55,57} Due to the long half-life at room temperature, i.e. high thermal stability, of their photo-generated metastable isomers, they allow for the design of systems capable of displaying dual stereocontrol while retaining the desired configuration for extended time intervals at elevated temperatures. This property, combined with their unique dynamic helical chirality, is highly desirable in the field of switchable catalysis. We envisioned that merging a flexible 2,2'-biphenol core with the rotor of a rigid second generation overcrowded alkene scaffold would result in transfer of chirality from the helical core of the overcrowded alkene to the biphenyl unit by steric interactions (Scheme 5.2). In this way the distinctive dynamic helicity of the switch unit and the versatility of the substituted biaryl motif are combined. Based on our recent study,\textsuperscript{57} we envisioned the combination of a tetrahydroanaphthalenyl upper half and a fluorenyl lower half to ensure desirable photoswitching properties, inversion of helicity and high thermal stability. A similar scaffold (tetrahydrophenanthrenyl upper half) in fact displayed a long living metastable isomer ($t_{1/2}$ at 20°C = 1.3 years) and efficient reversible photoswitching properties, allowing to selectively address both the stable (S) and metastable (MS) isomer achieving high photostationary state (PSS) ratios (S:MS = 93:7 at 420 nm; S:MS = 3:97 at 365 nm).
Scheme 5.1. Isomerization processes leading to unidirectional rotation in second generation molecular motor. Four-stage cycle with only two distinctive stereoisomers in case of symmetrically substituted lower half (here $R \equiv R'$). S = stable isomer, MS = metastable isomer.

Introduction of an additional aryl substituent ($R = \text{Ar}$) in the fjord region of such a molecular switch would result in a biaryl of which the chirality is governed by the photochemically induced rotation of the overcrowded alkene. The system described herein features three stereochemical elements (Scheme 5.2). The first element is the stereogenic center of the switch (highlighted in red), which can exist with either the $R$ or $S$ configuration. The second element is the helicity of the overcrowded alkene (highlighted in blue), which is controlled by the configuration at the stereogenic center but can be inverted upon photoisomerization.

Scheme 5.2. Design of photoswitchable 2,2'-biphenol-substituted overcrowded alkene 1. Axial helicity and chirality (green) of the 2,2'-biphenol core are coupled to axial helicity (blue) and point chirality (red) of the molecular switch scaffold. Here assigned descriptors are based on the structure of compound $(R)$-1 (for explanation of the chiral descriptors, vide infra). Two isomers with opposite coupled helicity can be selectively addressed by irradiation with UV-light: $(R,P,S_a)$-1 (S); $(R,M,R_a)$-1 (MS).
More precisely, the more stable diastereoisomer (stable isomer) of the R enantiomer will adopt a P helicity, while the photo-generated diastereoisomer with higher energy (metastable isomer) will adopt an M helicity. Third is the axial chirality of the biaryl unit (highlighted in green), which can be assigned to either R<sub>a</sub> or S<sub>a</sub> according to the CIP rules. For biphenyls with an average dihedral angle of 90°, such as ortho substituted biphenyls, these stereochimistry descriptors are interchangeably used with R and P, respectively. Depending on the size of the groups and substitution pattern at the ortho positions, the dihedral angle can be smaller than 90°. Each rotamer with either R<sub>a</sub> or S<sub>a</sub> absolute configuration possesses two conformational helical geometries, also assigned as right-handed (P) or left-handed (M) according to the CIP rules. Recently our group reported a study on the tidal locking of an aryl moiety in a molecular motor, showing that among the four theoretically possible conformations of a biaryl unit only conformations in which the non-annulated aryl group was parallel to the fluorenyl lower half were adopted. Similarly, the other conformations, with the aryl orientated perpendicular with respect to the lower half, are expected to induce significant steric strain also in the system described here (see Figure 5.2b). With such a diastereotopic constraint, the true helicity (P<sub>a</sub>/M<sub>a</sub>) of the biaryl is inextricably connected to the helicity (P<sub>/M<sub>) of the overcrowded alkene chromophore, and is identical to it in each isomer. Therefore, three stereodescriptors (R/S, P/M and R<sub>a</sub>/S<sub>a</sub>) will be sufficient for the assignment of any expected isomer reported in this work. So for isomer (R<sub>P</sub>,P<sub>S</sub>,S<sub>a</sub>)-1: R = configuration of stereogenic center, P<sub>/> = helicity of alkene, S<sub>a</sub> = axial chirality of biaryl (see Figure 5.2a). The asterisks at the stereodescriptors throughout the text denote a racemic mixture of isomers with identical relative stereochemistry (e.g. R<sup>*</</sup>,P<sup>*</</sup>,S<sub>a</sub> means a mixture of R,P,S<sub>a</sub> and S,M,R<sub>a</sub>). The doubly expressed axial stereodescriptor (R<sub>a</sub>/S<sub>a</sub>) throughout the text denote a mixture of rotamers with identical absolute stereochemistry at the stereocenter and configurational helicity but opposite axial chirality (e.g. R,P,S<sub>a</sub>/R<sub>a</sub> means a mixture of atropisomers R,P,S<sub>a</sub> and R,P,R<sub>a</sub>).

Figure 5.2. a) Example of top-down schematic view and front structural view of (R<sub>P</sub>,P<sub>S</sub>,S<sub>a</sub>)-1. Upper half ring (red, methyl substituent omitted); fluorenyl lower half (blue); biaryl moiety (black). Assigned stereodescriptors based on the structure of compound (R)-1 (see main text for details). b) Depiction of the four possible conformations of the biaryl moiety as viewed from the top along the central double bond and biaryl single bond. c) H-bond assisted biaryl rotation of 2,2'-biphenol with inversion of stereochemistry. d) Schematic energy vs. biaryl torsional angle profile upon clockwise rotation of lower phenol group around aryl-aryl bond.

Central-to-Helical-to-Axial-to-Central Transfer of Chirality in a Photoresponsive Catalyst
Chapter 5

The inversion of axial chirality in biphenols is likely to take place via a coplanar transition state along the syn-periplanar conformation of the phenol rings taking advantage of the intramolecular hydrogen bonds between the hydroxyl groups (Δ\^G° = 48.1 kJ mol\(^{-1}\), T = 298.15 K; Figure 5.2c), based on a DFT study by Fujimura and co-workers.\(^5\) These calculations support the proposal of reversible axial chirality when applied to our system, as we expected the syn- and anti-conformers (hydroxyl groups in proximity or pointing away from each other, respectively) to be in equilibrium in solution in the absence of metals or other coordinating species. A schematic representation of the four possible conformations of 1 upon rotation of the aryl-aryl bond is presented in Figure 5.2b. We expect conformations with matching helicities of biaryl and overcrowded alkene units to be highly favored (A and C), while the two conformers with the aryl perpendicular to the lower half experience steric hindrance (B and D), as shown in the relative energy vs. torsional angle profile plot based on DFT calculations (vide infra) (Figure 5.2d). Our proposed model entails a coupled helical-to-axial transfer of helicity, in which the most favored conformation of the rotor aryl substituent is parallel to the fluorenyl lower half of the switch core. Scheme 5.3 illustrates the delicate interplay of dynamic stereochemical elements and the switching process between the stable isomer and metastable isomer of (R)-1 with all the expected conformers. Starting from the stable isomer, rotamers \((R,P,R_a)\)-1 and \((R,P,S_a)\)-1 interchange via atropisomerization (A) presumably facilitated by an internal hydrogen bonding between the two phenolic moieties.\(^5\) We envisioned that upon irradiation with UV-light of \((R,P,S_a)\)-1 and \((R,P,R_a)\)-1 into the corresponding conformers of metastable isomer \((R,M,R_a)\)-1 and \((R,M,S_a)\)-1 the upper half containing the biaryl motif rotates with respect to the fluorenyl lower half yielding isomers with opposite helicity (\(P\to M\)). Notably, the metastable isomer was also expected to display atropisomerization (B). We undertook a theoretical study a priori to verify the design as shown in Figure 5.2, with particular attention to the barrier for biaryl rotation and the relative energy of the four accessible conformers upon reversible irradiation.

**Scheme 5.3.** Schematic representation of switching process between the rotamers of stable isomer \((R,P,R_a)\)-1 (top and bottom left) and metastable isomer \((R,M,R_a)\)-1 (top and bottom right). Proposed ground states of rotamers (top and bottom) and transition states (middle) of atropisomerization processes, as viewed from the top along the axis given by the double bond. Proposed catalytically active syn-isomers highlighted in the boxes.
The structures of the four ground states were computed via DFT method calculations (see J.C.M. Kistemaker’s PhD thesis for further details), which suggested an energetic preference in both biaryl rotation equilibriums (A and B, Scheme 5.3) for the conformers (\(R.P.S.a\)-1 and (\(R.M.R.a\)-1, respectively. The latter are characterized by having the lower hydroxyl substituent pointing away from the central overcrowded alkene in a syn conformation with the upper phenol group. In summary, our design is based on the following elements: a) the selective and reversible photo-isomerization of the overcrowded alkene; b) the unique change in helicity governed by the configuration of the stereo-genic center; c) the coupled change in axial chirality of the biaryl core achieved via a central-to-helical-to-axial transfer of chirality, d) application of the switchable chiral biphenol functionality with potentially manifold applications in catalytic enantioselective transformations.

### 5.2.2 Synthesis

Key steps in the synthesis of 1 are the Barton-Kellogg coupling of thiofluoren-9-one 7 and 1-diazo-7-methoxy-8-(2-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydronaphthalene 6, followed by deprotection of the bis-phenol moiety and chiral resolution of the target molecule 1 as illustrated in Scheme 5.4.

**Scheme 5.4.** Synthesis and chiral resolution of 2,2'-biphenol molecular switch 1. Note on resolution of 1: i) result from first resolution; ii) \((S.M.R/S.a\)-1 obtained by second resolution of the solid fraction: (R,9R)-(-)-N-benzylcinchonidinium chloride 10 0.9 equiv, 79% yield, >99% ee (solid); (R,9R)-1 obtained by second resolution of the residue from solution: 10 0.3 equiv, 81% ee (residue from solution), followed by recrystallization from EtOH/H\(_2\)O = 1:1 of the residue from solution, 15% yield, 96% ee.
Commercially available 7-methoxy-1-tetralone was brominated with N-bromosuccinimide in acetonitrile to yield 2.\textsuperscript{60} follow by Suzuki-Miyaura cross-coupling catalyzed by Pd$_3$dba$_5$ and SPhos to provide the dimethoxy-biaryl motif in ketone 3.\textsuperscript{61} α-Methylation provided ketone 4 (86%), which was converted to the corresponding hydrazone 5 (75%) via condensation with hydrazine monohydrate using Sc(OTf)$_3$ as a catalyst. The diazo coupling partner 6 was accessed via in situ oxidation with [bis(trifluoroacetoxy)iodo]benzene at low temperature. Fluorene-9-thione 7, freshly synthesized by thionation of 9-fluorenone with Lawesson's reagent, was subsequently added to yield a variable mixture of episulfide 8 and overcrowded alkene 9 (see Experimental section). After separation, the remaining episulfide was desulfurized by treatment with HMPT at elevated temperature to provide 9 (85%, for the 3-step sequence). The use of boron tribromide, widely applied for the deprotection of methoxy-substituents, resulted in partial decomposition of the overcrowded alkene and in an inseparable mixture of target compound and side-products. Successful deprotection was accomplished using methyl magnesium iodide at 165 °C\textsuperscript{62} to afford racemic (R*,P*,S$_a$/R$_a$)-1 (86%) as a mixture of two atropisomers in their thermodynamic ratio (60:40 in CDCl$_3$) according to $^1$H NMR analysis. Optical resolution of 1 was accomplished by two-step resolution with (8S,9R)-(−)-N-benzylcinchonidinium chloride (10) in ethyl acetate.\textsuperscript{62} Both enantiomeric mixtures of conformers were obtained in high optical purity: (R,P,S$_a$/R$_a$)-1 (96% ee, 15%); (S,M,R$_a$/S$_a$)-1 (>99% ee, 31%). The structure of 1 was proven by NMR spectroscopy (see following section), HRMS, as well as by single-crystal X-ray structure analysis. By means of a high-brilliance Cu IμS microfocus source (Cu K$_\alpha$ radiation wavelength = 1.54178 Å), the absolute configuration of enantiomerically pure (R)-1 was determined despite the absence of atoms that show significant anomalous scattering.\textsuperscript{63–65} The reconstructed unit cell of the lattice was shown to contain only the syn-conformer (R,P,S$_a$)-1 (Figure 5.3).

**Figure 5.3.** a) X-Ray structure of (R,P,S$_a$)-1. Left: front view; right: top view. Ellipsoids set at 50% probability. Hydrogen bond lengths (intra: H101–O1 1.874 Å, inter: H100–O1’ 1.826 Å) and Oxygen-Oxygen distances (intra: O1–O2 2.629 Å, inter: O1–O2’ 2.685 Å). b) Newman projections. Left: Left: top view through overcrowded alkene bond. Right: top view through aryl-aryl bond of biaryl unit. Torsional angles of alkene unit (13.92°) and biaryl unit (55.71°) are shown.
The experimental data confirmed the proposed model of coupled helical-to-axial transfer of helicity, demonstrating the most favored conformation of the lower aryl substituent to be parallel to the fluorenyl lower half of the switch core (synclinal) in the crystal lattice. The dihedral angle over the biaryl motif determined from the X-ray structure in the solid state was found to be 55.7°.

5.2.3 NMR spectroscopy and atropisomer assignment

The experimental data confirmed the proposed model of coupled helical-to-axial transfer of helicity, demonstrating the most favored conformation of the lower aryl substituent to be parallel to the fluorenyl lower half of the switch core (synclinal) in the crystal lattice. The dihedral angle over the biaryl motif determined from the X-ray structure in the solid state was found to be 55.7°.

5.2.3 NMR spectroscopy and atropisomer assignment

The $^1$H NMR spectra of an enantiomerically pure solution of stable ($R,P,S_a/R_a$)-1 in toluene-$d_8$ (Figure 5.4) revealed a relative integration of the best resolved absorptions of the atropisomers ($R,P,S$)-1 (A) and ($R,P,R_a$)-1 (B) in a ratio of A:B = 67:33 [Figure 5.5 for proton positions and Figure 5.4 for corresponding NMR absorptions – fluorenyl proton 37: δ 7.78 ppm (A), 7.70 ppm (B); proton 19 at the stereogenic center: δ 3.95 ppm (A), 3.86 ppm (B); methyl protons 45-46-47: δ 1.34 ppm (A), 1.22 ppm (B)].

![Figure 5.4](image-url) **Figure 5.4.** $^1$H NMR spectrum (toluene-$d_8$) of 1, with highlighted sets of characteristic absorptions of major (A) and minor (B) atropisomers. The same spectrum was obtained from either racemic mixture or enantiomerically enriched fractions of 1.

Similar behavior with minor variation in the ratio where obtained in other deuterated solvents (solvent, A:B ratio: CDCl$_3$, 60:40; DMSO-$d_6$, 60:40; MeOD, 63:37; CD$_3$CN, 66:34; benzene-$d_6$, 66:34). Based on calculated $^1$H NMR spectra, we assigned the experimental sets of peaks to the corresponding atropisomers of stable 1 as follows. Figure 5.5a depicts the schematic 2D-representation of the biaryl isomerization equilibrium of the atropisomers of stable 1, with stereochemical assignment. Figure 5.5b reports the schematic representation with labeling of carbon atoms of conformer ($R,P,S_a$)-1. Figures 5.5c-d illustrate the calculated optimized geometries of conformers ($R,P,S_a$)-1 and ($R,P,R_a$)-1, respectively, with labelled atoms for NMR peak assignment listed in Tables 5.1 and 5.2. Calculated $^1$H and $^{13}$C NMR spectra of ($R,P,S_a$)-1 and ($R,P,R_a$)-1 (DFT giao mPW1PW91/6-311+G(2d,p) in toluene (SMD)) were compared with experimental spectra of ($R,P,S_a/R_a$)-1 (in toluene) (vide infra, Figures 5.6 and 5.7). According to the calculated chemical shifts, the experimental peaks were assigned to conformers ($R,P,S_a$)-1 (major) and ($R,P,R_a$)-1 (minor), respectively. Despite the difference in absolute chemical shift value, the relative
position of the experimentally assigned absorptions peaks for the major and minor atropisomer in the experimental $^1$H NMR spectra are in full agreement with the corresponding calculated absorption peaks for $(R,P,S_a)$-1 and $(R,P,R_a)$-1, respectively (Table 5.1). Notably, every resonance absorption (except the one assigned to atom 52) of the major isomer $(R,P,S_a)$-1 resonates at higher frequency than the minor isomer $(R,P,R_a)$-1. However, comparison of the $^{13}$C NMR spectra did not display a consistency to such a high extend in this regard (Table 5.2).

![Diagrams](image)

**Figure 5.5.** a) Schematic 2D-representation of the biaryl isomerization equilibrium of atropisomers of stable state $(R,P,S_a/R_a)$-1. b) C-labelled structure of $(R)$-1. Calculated optimized geometries of $(R,P,S_a)$-1. c) Calculated optimized geometries of $(R,P,R_a)$-1. Calculations and rendering performed by J.C.M. Kistemaker and T. van Leeuwen.
Table 5.1. List of $^1$H NMR chemical shifts of labelled atoms for atropisomer assignment, obtained and assigned via experimental 1D- and 2D-NMR and via calculation.

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Table 5.2. List of $^{13}$C NMR chemical shifts of labeled atoms for atropisomer assignment, obtained and assigned via experimental 1D- and 2D-NMR and via calculation.

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<tr>
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<td>152.86</td>
<td>153.43</td>
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Figure 5.6. $^1\text{H}$ NMR spectra (toluene-$d_8$) comparison of calculated optimized structures of atropisomers $(R,P,S_a)-1$ (middle) and $(R,P,R_a)-1$ (bottom) with experimental spectra of $(R,P,S_a/R_a)-1$ (top), atom label assignment as listed in Table 5.1.

Figure 5.7. $^{13}\text{C}$ NMR spectra (toluene-$d_8$) comparison of calculated optimized structures of atropisomers $(R,P,S_a)-1$ (middle) and $(R,P,R_a)-1$ (bottom) with experimental spectra of $(R,P,S_a/R_a)-1$ (top), atom label assignment as listed in Table 5.2.
5.2.4 Atropisomerization process

The chiral resolution and initial characterization of 1 by \(^1\)H NMR disclosed a very interesting yet initially unexpected phenomenon. Although stable isomer 1 could be resolved in two enantiomerically pure fractions, which by chiral HPLC analysis appeared to comprise single compounds and eluted as sharp symmetric peaks (see Experimental section, both racemic and enantiopure fractions comprised two inseparable species, as displayed by \(^1\)H NMR spectroscopy analysis. Notably, no variation in the atropisomers ratio was observed upon \(^1\)H NMR spectra comparison of several samples of either racemic or enantioenriched fractions of 1. Based on our design, we assumed these can be attributed to two equilibrating syn- and anti-atropisomers (Scheme 5.3).

\(^1\)H NMR spectroscopy coalescence experiments

Initial attempts to determine the rate of the atropisomerization process via dynamic NMR focused on the coalescence of the aforementioned diagnostic absorption peaks corresponding to the proton in position 1 of the fluorenyl stator (H37, see Figures 5.4 and 5.5). With this technique, dynamic aspects of systems that are at chemical equilibrium can be studied. In particular, the NMR time scale includes a range of reaction rates that are often encountered in the laboratory, \(10^{-1}-10^{-5}\) s\(^{-1}\). In addition, rotational barriers in the range 12-80 kJ mol\(^{-1}\) can be studied by this method. The requirements for the use of dynamic NMR are (a) the chemical exchange between the proton associated to the inspected peaks and (b) the exchange time scale to be slow or fast enough to cause broadening of the NMR lines. The coalescence temperature \((T_c)\) is used in conjunction with the maximum peak separation in the low-temperature (i.e. slow-exchange) limit \((\Delta \nu\) in Hz) to determine the activation energy parameters. The exchange rate constant \((k_{\text{exc}})\) in these calculations, for nearly all NMR exchange situations, is actually \(k_1+k_2\) in a system for X exchanging with Y, where:

\[
\text{X} \xlongrightleftharpoons[k_1][k_2]{\text{Y}}
\]

and the rate of exchange \(k_{\text{exc}}\) at the coalescence temperature:

\[
k_{\text{exc}} = \frac{m \Delta \nu}{\sqrt{2} h} = \frac{k_B T}{h} e^{-\Delta^f G/RT}
\]

The equation to estimate \(\Delta^f G\) using the coalescence temperature is:

\[
\Delta^f G = RT \left[ \ln \left( \frac{k_B T}{h} \right) - \ln(k_{\text{exc}}) \right] = RT \left[ 23.760 + \ln \left( \frac{T_c}{k_{\text{exc}}} \right) \right]
\]

\(^1\)H NMR spectra (300 MHz) of a sample of stable state \((R,P,S)\)-1 in toluene-\(d_8\) were recorded at temperatures ranging from 50 to 100 °C (highest working temperature allowed for our NMR spectrometer). No coalescence of the aforementioned diagnostic absorption peaks (A-B, see Figures 5.8 and 5.9) was observed, suggesting a high activation barrier for the biaryl rotation process, not evaluable via this technique. Focusing our attention on the diagnostic absorption peaks in the downfield aromatic region (\(\delta_A = 7.78\) ppm; \(\delta_B = 7.70\) ppm; \(\Delta \nu = 24\) Hz), an exchange rate of 53.3 Hz would be required to observe coalescence, as calculated using equation 2. Since no coalescence was observed at 100 °C, the value of \(\Delta^f G_{\text{BI}}\) at rt could be estimated to be higher than 63 kJ mol\(^{-1}\) from equation 3 (similarly: \(\Delta^f G_{\text{BI}} > 70\) kJ mol\(^{-1}\) at 50 °C; \(\Delta^f G_{\text{BI}} > 80\) kJ mol\(^{-1}\) at 100 °C).
Figure 5.8. $^1$H NMR spectra (full spectrum) from coalescence experiments of $(R,P,S,R)$-1 in toluene-$d_8$.

Figure 5.9. $^1$H NMR spectra (partial spectrum, magnification of aromatic region) from coalescence experiments of $(R,P,S,R)$-1 in toluene-$d_8$. 

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$^1$H NMR spectra of a sample of stable isomer (R, P, S/R$_e$)-1 in toluene-$d_6$ were recorded at temperatures ranging from 50 °C to 100 °C. No coalescence of the aforementioned diagnostic absorption peaks was observed, suggesting the activation barrier for the biaryl rotation process to be higher than typical exchange processes usually determined via Dynamic NMR. Hence, the thermodynamic parameters of this isomerization process could not be determined via this technique at the investigated conditions, as higher temperatures would be required to display coalescence.

Dynamic HPLC experiments

Dynamic HPLC (DHPLC) analysis was also considered, as it was previously reported to allow for the successful determination of rotational barriers for other substituted biphenyl atropisomers. Dynamic HPLC on enantioselective stationary phases has become a well-established technique to investigate chiral molecules with internal motions that result in stereo-inversion and occur on the time scale of the separation process. Kinetic parameters for the on-column interconversion phenomena can be extracted from experimental peak profiles by computer simulation or by direct calculation methods. The technique has been used in a wide range of temperatures and is complementary in scope to dynamic NMR spectroscopy. The dynamic chromatographic profiles are dependent on the eluent flow rate and column temperature. By comparison of the experimental separation with computer simulated chromatographic profiles, the rotational energy barrier of atropisomers (or racemization barrier of enantiomers) can be determined. Resolution of peaks can be achieved when, at the elution conditions, half-life of racemization $t_{0.5}$ is in the scale of hours or longer, with $k_{rac} = 10^{-5}$ s$^{-1}$ (see equations 2-3). Complete coalescence is obtained when $t_{0.5}$ in the scale of ~10 min or shorter, with $k_{rac} = 10^{-3}$ s$^{-1}$. Despite the screening of temperatures down to 0 °C (lowest working temperature allowed by our HPLC instrument and AD-H column used for HPLC analysis of 1) and various mixtures of heptane:2-propanol, no splitting of the elution peaks was observed, indicative of a fast equilibration process even at lower temperatures. As complete coalescence is observed for stable state (R, P, S/R$_e$)-1 at 0°C, $\Delta \theta G$ could be estimated, using equation 2, to be lower than 88 kJ mol$^{-1}$ at rt ($\Delta \theta G_{BI} < 82$ kJ mol$^{-1}$ at 0°C; $\Delta \theta G < 94$ kJ mol$^{-1}$ at 40 °C).

Exchange spectroscopy measurements (EXSY)

The rotational process was eventually demonstrated and studied by one dimensional exchange spectroscopy (EXSY, $^1$H-$^1$H nuclear Overhauser enhancement spectra). When two NMR signals are undergoing dynamic exchange on the timescale of $T_1$, then saturation of one of the signals causes intensity changes in the other, since saturated nuclei will be transferred between the two forms by the exchange process. These intensity changes can be used to obtain quantitative rate data, as the change of relative intensities are temperature and mixing time dependent. According to the initial rate approximation method proposed by Ernst and co-workers, the rate of exchange (rate of atropisomerization $k$) can be calculated directly from the ratio of cross- ($a_{AB}$ and $a_{BA}$) and autopeak integrations ($a_{AA}$ and $a_{BB}$) and the mixing time using the formula:

$$\frac{a_{AA}}{a_{AB}} = \left(1-k t_m\right)/k t_m$$

provided a slow exchange situation and absence of scalar spin-spin coupling. This equation can be transformed into:

$$k = \frac{1}{t_m} \frac{a_{AB}}{a_{AA} + a_{AB}}$$

A plot of $t_m$ versus ($a_{AB} / (a_{AA} + a_{AB})$) will therefore directly give the rate constant $k$ at a given temperature. These $k$-values can be used subsequently to determine the thermodynamic constants, $\Delta \theta G$, $\Delta \theta H$ and $\Delta \theta S$, via a direct Eyring plot ($k$ versus $T$). The absorption peaks assigned to proton (H$_{37}$) at position 1 of the fluorenyl stator were also chosen for the EXSY experiments. The measurements were conducted in the temperature range of 39.2–60.9 °C, consisting of an arrayed cluster of multiple mixing times ($t_m$ from 0.10 s to 2.00 s) per temperature (samples: 10.0 mg of 1 in 0.7 mL of toluene-$d_6$) (Figure 5.10).
Their difference in chemical shift of the chosen absorptions is sufficiently large, due to the local anisotropy caused by the different conformation of the lower 2-phenol ring. Their resolved profile allowed successful monitoring of the exchange process at different temperatures. The biaryl isomerization process of I corresponds to an equilibrium process (i.e. comprising a pair of forward and reverse reactions). Thus a kinetic analysis as two opposite 1st order reactions system can be performed. In a simple equilibrium between two species:

\[ \text{A} \xleftrightarrow{k_\text{f}} \text{B} \]  

The constant \( K \) at equilibrium is expressed as:

\[
K = \frac{k_\text{f}}{k_\text{b}} = \frac{[\text{B}]_e}{[\text{A}]_e}
\]

where \([\text{A}]_e\) and \([\text{B}]_e\) are the concentrations of species A and B at equilibrium, respectively. The concentration of A at time t \(([\text{A}]_t)\) is related to the concentration of B at time t \(([\text{B}]_t)\) by the equilibrium reaction equation:

\[
[A]_t = [A]_0 - [B]_t
\]

This applies as well when time \( t \) is at infinity, i.e. when equilibrium has been reached:

\[
[A]_e = [A]_0 - [B]_e
\]

By definition of \( K \), it follows:
Chapter 5

\[ [B]_e = x_e = \frac{k_f}{k_f + k_b} [A]_0 \]  

and:

\[ [A]_e = [A]_0 - x_e = \frac{k_b}{k_f + k_b} [A]_0 \]  

The rate law for two equilibrating unimolecular reactions is described by the following equation:

\[ r = -\frac{d[A]}{dt} = k_f [A]_t - k_b [B]_t \]  

The derivative is negative because this is the rate of the reaction going from A to B, and therefore the concentration of A is decreasing. To simplify notation, let \( x \) be \([A]_0\), the concentration of A at time \( t \). Let \( x_e \) be the concentration of A at equilibrium. Then:

\[ r = -\frac{d[A]}{dt} = -\frac{dx}{dt} = k_f x - k_b [B]_t = k_f x - k_b ([A]_0 - x) = (k_f + k_b) x - k_b [A]_0 \]  

Since:

\[ k_f + k_b = k_b \frac{[A]_0}{x_e} \]  

The reaction rate becomes:

\[ \frac{dx}{dt} = k_b \frac{[A]_0}{x_e} (k_f + k_b) \]  

which results in:

\[ \ln \left( \frac{[A]_0 - [A]_e}{[A]_0 - [A]_e} \right) = (k_f + k_b) t \equiv [A]_t = ([A]_0 - [A]_e) e^{-(k_f+k_b)t} + [A]_e \]  

If the concentration at the time \( t = 0 \) is different from above, the simplifications above are invalid, and a system of differential equations must be solved. However, this system can also be solved exactly to yield the following generalized expressions:

\[ [A] = [A]_0 \frac{1}{k_f + k_b} \left( k_f + k_b e^{-(k_f+k_b)t} \right) + [B]_0 \frac{k_b}{k_f + k_b} \left( 1 - e^{-(k_f+k_b)t} \right) \]  

\[ [B] = [A]_0 \frac{k_f}{k_f + k_b} \left( 1 - e^{-(k_f+k_b)t} \right) + [B]_0 \frac{1}{k_f + k_b} \left( k_f + k_b e^{-(k_f+k_b)t} \right) \]

The observed rate constant is the sum of the individual rate constants \((k_f \text{ and } k_b)\):

\[ k_{\text{tot}} = k_f + k_b \]  

From the ratio \([B]/[A]_t\), the ratio of rate constants \(k_f/k_b\) can be calculated as expressed in eq. 9. Each formation rate constant can then be calculated as follows:

\[ k_f = \frac{k_{\text{tot}}}{[A]_t \left( 1 + \frac{[A]_t}{[A]_0} \right)} \]  

\[ k_b = \frac{k_{\text{tot}}}{[B]_t \left( 1 + \frac{[B]_t}{[B]_0} \right)} \]

It should be noted that throughout the entire NMR experiments both atropisomers are always present at the thermodynamic equilibrium ratio, which can vary with the temperature. However, as the EXSY experiment allows us to focus the attention on the evolution of single atropisomer upon selective excitation, the kinetic analysis was performed according to the simplified case as described above. The integral fraction \( f_{AB} = \text{integral fraction of cross-peak B upon excitation of A} \) of the obtained absorption peaks at \( \delta \) 7.78 ppm (A) and \( \delta \) 7.70 ppm (B), as assigned to the major and minor atropisomers of \((R.P,S)/(R,S)\)-1, respectively, was calculated for each experiment (temperature and mixing time) as follows:
Central-to-Helical-to-Axial-to-Central Transfer of Chirality in a Photoresponsive Catalyst

\[ f_{AB} = \frac{a_{AB}}{a_{AA} + a_{AB}} \]  \hspace{1cm} (22)

Exponential growth curves of the absorption peak of the minor atropisomer were obtained by plotting the integral fraction \( f_{AB} \) vs mixing time at each temperature. Curve fitting provided the total growth constant \( (k_{tot}) \) and associated standard error \( (\sigma_{ktot}) \) for each temperature, while the atropisomers ratio for each experiment was determined by \( ^1H \) NMR spectroscopy. The latter equalled to the \( k_f/k_b \) ratio for each experiment, from which each isolated rate constant \( k_f \) and \( k_b \) could be calculated as described above. The temperature of the NMR probe compartment during the EXSY experiments was measured with a Pt1000 RTD Temperature Sensor and the error \( (3\sigma_{st-T}) \) associated was assumed to be ±1 K. The standard error associated to each kinetic constant was determined through the quadratic variance of each variable. When a function used to calculate a value \( (f) \) involves multiplications or divisions:

\[ f = xy \]  \hspace{1cm} (23)

\[ f = x/y \]  \hspace{1cm} (24)

the associated standard error \( (\sigma_f) \) is calculated from the standard errors of the function parameters \( (\sigma_x, \sigma_y) \) as follows:

\[ \left( \frac{\sigma_f}{f} \right)^2 = \left( \frac{\sigma_x}{x} \right)^2 + \left( \frac{\sigma_y}{y} \right)^2 \]  \hspace{1cm} (25)

\[ \sigma_f = f \sqrt{ \left( \frac{\sigma_x}{x} \right)^2 + \left( \frac{\sigma_y}{y} \right)^2 } \]  \hspace{1cm} (26)

As described in eq. 21 or 22, in this work \( f \) denotes \( k_f \) or \( k_b \), while \( x \) denotes \( k_{tot} \) and \( y \) denotes the equilibrium ratios of atropisomers. The standard error associated to the equilibrium ratios was also determined accordingly, accounting for an error of 5% of the integral ratio value. A least squares analysis of the rates of isomerization versus the temperature on the original Eyring equation:

\[ k = k_{B,T} \cdot e^\left( \frac{\Delta H^\ddagger}{RT} \right) e^\left( -\frac{\Delta S^\ddagger}{R} \right) \]  \hspace{1cm} (28)

with appropriate weighing \( (1/k^2) \) afforded the entropies and enthalpies of activation of the forward isomerization (major into minor atropisomer). The standard errors \( (\sigma) \) were obtained from a Monte Carlo error analysis on the linearized Eyring equation:

\[ T \cdot \ln \left( \frac{k}{k_{B,T}} \right) = T \cdot \left( \ln \left( \frac{k_{B,T}}{k_B} \right) + \frac{\Delta S^\ddagger}{R} \right) - \frac{\Delta H^\ddagger}{R} \]  \hspace{1cm} (29)

from forty thousand randomly generated samples using calculated standard errors on rates \( (\sigma_k) \) and estimated standard errors on temperatures \( (3 \sigma_T = 1 K) \).\(^5\) Integral fraction versus mixing time curves and Eyring plot are reported in Figure 5.11b-c. The half-life of biaryl isomerization at room temperature \( (t_{1/2} \text{ at rt}, 20 \text{ °C}) \) is extrapolated to be in order of minutes \((1.2 \pm 0.4 \text{ min})\), while the ‘hour half-life temperature’ (temperature at which the half-life equals one hour) is calculated to be equal to -50.5±0.5 °C. This analysis explains why the isolation of atropisomers was not successful (requiring temperatures of -50 °C), the lack of coalescence in the \( ^1H \) NMR spectrum at high temperatures (extrapolated coalescence temperature: \( T_c \approx 177 \text{ °C} \) and the unresolved elution profile in the HPLC chromatograms. The value of \( \Delta^\ddagger G^\ddagger_{BI} \) was calculated at the average temperature of the EXSY measurements \( T_{AVG} = 49.7 \text{ °C} (322.9 K) \), while \( \Delta^\ddagger G^\ddagger_{BI} \) at rt was calculated at 20 °C. All the mentioned thermodynamic data are reported in Table 5.3. The value of \( \Delta^\ddagger G \) at \( \text{rt} \) \((78.2 \pm 1.1 \text{ kJ·mol}^{-1}) \) is within the expected range \((63 \text{ kJ·mol}^{-1} < \Delta^\ddagger G < 88 \text{ kJ·mol}^{-1}) \), vide supra) as estimated by comparison from the unsuccessful determination via dynamic \( ^1H \) NMR and dynamic HPLC techniques.
Figure 5.11. Integral fraction vs. mixing time curves and Eyring plot for the biaryl isomerization process of stable state \((R,P,S_{a})\)-1 to \((R,P,R_{a})\)-1. a) Schematic representation of the biaryl isomerization process of \((R,P,S_{a})\)-1 to \((R,P,R_{a})\)-1. b) Graph showing the relation between the mixing time \((t_{m})\) and the integral fraction \(f_{AB}\) (see Eq. 3) for stable state \((R,P,S_{a}/R_{a})\)-1 (10.0 mg in 0.7 mL of toluene-\(d_{8}\)), obtained by recording, upon excitation of peak A, 1D-NOESY experiments at fixed temperatures (312.32, 318.00, 322.45, 327.58, and 334.01 K) consisting of an arrayed cluster of mixing times \((t_{m}= 0.10, 0.20, 0.30, 0.40, 0.50, 0.65, 0.80, 0.95, 1.10, 1.30, 1.50, 1.70, 2.00 \text{s})\) per temperature. c) Least-squares analysis on the original Eyring equation (Eq. 4) with error bars of 3\(\sigma\).
Table 5.3. Thermodynamic parameters for biaryl isomerization (BI) of stable (R,P,Sa/Ra)-1 determined by the direct Eyring analysis (Figure 5.11c), with standard errors obtained from a Monte Carlo analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>( t_{0.5} ) at rt (s) [^{[a]}]</td>
<td>73.4±23.8</td>
</tr>
<tr>
<td>T at ( t_{0.5} = 1 ) h (°C)</td>
<td>-50.5±0.5</td>
</tr>
<tr>
<td>( \Delta^\circ H^\ddagger_{\text{BI}} ) (kJ·mol(^{-1}))</td>
<td>45.0±11.8</td>
</tr>
<tr>
<td>( \Delta^\circ S^\ddagger_{\text{BI}} ) (J·K(^{-1})·mol(^{-1}))</td>
<td>-113±37</td>
</tr>
<tr>
<td>( \Delta^\circ G^\ddagger_{\text{BI}} ) (kJ·mol(^{-1})) [^{[b]}]</td>
<td>81.6±0.4</td>
</tr>
<tr>
<td>( \Delta^\circ G_{\text{BI}} ) at rt (kJ·mol(^{-1})) [^{[a]}]</td>
<td>78.2±1.1</td>
</tr>
</tbody>
</table>

\[^{[a]}\] rt: 20 °C (293.15 K). \[^{[b]}\] Standard condition: \( T_{\text{AVG}} = 49.7 \) °C (322.9 K) and atmospheric pressure.

Notably, when the isolated metastable state (\( R,M,R,Sa/Ra \))-1 (via preparative HPLC, see Experimental section) was subjected to the same EXSY experiments (5.0 mg in 0.7 mL of toluene-\( d_8 \)), no exchange of the aromatic peaks (C, \( \delta \) 7.61 ppm; D, \( \delta \) 7.47 ppm; see Figure 5.12e) was observed (temperatures up to 60 °C). This observation, in accordance with the large elution band of the metastable state fraction obtained in the analytical HPCL run (see Experimental section), suggests a higher activation barrier, hence a slower isomerization rate, for the biaryl rotation process in the photo-generated state. No further investigation was performed due to the low signal-to-noise ratio obtained in the NMR spectra, which we hypothesized to be caused by detrimental convection effects in the toluene solution at high temperatures. As observed in the X-ray structure analysis and based on the model investigated by Fujimura and co-workers (\vide supra\), we proposed a thermodynamically favored cyclic seven-membered ring conformation generated upon internal coordination via hydrogen bonding of the two hydroxyl substituents (see Figure 5.2 and Scheme 5.3). Experimental evidence and calculation data suggest that such a conformation provides access to a transition state with a relatively low barrier for atropisomerization, allowing for a fast exchange of two atropisomers in solution at room temperature. In these two transition states (TS\(_{\text{BI}}\)-(\( R,P,\text{Syn} \))-1 and TS\(_{\text{BI}}\)-(\( R,M,\text{Syn} \))-1, see J. C. M. Kistemaker’s PhD thesis for further details)\(^8\) the hydrogen bond between the two phenol moieties is shorter than it is in any other conformation suggesting additional stabilization of the transition state with respect to its corresponding minima explaining the relatively low barrier for atropisomerization. Moreover, the barrier for biaryl rotation is sufficiently low to allow the desired syn atropisomer to act as a thermodynamic sink upon its depletion in a reaction selective for it, for instance by biphenol bidentate coordination to a metal center (\vide infra\, Scheme 5.5a). Indeed, the product of a metal bidentate complexation would require a syn conformation of the biaryl motif and concordant alkene and biaryl helicity, as the clash of the lower phenol moiety with the fluorenyl lower half in the conformation with discordant helicities would otherwise lead to very energetically unfavored species (Figure 5.2; \vide infra\, Scheme 5.5b).

### 5.2.5 Photochemical isomerization

**NMR spectroscopy**

In order to investigate the photochemical behavior of 1 (Figure 5.12a) in more detail, an NMR sample of stable isomer (\( R,P,Sa/Ra \))-1 in toluene-\( d_8 \) was irradiated with UV light (365 nm) for 30 min at room temperature. \(^1\)H NMR spectra were taken before (Figure 5.12b), during (Figure 5.12c) and after irradiation (Figure 5.12d). Upon irradiation two new sets of absorptions C and D with intensities increasing over time were obtained [proton H\(_{37}\) at fluorenyl stator: \( \delta \) 7.61 ppm (C), 7.47 ppm (D); proton H\(_{19}\) at the stereogenic center: \( \delta \) 3.75 ppm (C), 3.35 ppm (D); methyl protons H\(_{35-37}\): \( \delta \) 1.22 ppm (C+D, peaks not resolved)], which is indicative of the photo-induced isomerization to the metastable isomer (\( R,M,R,Sa/Ra \))-1 comprising of two distinct atropisomeric species, (\( R,M,Ra \))-1 (C) and (\( R,M,Sa \))-1 (D), respectively.

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Figure 5.12. a) Schematic representation of the photochemical E-Z isomerization of stable isomer \((R.P.S/R_a)-1\) to metastable isomer \((R.M.R/S_a)-1\). \(^1\)H NMR spectra of \((R)-1\) (~5.0 mg, toluene-\(d_8\) (0.7 mL), 25 °C): b) stable isomer \((R.P.S/R_a)-1\) (A:B = 67:33); c) after irradiation with UV light (365 nm) over 15 min of stable \((R.P.S/R_a)-1\) to the metastable isomer \((R.M.R/S_a)-1\) (~50% of MS); d) after irradiation over 30 min (~65% of MS). e) \(^1\)H NMR spectra of atropisomers of metastable isomer \((R.M.R/S_a)-1\), (C:D = 55:45), isolated by preparative HPLC (see Experimental section). Note: the codes A-B and C-D indicate the characteristic sets of absorptions of mixtures of atropisomers for stable and metastable isomer, respectively.
Their relative integration revealed a final ratio in toluene-$d_8$ of, $(R,P,S_a/R_a)$-1 $(A+B) : (R,M,R_a/S_a)$-1 $(C+D) = 35:65$, respectively, upon irradiation over 30 min. Due to the high thermal stability of the metastable isomers ($(R,M,R_a/S_a)$-1), isolation of the latter from a crude mixture of an irradiated solution of $(R)$-1 was achieved by preparative HPLC (see Experimental section). Analysis by $^1$H NMR revealed the metastable isomer to comprise a mixture of atropisomers $(R,M,R_a)$-1 (C) and $(R,M,S_a)$-1 (D) in a ratio of C:D = 55:45 (Figure 5.12e).

**UV-vis and CD spectroscopy**

The switching properties of $(R)$-1 were monitored by UV-vis absorption and circular dichroism (CD) spectroscopy (Figure 5.13). A schematic representation of the reversible photochemical E-Z isomerization process of $(R)$-1 is shown in Figure 5.13a. A solution of stable $(R,P,S_a/R_a)$-1 (toluene, 4.5·$10^{-5}$ M) in quartz cuvettes was purged with argon and irradiated at room temperature towards either the metastable isomer using UV light (365 nm, Figure 5.13b, black to red gradient) or the stable isomer using visible light (420 nm, Figure 5.13c, red to blue gradient). The reversible photochemical E-Z isomerization was found to be characterized by a clear isosbestic point at 368 nm, indicating the absence of side reactions. A bathochromic shift of the major absorption band $(\pi \to \pi^*)$ of about 40 nm was observed, indicative of an increase in alkene strain and consistent with other second generation motors and switches as is expected for the metastable form $(R,M,R_a/S_a)$-1. The sample was subsequently subjected to irradiation cycles (see Experimental section, Figure 5.14), displaying non-perfect switching fatigue resistance with a minor decomposition, as opposed to the highly resistant unfunctionalized parent compounds studied recently. This problem could be solved by irradiation of $(R)$-1 (solution in toluene, $\sim$4.0·$10^{-5}$ M) in presence of the radical scavenger TEMPO ($\sim$10$^{-5}$ M) towards opposite PSS mixtures, which resulted in no evidence of degradation after six irradiation cycles (Figure 5.13d). This observation suggests that radicals may be involved in the decomposition process. Lastly, a solution of stable $(R,P,S_a/R_a)$-1 (toluene, 4.5·$10^{-5}$ M) was subjected to CD spectroscopy in order to perform a qualitative analysis of the change in its helical structure (Figure 5.13e). The CD spectrum displayed a strong Cotton effect in the area of 320–370 nm. Upon irradiation with 365 nm light an inversion of the absorption band was observed, which is indicative of an inversion in helicity and shows that the photochemical isomerization of the stable isomers $(R,P,S_a/R_a)$-1 to the metastable isomers $(R,M,R_a/S_a)$-1 has occurred. Upon irradiation with 420 nm light, the original absorption band could be recovered. The presence of the metastable species was further confirmed by chiral HPLC analysis of irradiated mixture (see Experimental section). The ratio between the stable and metastable isomer in the PSS in a toluene solution was determined by a chiral HPLC analysis of the PSS mixtures using a detection wavelength at the isosbestic point (368 nm). An efficient photoswitching process was observed upon irradiation with 365 nm light, with a high ratio towards the metastable diastereoisomer (S:MS = 17:83) at the PSS$_{365}$. However, the reverse process upon irradiation at 420 nm light was found to be less selective, affording an equimolar mixture of stable and metastable isomers (S/MS = 50:50) at the PSS$_{420}$. 

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Figure 5.13. a) Schematic representation of photochemical E-Z isomerization of stable isomer \((R,P,S_a/R_a)-1\) to metastable isomer \((R,M,R_a/S_a)-1\). b) Experimental UV-vis absorption spectra of stable \((R,P,S_a/R_a)-1\) (toluene, \(4.5 \times 10^{-5}\) M, black) and irradiation with UV-light (365 nm) of \((R,P,S_a/R_a)-1\) towards the metastable isomer affording a PSS\(_{365}\) mixture (S:MS = 17:83, red) with isosbestic point at 368 nm. c) Experimental UV-vis absorption spectra of irradiation of the previous PSS\(_{365}\) sample using visible light (420 nm), resulting in reversed E-Z isomerization towards the stable isomer affording a new PSS\(_{420}\) mixture (S:MS = 50:50). d) Irradiation cycles of \((R)-1\) (toluene, \(-4.0 \times 10^{-5}\) M) in the presence of TEMPO \((-10^{-5}\) M) towards opposite PSS mixtures (red: 365 nm, 4 min; blue: 420 nm, 15 min). e) Experimental and calculated CD spectra of \((R)-1\) (toluene, \(5.0 \times 10^{-1}\) M): black, starting stable isomer \((R,P,S_a/R_a)-1\); red: CD spectra of PSS\(_{365}\) mixture; blue: CD spectra of PSS\(_{420}\) mixture; cyan: metastable isomer \((R,M,R_a/S_a)-1\). Note: PSS ratios determined by HPLC analysis of the irradiated solutions via quantitative analysis with PDA detector wavelength set at the isosbestic point (368 nm).
5.2.6 Switchable asymmetric catalysis

Having established the reversible switching process between \((R,P,S,R)\)-1 and \((R,M,R,R)\)-1, we investigated their abilities for dual stereocontrol in a model asymmetric catalysis reaction. As a proof of principle, we envisioned to use compound \((R)\)-1 as a switchable bidentate ligand, which could coordinate a metal center and eventually be applied to an asymmetric transformation acting as a tunable stereoselective catalyst (Scheme 5.5). We anticipated the isomers of 1 having an anti conformation of the biphenol unit (torsion angle = ±90°–180°, hydroxyl groups pointing away from each other) to be poor bidentate ligands. Therefore only the isomers with syn conformation (torsion angle = 0°–±90°, hydroxyl groups in proximity) were expected to efficiently bind an organometallic center and successfully transfer the chirality within a catalytically active complex (Scheme 5.5a,b). Hence we proposed that the tunable helicity (P or M) of the switch core in turn would dictate the preferential axial configuration (R\(\alpha\) or S\(\alpha\)) of the desirable syn conformation of the biaryl moiety and eventually, for instance, the configuration (R or S) of a newly formed stereogenic center when applied to an enantioselective catalytic event (Scheme 5.5c).

![Scheme 5.5](image-url)

Scheme 5.5. Schematic representation of mono- and bidentate coordination equilibrium upon reaction of \((R)\)-1 with organoalkyl reagents. We anticipated light-assisted dual stereocontrol in a catalyzed organometallic reaction. a) Depiction of the possible mono- and bidentate coordination species upon reaction of stable isomers of 1 with ZnR\(_2\). b) Only the isomer with syn conformation (torsion angle = 0°–±90°) were expected to efficiently bind a metal center and successfully transfer the chirality within a catalytically active complex. c) Light-assisted dual stereocontrol could be achieved in a catalyzed organometallic reaction upon photoisomerization of \((R)\)-1 and internal transfer of chirality to the coordinated metal site.

Zn-BINOL-derived complexes have previously been reported to successfully mediate the catalytic asymmetric aldol\(^{82-84}\) and hetero-Diels-Alder\(^{35}\) reactions. We decided to use compound \((R)\)-1 as a switchable bidentate ligand in 1,2-addition of diethylzinc to benzaldehyde. Numerous efforts have been devoted in the past decades to develop new effective chiral ligands for asymmetric addition of diethylzinc to benzaldehyde.\(^{86-90}\) However, only few cases have been reported in which dual stereocontrol was achieved by tuning the reaction conditions. The switching of enantioselectivity in the catalytic addition of diethylzinc to aldehydes was obtained by changes in the reaction conditions (e.g. solvent, temperature) while using the same chiral additive.\(^{91-94}\) Alternatively, complementary catalytic systems were developed by the use of distinctive structural derivatives from a common chiral catalyst scaffold to access both enantiomers of the desired products.\(^{95-98}\)
Chapter 5

In the representative reaction (see Scheme in Table 5.4), benzaldehyde 11a was added to a mixture of ligand (R)-1 and a solution of diethylzinc in toluene, yielding a mixture of secondary alcohol 12a and the side-product benzyl alcohol 13a. The latter is the product of the aldehyde reduction, a known process occurring in the case of a slow addition process and proposed to derive from the β-hydride elimination of organozinc species and subsequent reduction of the substrate in case of poorly activated zinc complexes.99,100 As we anticipated, photo-induced switching of ligand (R)-1 allowed successful reversing of stereoselectivity in the 1,2-addition of diethylzinc to benzaldehyde. The results of the catalysis experiments are presented in Table 5.4. 1H NMR analysis allowed determining the conversion and selectivity of organozinc addition versus aldehyde reduction to benzylic alcohol. The enantiomeric excess (ee) of chiral secondary alcohols 12a-g was determined by chiral HPLC or GC analysis. In addition to benzaldehyde, several para- and ortho-substituted aromatic aldehydes bearing electron-withdrawing or electron-donating groups were tested as substrates. In all cases, when the stable form (R,P,S,R)-1 was used as a catalyst, the preferred formation of the (R)-enantiomer of secondary alcohols 12 was observed, with ee’s up to 68% (entry 1, Table 5.4).101

Table 5.4. Dynamic enantioselective addition of organozinc to aromatic aldehydes with (R)-1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conversion of 11 (%)</th>
<th>Yield of 12 (%)</th>
<th>ee of 12 (%)</th>
<th>Δee of 12 (%)</th>
<th>12/13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>(R)-1</td>
<td>&gt;95</td>
<td>86</td>
<td>68 (R)-12a</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>87</td>
<td>45 (S)-12a</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>(R)-1</td>
<td>94</td>
<td>80</td>
<td>35 (R)-12b</td>
<td>81:19</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>80</td>
<td>24 (S)-12b</td>
<td>81:19</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>(R)-1</td>
<td>94</td>
<td>87</td>
<td>40 (R)-12c</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>86</td>
<td>42 (S)-12c</td>
<td>88:12</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>(R)-1</td>
<td>66</td>
<td>37</td>
<td>40 (R)-12d</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>76</td>
<td>55 (S)-12d</td>
<td>97:3</td>
</tr>
<tr>
<td>9</td>
<td>Et</td>
<td>(R)-1</td>
<td>&gt;95</td>
<td>58</td>
<td>48 (R)-12e</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>79</td>
<td>50 (S)-12e</td>
<td>85:35</td>
</tr>
<tr>
<td>11</td>
<td>Et</td>
<td>(R)-1</td>
<td>&gt;95</td>
<td>81</td>
<td>46 (R)-12f</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>Et</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>72</td>
<td>31 (S)-12f</td>
<td>83:17</td>
</tr>
<tr>
<td>13</td>
<td>i-Pr</td>
<td>(R)-1</td>
<td>95</td>
<td>40</td>
<td>&lt;5 (±)-12g</td>
<td>N.A</td>
</tr>
<tr>
<td>14</td>
<td>i-Pr</td>
<td>(R)-1 + 365 nm</td>
<td>&gt;95</td>
<td>57</td>
<td>&lt;5 (±)-12g</td>
<td>58:42</td>
</tr>
<tr>
<td>15</td>
<td>Et</td>
<td>/</td>
<td>59</td>
<td>24</td>
<td>N.A</td>
<td>N.A</td>
</tr>
</tbody>
</table>

* General reaction conditions: 0.0125 mmol of (R,P,S,R)-1 in 0.5 mL of dry toluene at 0 °C; 0.375 mmol of R,Zn (Et,Zn, 1.0 M in hexane; i-Pr,Zn, 1.0 M in toluene) added dropwise and stirred over 10 min; 0.125 mmol of 11 added to the mixture. Reaction mixture stirred for 7 d at 0 °C. Reaction with irradiated mixture of (R)-1: 0.00125 mmol of (R,P,S,R)-1 in 15 mL of dry, degassed Et,O, irradiated with UV-light (365 nm) for 30 min until the PSS was reached (S:MS = 17:83). PSS ratio determined by chiral HPLC analysis. Reaction procedure follows as described above. Determined by 1H NMR analysis of crude. Determined by chiral GC or chiral HPLC analysis of isolated product. Isolated yield. Abbreviations: N.A., Not Applicable.

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In sharp contrast, upon use of the irradiated mixture of catalyst \((R,P,S/R_3)-1\) (365 nm light, PSS ratio S:MS \(= 17:83\)), the addition proceeded with reversed enantioselectivity under the same conditions. Preferred formation of the \((S)\)-enantiomer of secondary alcohols 12 was observed in all cases after irradiation, with ee’s up to 55% (entry 8). The difference in enantioselectivity (\(\Delta ee\)) between non-irradiated and irradiated catalyst solution was up to 113% (from 68% \((R)\) to 45% \((S)\), entries 1-2). When compared to the stable \((R,P,S/R_3)-1\) isomer, no significant change in the reaction rate was observed upon use of the irradiated mixture of the catalyst. Notably, use of diisopropylzinc led to no enantioselectivity in either case (entries 13-14).  

Compared to entry 1, in a control experiment performing the addition of diethylzinc in absence of stable \((R,P,S/R_3)-1\) led to a marked decrease in conversion, addition vs. reduction selectivity and isolated yield of 12a (entry 15). Addition of tetrabutylammonium bromide did not improve the catalytic activity, as otherwise observed in previously reported systems (see Experimental section for further details).  

Noticeably, under the reaction conditions no decomposition, racemization or significant thermal relaxation of the recovered catalyst (90% average catalyst recovery) was observed, as determined by \(^1\)H NMR and chiral HPLC analysis (see Experimental section for further details). Moreover, several times the catalyst was recovered after an experiment using a non-irradiated reaction mixture and recycled to perform a subsequent experiment on the same substrate with irradiated catalyst without notable loss of catalytic performance (see Supplementary material for further details). Point chirality dictates or governs helical chirality, which in turn is coupled to the axial chirality and with a limitation of a syn conformation in the ligand. The chirality is eventually transferred to the reagent providing an asymmetric product. The inversion of enantioselectivity is an indication of the reversed local chirality around the transferring zinc center and the coordinated aldehyde, achieved by using a ligand with opposite chiral induction. In the current case, we suggest that upon irradiation and subsequent inversion of the biaryl axial chirality, the metastable isomer \((R,M,R/S)-1\) resembles the enantiomer of the stable isomer \((R,P,S/R_3)-1\) (Scheme 5.5e). As the biphenol unit is the chiral ligand for zinc, opposite chiral induction is achieved in the proximity of the zinc-complexed aldehyde substrate, affording the opposite enantiomers of the 1,2-addition products.

5.3 Conclusions

The synthesis and resolution of a photosensitive molecular switch featuring a versatile 2,2’-biphenol motif in which chirality is transferred across three stereochemical elements has been designed and successfully executed. 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 fluoranyl lower half of the switch core. Compared with previously reported molecular motor based systems, the reduction from four to two isomerization stages featured by the biaryl-functionalized design described herein provides a simpler, reusable and more efficient dynamic responsive core. Extensive studies with CD and UV-vis absorption spectroscopy, \(^1\)H NMR spectroscopy and chiral HPLC analysis proved the reversible photoswitchability of 1, with no switching fatigue over multiple cycles in presence of substoichiometric amount of TEMPO. The chirality transfer was successfully applied to creation of another stereogenic element as demonstrated via dynamic central-to-helical-to-axial-to-central transfer of chirality by using \((R)-1\) as switchable catalyst in the enantioselective addition of diethylzinc to benzaldehydes. Clear reversal of enantioselectivity was accomplished for each substrate, with ee’s of 12 up to 68%, \(\Delta ee\)’s up to 113% and yields up to 87%. These results achieved in switchable asymmetric catalysis highlight the proof-of-principle of a two-stage dynamically tunable and responsive chiral biaryl-functionalized switch scaffold. The further development of analogous biaryl-switch designs combined with the established precedence of numerous catalysts based on biaryl scaffolds may lead to the construction of unprecedented switchable chiral catalysts that could perform multiple enantioselective transformation in a sequential manner. In addition, this switch system has considerable potential as chirality selector for a wide range of purposes beyond the field of asymmetric catalysis, such as control of supramolecular architecture, host-guest interaction, and polymer or liquid crystal morphology.
5.4 Acknowledgements
The author would like to thank P. Štacko J. C. M. Kistemaker, T. van Leeuwen and Prof. E. Otten for their fundamental contribution to this work. Design, synthesis and characterization were performed in collaboration with P. Štacko, J. C. M. Kistemaker and T. van Leeuwen. Computational study was performed by J. C. M. Kistemaker. X-ray structure determination was performed by Prof. E. Otten. The authors would like to thank Ing. P. van der Meulen for the technical support during the EXSY experiments.

5.5 Experimental section

5.5.1 General methods
Chemicals were purchased from Sigma Aldrich, Acros or TCI Europe. Commercially available solutions of \(\text{Et}_2\text{Zn} (1.0 \text{ M in hexane}), \text{i-Pr}_2\text{Zn} (1.0 \text{ M in toluene})\) and \(\text{EtMgBr} (3.0 \text{ M in Et}_2\text{O})\) were used without dilution. Solvents were reagent grade and distilled and dried before use according to standard procedures. Dichloromethane, ether and toluene were used from the solvent purification system using a MBräun SPS-800 column. Tetrahydrofuran was distilled over sodium under a nitrogen atmosphere prior to use. Column chromatography was performed on silica gel (Silica Flash P60, 230–400 mesh, mixtures of pentane, \(\text{EtOAc}, \text{Et}_2\text{O}, \text{CH}_2\text{Cl}_2\) or \(\text{MeOH}\) were used as eluent as reported for each case). Components were visualized by UV and phosphomolybdic acid or potassium permanganate staining. Progress and conversion of the reaction were determined by GC–MS (GC, HP6890 – MS, HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). NMR spectra were recorded on a Varian Gemini-200, a Varian Mercury 300, a Varian AMX400 or a Varian Unity Plus 500 spectrometer, operating at 200 MHz, 300 MHz, 400 MHz, and 500 MHz for \(^1\text{H} \text{NMR}\), respectively. EXSY experiments were performed on a Varian Unity Plus 500 spectrometer. Chemical shifts are denoted in δ values (ppm) relative to CDCl\(_3\) (\(^1\text{H} : \delta = 7.26; ^{13}\text{C} : \delta = 77.00\) or toluene-\(d_6\) (\(^1\text{H} : \delta = 2.09\)). Unless mentioned otherwise, all NMR spectra were recorded at 25 °C. Three peaks are described, the integral value of an absorption assigned to a specific atropisomer is reported as the corresponding fraction of the total number of nuclei of a specific chemical position. Mass spectra were obtained with an AEI MS-902 spectrometer (EI+) or with a LTQ Orbitrap XL (ESI+). Melting points were measured on a Büchi Melting Point B-545 apparatus. Optical rotations were measured on a Perkin Elmer 241 Polarimeter with a 10 cm cell (c given in g/100 mL). Chiral HPLC analysis was performed using a Shimadzu LC 10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector using a Chiralpak (Daicel) AD-H column. The elution speed was 0.5 mL/min, with mixtures of HPLC-grade heptane and 2-propanol (BOOM) as eluent and column temperature of 40 °C. Sample injections were made using a HP 6890 Series Auto sample Injector. Preparative HPLC was performed on a Shimadzu semi-prep HPLC system consisting of an LC-20T pump, a DGU-20A degasser, a CBM-20A control module, a SIL-20AC autosampler, a SPD-M20A diode array detector and a FRC-10A fraction collector, using a Chiralpak (Daicel) AD-H column. Elution speed was 0.5 mL/min with mixtures of HPLC-grade heptane and 2-propanol (BOOM) as eluent. Chiral GC analysis was performed using a HP6890, equipped with capillary column CP-Chirasil-Dex-CB, 25m x 0.25mm, He-flow 1.0 mL/min, equipped with a flame ionization detector. UV-vis absorption spectra were measured on a SPECORD S600 Analytik Jena spectrophotometer, equipped with a QUANTUM Northwest TC-1 temperature controller and fluorescence temperature control cell. CD spectra were measured on a Jasco J-815 CD spectrometer. All spectra were recorded at 20 °C using Uvasol-grade toluene (Merck) as solvent. Irradiation was performed using Thorlabs M365F1/M420F2 fiber-coupled high power LEDs (at 365 nm and 420 nm, respectively). Room temperature (rt) as mentioned in the experimental procedures and characterization sections is to be considered equal to 20 °C. The chiral descriptors for each species described in this work (e.g. \((R,P,S)_1\)) indicate respectively: the absolute stereochemistry of the stereogenic center (\(R\) or \(S\)), the configurational helicity of the switch core (\(P\) or \(M\)), and the axial stereochemistry of the biaryl unit (\(R_a\) or \(S_a\)). The asterisks at the stereodecriptors
throughout the text denote a racemic mixture with identical relative stereochemistry (S\(^*\),M\(^*\),R\(^*\)) means a mixture of S,M,R\(^*\) and R,P,S\(^*\)). The doubly expressed axial stereodescrptor (R/\(S\)) throughout the text denote a mixture of conformers with identical absolute stereochemistry and configurational helicity, with the first axial descriptor indicating the major species (R,P,S/\(R\) means a mixture of R,P,S\(^*\), major conformer, and R,P,R\(^*\), minor conformer).

5.5.2 Synthetic procedures

8-bromo-7-methoxy-3,4-dihyronaphthalen-1(2\(H\))-one (2)

Compound 2 was prepared from 7-methoxy-3,4-dihyronaphthalen-1(2\(H\))-one following the procedure previously reported.\(^6\) To a solution of 7-methoxy-3,4-dihyronaphthalen-1(2\(H\))-one (3.80 g, 21.40 mmol) in acetonitrile (30 mL) was added portionwise N-bromosuccinimide (4.20 g, 23.60 mmol, 1.1 equiv) under stirring at rt. The reaction suspension was stirred over 24 h. Due to a low conversion, more N-bromosuccinimide (1.00 g, 5.62 mmol, 0.25 equiv) was added and the stirring was continued for 24 h. After the volatiles were removed under reduced pressure, the red crude product was adsorbed on celite and diluted with EtOAc (50 mL). The reaction mixture was stirred at rt for 2 min. The resulting mixture was stirred at rt for 24 h. The reaction mixture was heated at 100 °C over 24 h. The reaction mixture was then allowed to cool to rt, sonicated with heptane (40 mL) and evaporated at reduced pressure. The red crude product was adsorbed on celite and diluted with EtOAc (50 mL) was added through the septum via a syringe and the resulting mixture was stirred at rt for 2 min. Subsequently the Schlenk tube was charged with 2 (6.00 g, 23.55 mmol), 2-methoxyphenyl-boronic acid (7.15 g, 47.00 mmol, 2.0 equiv) and powdered, anhydrous K\(\text{PO}_4\) (15.00 g, 70.6 mmol, 3.0 equiv). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon three times. Dry toluene (50 mL) was added through the septum via a syringe and the obtained precipitate was washed with a mixture of heptane:toluene = 1:1, sonicated with heptane (40 mL) and evaporated at reduced pressure to remove traces of toluene, to yield 3 (6.45 g, 22.8 mmol, 97%) as light brown crystals. m.p. 110.8–111.0 °C; \(^1\)H NMR (300 MHz, CDCl\(3\)) \(\delta\) 7.31 (t, \(J = 7.5\) Hz, 1H), 7.23 (d, \(J = 8.8\) Hz, 1H), 7.11 (d, \(J = 8.5\) Hz, 1H), 7.07–7.96 (m, 2H), 6.94 (d, \(J = 8.2\) Hz, 1H), 3.70 (br s, 6H), 2.98–2.89 (m, 2H), 2.60–2.47 (m, 2H), 2.17–2.01 (m, 2H); \(^1\)C NMR (75 MHz, CDCl\(3\)) \(\delta\) 198.8, 156.8, 156.4, 137.2, 133.2, 130.4, 129.2, 128.4, 128.1, 127.4, 120.7, 116.5, 111.1, 56.8, 56.0, 40.5, 30.3, 23.6; HRMS (APCI, m/z): calcd for C\(_{11}\)H\(_{13}\)BrO\(_2\) [M+H]+: 255.0015, found: 254.9996.

7-methoxy-8-(2-methoxyphenyl)-3,4-dihyronaphthalen-1(2\(H\))-one (3)

Compound 3 was prepared from 2 by a modified procedure previously reported.\(^6\) To a solution of 2 (6.00 g, 23.55 mmol) in acetonitrile (30 mL) cooled at 0 °C was added dropwise a solution of nBuLi (1.6 M in hexane, 14.28 mL, 22.85 mmol, 1.25 equiv) under argon. The reaction mixture was stirred for 30 min at 0 °C and then cooled to -78 °C. A solution of 3 (5.16 g, 18.28 mmol, 1 equiv) in dry THF (70 mL) was added dropwise to the cooled mixture, which was

7-methoxy-8-(2-methoxyphenyl)-2-methyl-3,4-dihyronaphthalen-1(2\(H\))-one (4)

To a solution of diisopropylamine (3.33 mL, 23.75 mmol, 1.30 equiv) in dry THF (70 mL) cooled at 0 °C was added dropwise a solution of nBuLi (1.6 M in hexane, 14.28 mL, 22.85 mmol, 1.25 equiv) under argon. The reaction mixture was stirred for 30 min at 0 °C and then cooled to -78 °C. A solution of 3 (5.16 g, 18.28 mmol, 1 equiv) in dry THF (70 mL) was added dropwise to the cooled mixture, which was...
stirred over 1 h at -78 °C. Methyl iodide (2.27 mL, 27.4 mmol, 1.5 equiv) was added to -78 °C, the reaction mixture was stirred for 1 h at rt, quenched with sat. aq. NH₄Cl (100 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and the solvent evaporated at reduced pressure. The crude solid was purified by column chromatography (SiO₂, pentane:EtOAc = 7:1) to yield 4 (4.66 g, 15.72 mmol, 86%, variable mixture of two atropisomers) as a light brown solid. m.p. 103–105 °C (partial melting of solid residue); ¹H NMR (200 MHz, CDCl₃, 1:1 mixture of two atropisomers) δ 7.52–7.40 (m, 1H), 7.40–7.29 (m, 1.3H), 7.29–7.24 (m, 0.3H), 7.24–7.15 (m, 0.5H), 7.14–7.01 (m, 2H), 3.85 (s, 1.5H), 3.83 (s, 3H), 3.81 (s, 1.5H), 3.30 (m, 1H), 2.99 (m, 1H), 2.98 (m, 1H), 2.96 (m, 1H), 2.55 (m, 1H), 2.52–2.32 (m, 1H), 2.30–2.12 (m, 1H), 1.86 (m, 1H), 1.29 (d, J = 6.5 Hz, 1.5H), 1.24 (d, J = 6.5 Hz, 1.5H); ¹³C NMR (50 MHz, CDCl₃) δ 155.9, 155.0, 151.0, 135.4, 133.6, 133.2, 127.3, 126.8, 126.6, 125.1, 119.7, 111.0, 109.9, 56.1, 55.0, 32.4, 29.6, 28.7, 16.7; HRMS (ESI, m/z): calcd for C₁₉H₂₂N₂O₂ [M+H]+: 297.1485, found: 297.1473.

(7-methoxy-8-(2-methoxyphenyl)-2-methyl-3,4-dihydronaphthalen-1(2H)-ylidene)hydrazine (5)

To a mixture of 4 (2.00 g, 6.75 mmol), hydrazine monohydrate (7 mL) in EtOH (15 mL) was added Sc(OTf)₃ (83 mg, 0.17 mmol, 2.5 mol%). Three cycles of vacuum and nitrogen backfill were applied to the reflux setup. The mixture was then heated at reflux for 3 d and subsequently, upon cooling down, concentrated to ~5 mL. CH₂Cl₂ (50 mL) and H₂O (70 mL) were added and the layers separated. The water layer was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers was washed with water (70 mL) and brine (70 mL), dried over Na₂SO₄, filtered and the solvents were removed at reduced pressure. The residue was purified by column chromatography (SiO₂, CH₂Cl₂:MeOH = 95:5) to yield 5 (1.57 g, 5.06 mmol, 75%) as a slight brown solid. m.p. 151.3–151.5 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.16 (m, 2H), 7.13–6.95 (m, 2H), 6.95–6.75 (m, 2H), 3.68 (s, 3H), 3.62 (s, 3H), 2.96–2.80 (m, 1H), 2.72–2.55 (m, 1H), 2.52–2.32 (m, 1H), 2.30–2.12 (m, 1H), 1.41 (ddt, J = 12.8, 9.3, 4.6 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 155.9, 155.0, 151.0, 135.4, 133.6, 133.2, 127.3, 126.8, 126.6, 125.1, 119.7, 111.0, 109.9, 56.1, 55.0, 32.4, 29.6, 28.7, 16.7; HRMS (ESI, m/z): calcd for C₁₉H₂₂N₂O₂ [M+H]+: 311.1754, found: 311.1752.

Dispiro[7-(7-methoxy-8-(2-methoxyphenyl)-2-methyl-3,4-dihydronaphthalen-1(2H)-ylidene)hydrazine (5)]-9H-fluorene (8) and 9-(7-methoxy-8-(2-methoxyphenyl)-2-methyl-3,4-dihydronaphthalen-1(2H)-ylidene)-9H-fluorene (9) Under nitrogen, Lawesson’s reagent (3.00 g, 7.40 mmol) was added to a stirred solution of 9-fluorenone (2.00 g, 11.1 mmol) in dry toluene (50 mL). Three cycles of vacuum and nitrogen backfill were applied to the reflux setup. The mixture was then heated at 85 °C for approximately 2 h, until TLC analysis started showing degradation (pentane:CH₂Cl₂ = 10:1, Rf product = 0.8, Rf decomposed product = 0.5, Rf substrate = 0.15). The mixture was diluted with a solution of pentane:CH₂Cl₂ = 1:1 (70 mL) to precipitate most of the Lawesson’s reagent and filtered. The liquid fraction was concentrated under reduced pressure and the residue was purified by a quick column chromatography (SiO₂, pentane:CH₂Cl₂ = 10:1). The green fraction was concentrated under reduced pressure to yield 9H-fluorene-9-thione 7 (1.150 g, 5.85 mmol) as dark green needles (note: the purity of the thioketone appeared to significantly influence the outcome of the following step; occasionally a second purification by flash column chromatography was required). Under
nitriger, a solution of 5 (780 mg, 2.51 mmol) in dry DMF (25 mL) was cooled to -50 °C and a solution of bis(trifluoroacetoxy)iodobenzene (1.19 g, 2.75 mmol, 1.1 equiv) in dry DMF (10 mL) was added to the stirred solution. The reaction mixture was stirred for 1 min while the color was turning from yellow to dark pink, indicating the in situ formation of the diazo compound 6. A solution of 7 (723 mg, 3.76 mmol, 1.5 equiv) in dry DMF (8 mL) and dry of CH₂Cl₂ (3 mL) was added to the mixture, which showed the release of nitrogen bubbles. The mixture was allowed to warm to rt and stirred for 16 h. The mixture was diluted with EtOAc (50 mL), washed with sat. aq. NH₄Cl (60 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The organic phases were collected, washed with water (100 mL), brine (100 mL) and dried over Na₂SO₄. The volatiles were removed under reduced pressure and the crude product containing mixture of episulfide 8 and overcrowded alkene 9 was triturated with hot EtOH:toluene ≈ 8:1 to yield 9 (778 mg, 1.76 mmol, 70%) as a light brown powder. The remaining residue consisting mainly of 8 was converted to 9 as follows: when an impure fraction of thioketone 7 was used, the conversion appeared to stop dramatically at the episulfide intermediate 8; to a solution of 8 in toluene (10 mL/g) was added tris(dimethylamino)phosphine (2 equiv) and the mixture heated at 150 °C for 2–3 d in a pressure tube until full conversion was reached (monitored by TLC, pentane:EtOAc = 25:1). The cooled mixture was concentrated under reduced pressure and triturated with EtOH:toluene ≈ 8:1 to yield additional 9 (167 mg, 0.376 mmol, additional 15%). In case of failed precipitation or when a large amount of impurities were still present, the residue was further purified by column chromatography (SiO₂, pentane:EtOAc = 25:1) providing 9 in variable yields. The various fractions of product 9 were collected (984 mg, 2.133 mmol, 85%). Notably, product 9 was occasionally found to be composed of two distinct conformers. The major conformer was isolated and fully characterized, while the minor conformer was observed in an impure fraction (large amount of leftover HMPT) after column chromatography. ¹H NMR spectra:

8 (mix of conformers): ¹H NMR (400 MHz, CDCl₃, 60:40 mixture of two atropisomers) δ 7.71 (d, J = 7.4 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.50–7.32 (m, 3H), 7.31–7.15 (m, 4.5H), 7.03 (t, J = 7.3 Hz, 1H), 7.00–6.94 (m, 1H), 6.92–6.82 (m, 1.5H), 6.81–6.73 (m, 2H), 3.82 (s, 1.8H), 3.73 (s, 1.8H), 3.71–2.66 (two overlapped s, 2.4H), 2.88 (s, 1H), 2.94–2.78 (m, 1.5H), 2.05–1.95 (m, 1.15H), 1.70–1.55 (m, 2H), 1.38–1.22 (m, 1.5 H), 1.16 (d, J = 6.9 Hz, 2.0H), 1.07 (d, J = 7.1 Hz, 1.2 H), 1.02–0.90 (m, 1H); ¹³C NMR (75 MHz, CDCl₃, 60:40 mixture of two atropisomers) δ 156.9, 156.2, 154.3, 146.8, 145.2, 143.8, 142.6, 141.8, 141.5, 141.1, 140.5, 140.0, 137.4, 136.7, 135.4, 134.4, 133.9, 132.9, 128.9, 128.8, 128.4, 128.4, 128.2, 128.1, 127.6, 127.3, 127.1, 126.3, 126.2, 126.0, 125.9, 125.7, 125.1, 124.7, 124.0, 123.6, 120.5, 120.5, 120.0, 119.9, 119.3, 119.2, 118.7, 110.2, 110.1, 56.3, 54.7, 53.6, 37.1, 30.6, 28.4, 22.7; HRMS (ESI, m/z): calcd for C₄₄H₅₎O₅S [M+H⁺]: 477.1883, found: 477.1881.

9 (major conformer): m.p. 172–173 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 7.6 Hz, 3H), 7.63 (d, J = 6.9 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.26–7.13 (m, 3H), 7.06 (d, J = 8.2 Hz, 1H), 7.00–6.89 (m, 2H), 6.81 (dd, J = 7.6, 1.4 Hz, 1H), 6.62 (d, J = 7.9 Hz, 2H), 6.34 (t, J = 7.2 Hz, 1H), 3.96 (app. sext, J = 6.8 Hz, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 2.68–2.52 (m, 1H), 2.40–2.24 (m, 2H), 1.29–1.21 (m, 1H) 1.25 (d, J = 6.8 Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 156.9, 156.35, 146.9, 140.6, 139.9, 139.4, 139.1, 138.8, 134.4, 134.0, 132.6, 128.3, 127.6, 127.1, 126.9, 126.8, 126.7, 125.0, 124.7, 124.6, 119.6, 119.2, 119.0, 111.9, 109.7, 56.7, 55.2, 44.8, 35.9, 32.5, 28.7, 20.7; HRMS (ESI, m/z): calcd for C₄₂H₅₁O₇S [M+H⁺]: 445.2162, found: 445.2153.

9 (minor conformer): ¹H NMR (200 MHz, CDCl₃) δ 7.70 (dd, J = 5.9, 3.0 Hz, 1H), 7.52–7.45 (m, 1H), 7.35 (dt, J = 7.5, 1.0 Hz, 1H), 7.21–7.11 (m, 3H), 7.01 (dd, J = 6.9, 3.8, 1.6 Hz, 2H), 6.93 (d, J = 8.2 Hz, 1H), 6.86–6.73 (m, 3H), 6.49 (td, J = 7.4, 1.1 Hz, 1H), 6.30 (dd, J = 8.2, 1.1 Hz, 1H), 4.00 (p, J = 7.0 Hz, 1H), 3.71 (s, 3H), 3.24 (s, 3H), 2.47 (q, J = 2.1 Hz, 1H), 2.36–2.13 (m, 2H), 1.39 (d, J = 6.9 Hz, 3H), 1.16–0.97 (m, 1H).
Compound \((R^*,P^*,R/S_*)\)-I was prepared from 9 by modification of a previously reported procedure.\(^{105}\) A Schlenk tube is charged with 9 (690 mg, 1.55 mmol), sealed with a rubber septum and evacuated and backfilled with nitrogen three times. A solution of MeMgl (3M in Et\(_2\)O, 2.60 mL, 7.76 mmol, 5 equiv) was injected through the septum with a syringe. To ensure optimal contact between the reagents, the slurry was sonicated for few seconds. Keeping overpressure of nitrogen, the septum was pierced with a needle and the Schlenk tube was heated up to 80 °C over 1 h to gently evaporate the ether. Subsequently the Schlenk tube was sealed and heated at 165 °C over 5 h. The mixture was allowed to cool down to rt and the reaction was quenched first with ice and then sat. aq. NH\(_4\)Cl (20 mL). After addition of CH\(_2\)Cl\(_2\) (20 mL), the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The organic phases were collected, washed with water (80 mL) and brine (80 mL), dried over Na\(_2\)SO\(_4\), filtered and the solvent evaporated under reduced pressure. The crude residue was purified by column chromatography (SiO\(_2\), gradient pentane:EtOAc = 6:1) to yield racemic \((R^*,P^*,R/S_*)\)-I (540 mg, 1.30 mmol, 84%, 60:40 mixture of two atropisomers as observed by \(^1\)H NMR spectroscopy analysis of a solution in CDCl\(_3\)) as a yellow foam. m.p. 167–168 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\), 60:40 mix. of two atropisomers) \(\delta\) 7.83–7.76 (m, 1H), 7.71 (d, \(J = 7.4\) Hz, 0.4H), 7.63 (dd, \(J = 6.8, 1.7\) Hz, 0.4H), 7.60–7.55 (m, 1H), 7.50 (d, \(J = 7.5\) Hz, 0.6H), 7.35–7.28 (m, 1.2H), 7.28–7.18 (m, 32.2H), 7.18–7.09 (m, 2H), 7.03–6.82 (m, 2H), 6.75 (dt, \(J = 7.9, 1.9\) Hz, 0.8H), 6.72–6.61 (m, 1H), 6.58 (d, \(J = 7.9\) Hz, 0.4H), 6.53 (dd, \(J = 8.1, 1.3\) Hz, 0.6H), 6.42 (td, \(J = 7.5, 1.2\) Hz, 0.4H), 5.56 (br s, 0.6H), 4.82 (br s, 0.4H), 4.77 (br s, 0.6H), 4.58 (br s, 0.4H), 4.18–3.88 (m, 1H), 2.74–2.61 (m, 1H), 2.49–2.26 (m, 1H), 1.53 (d, \(J = 6.9\) Hz, 1.8H), 1.31 (d, \(J = 6.8\) Hz, 1.2H), 1.39–1.18 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), 60:40 mix. of two atropisomers) \(\delta\) 155.0, 153.6, 153.3, 153.1, 152.6, 152.5, 144.8, 140.7, 140.5, 139.8, 139.6, 138.7, 138.7, 138.5, 138.4, 138.4, 135.90, 134.9, 134.7, 133.4, 131.5, 130.6, 129.5, 129.4, 128.6, 127.5, 127.5, 127.4, 127.4, 127.1, 127.0, 126.9, 126.2, 126.5, 125.5, 124.9, 124.7, 124.5, 124.5, 123.3, 123.2, 121.4, 121.0, 120.4, 119.7, 119.7, 119.4, 119.3, 117.8, 117.6, 117.0, 116.5, 115.8, 35.5, 35.2, 32.3, 31.9, 29.0, 28.5, 21.9, 21.0; \(^1\)H NMR (400 MHz, toluene-d\(_8\), 67:33 mix. of two atropisomers) \(\delta\) 7.78 (d, \(J = 7.8\) Hz, 0.8H), 7.72–7.68 (m, 0.4H), 7.44–7.38 (m, 0.8H), 7.31 (dd, \(J = 15.5, 7.4\) Hz, 0.4H), 7.17 (dd, \(J = 7.5, 2.0\) Hz, 0.8H), 7.14–6.93 (m, 7.4H), 6.90 (dd, \(J = 7.5, 1.7\) Hz, 0.4H), 6.83–6.78 (m, 0.6H), 6.73 (t, \(J = 7.6\) Hz, 0.6H), 6.61–6.54 (m, 0.4H), 6.53–6.40 (m, 2H), 6.18 (t, \(J = 7.4\) Hz, 0.4H), 6.13 (dd, \(J = 7.7, 1.6\) Hz, 0.6H), 5.69 (br s, 0.6H), 4.73 (br s, 0.4H), 4.62 (br s, 0.6H), 4.31 (br s, 0.4H), 3.94 (app. sext, \(J = 7.2\) Hz, 0.6H), 3.85 (app. sext, \(J = 7.1\) Hz, 0.4H), 3.35–3.25 (m, 0.4H), 2.39–2.26 (m, 1.2H), 2.24–2.13 (m, 0.8H), 2.03–1.91 (m, 0.4H), 1.33 (d, \(J = 6.9\) Hz, 1.8H), 1.22 (d, \(J = 7.0\) Hz, 1.2H), 1.13–0.96 (m, 1H); note: a total amount of ca. 7.4H is expected to be hidden underneath the residual solvent signals of toluene-d\(_8\). \(^{13}\)C NMR (150 MHz, toluene-d\(_8\), 67:33 mix. of two atropisomers) \(\delta\) 153.4, 153.2, 152.9, 144.7, 140.9, 140.1, 139.9, 139.8, 138.77, 138.7, 138.5, 135.4, 135.3, 134.1, 134.0, 133.5, 131.6, 130.3, 129.1, 128.5, 128.4, 127.6, 127.6, 127.4, 127.4, 127.3, 127.3, 126.9, 126.9, 126.8, 126.8, 126.6, 126.5, 124.7, 124.7, 124.6, 124.3, 124.0, 123.4, 120.6, 120.2, 120.1, 119.8, 119.5, 119.3, 118.0, 117.3, 116.5, 115.8, 35.5, 35.2, 32.1, 31.8, 30.3, 29.0, 28.3, 21.6; note: multiple peaks are expected to be hidden underneath the residual solvent signals of toluene-d\(_8\). HRMS (ESI, m/z): calcd for C\(_{30}\)H\(_{32}\)O\(_2\) [M+H]+: 417.1849, found: 417.1850. Separation of the enantiomers was achieved by CSP-HPLC (Chiralpak AD-H, heptane:2-propanol = 85:15, flow rate = 0.5 mL/min, column temperature = 40 °C, R;: 12.3 min for \((S,M,R/S_*)\)-I, 18.0 min for \((R,P,S/R_*)\)-I.)
Resolution of 8-(9H-fluoren-9-ylidine)-1-(2-hydroxyphenyl)-7-methyl-5,6,7,8-tetrahydronaphthalen-2-ol (\((+)-(R,P,S,R_a)-1\) and \((-)-(S,M,R,S_a)-1\))

Note: the batch of EtOAc (analytical grade) used in the following step was purified beforehand from traces of acids and bases by flushing it through a column packed with neutral alumina (bottom), acidic-active alumina (middle), basic-active alumina (top). During this work it was observed that use of strong inorganic bases (eg. NaOH, KOH) caused the decomposition of 1 into an unidentified red impurity with loss of the overcrowded alkene moiety. Notably the decomposition was also occurring in minor extent when a non-purified batch of EtOAc was used.

To a solution of \((R^*,P^*,S/R_a^*)-1\) (380 mg, 0.91 mmol) in EtOAc (10 mL) was added \((8S,9R)-(−)-N\)-benzylcinchonidinium chloride 10 (176 mg, 0.46 mmol, 0.5 equiv). The reaction mixture was stirred at rt overnight, affording a slurry of a white precipitate in a light yellow solution. The slurry was filtered on a P4 glass fritted funnel under vacuum and the precipitate was washed three times with cold EtOAc. The reaction mixture was stirred at rt overnight, affording a slurry of a white precipitate in a light yellow solution. The slurry was filtered on a P4 glass fritted funnel under vacuum and the precipitate was washed three times with cold EtOAc. The solution was evaporated under reduced pressure to yield an enantiomerically enriched mixture of \((R,P,S/R_a)-1\) (230 mg, 55 mmol, 60%, 54% ee) as a yellow foam. The white solid was dissolved in CH$_2$Cl$_2$ (40 mL) and added to aq. 1M HCl (40 mL) and stirred vigorously over 1 h. The organic phase was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 mL). The organic phases were collected, washed with NaHCO$_3$ aq. (100 mL) and brine (100 mL), dried over Na$_2$SO$_4$, filtered and the solvent evaporated under reduced pressure. The yellow residue was stripped over CHCl$_3$ few times to yield an enantiomerically enriched mixture of \((S,M,R/S_a)-1\) (150 mg, 36 mmol, 40%, 94% ee) as a yellow foam. The procedure was repeated on an enantioenriched fraction of \((S,M,R/S_a)-1\) (94% ee, 290 mg, 70 mmol) with 10 (290 mg, 70 mmol, 1.0 equiv) in EtOAc (10 mL) to yield pure \((-)-(S,M,R,S_a)-1\) (230 mg, 55 mmol, 79%, >99% ee) from the solid fraction as previously described.

The procedure was repeated on an enantioenriched fraction of \((R,P,S/R_a)-1\) (54% ee, 1.02 g, 2.46 mmol) with 10 (310 mg, 74 mmol, 0.3 equiv) in EtOAc (10 mL) to yield \((R,P,S/R_a)-1\) (800 mg, 1.92 mmol, 78%, 81% ee) from the solution as previously described. After removal of the volatiles under reduced pressure, the residue was recrystallized from EtOH:water ~1:1 to yield highly enriched \((R,P,S/R_a)-1\) (150 mg, 0.36 mmol, 15%, 96% ee) as a light brown powder. The mother liquor was recovered, purified by flash column chromatography (SiO$_2$, pentane:EtOAc = 6:1) if minor impurities were present, combined with other scalemic batches and resubmitted to further resolution.

The data were identical in all respects to those previously reported for \((R^*,P^*,S/R_a^*)-1\). $\lbrack\alpha\rbrack_D^{22} +27.60$ (c 0.544, MeOH) for \((R,P,S/R_a)-1\) (96% ee).

During an attempt to purify \((R,P,S/R_a)-1\) (80% ee) from minor impurities by flash column chromatography (SiO$_2$, pentane:EtOAc = 20:1) few particularly concentrated fractions were left to evaporate slowly over night. Yellow monocrystals of enantiomerically and conformationally pure \((R,P,S_a)-1\) were obtained and analyzed by X-ray crystallography (see X-ray crystallography section for further details), which allowed to assign the relative and absolute configuration of the stereogenic center.
Final recrystallization from EtOH:water ~1:1: (+)-(R,P,S/Ra)-1, 96% ee

\[ \text{mAU} \]

![Peaks Table](image)

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2nd resolution cycle, precipitate: (−)-(S,M,R/Sa)-1, >99% ee

\[ \text{mAU} \]

![Peaks Table](image)

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### 5.5.3 X-ray Crystallography

A single crystal of compound (R,P,Sa)-1 was mounted on top of a cryoloop and transferred into the cold nitrogen stream (100 K) of a Bruker-AXS D8 Venture diffractometer. A high-brilliance Cu K\( \alpha \)S microfocus source was used (Cu K\( \alpha \), radiation wavelength = 1.54178 Å). The collection strategy was chosen such that high data multiplicity (average 9.4 for data up to 0.80 Å resolution) was achieved in order to be able to
determine the absolute configuration in the absence of atoms that show significant anomalous scattering. Data collection and reduction was done using the Bruker software suite APEX2.  The final unit cell was obtained from the xyz centroids of 9682 reflections after integration. A multiscan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (SADABS). The structures were solved by direct methods using SHELXT, and refinement of the structure was performed using SHELXL. The hydrogen atoms were generated by geometrical considerations, constrained to idealized geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms. Refinement of the Flack x parameter converged at 0.00(7) for the enantiomer with R stereochemistry at C(15); the Bijvoet Pair analysis implemented in PLATON (based on Bayesian statistics) is consistent with this being the correct enantiomer (P2(true) = 1.000; P3(true) = 1.000; Hooft y = -0.01(7) based on 1927 Friedel pairs). Crystal data and details on data collection and refinement are presented in Table 5.

Table 5.5. Crystallographic data for (R,P,Sa)-1.

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<tr>
<td>b (Å)</td>
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<td>wR(F²) (%)</td>
<td>7.28</td>
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<tr>
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<td>min, max resid dens</td>
<td>-0.177, 0.135</td>
</tr>
</tbody>
</table>

5.5.4 ¹H NMR spectroscopy coalescence experiments.
The sample was prepared by dissolving stable isomers (R,P,Sa/Ra)-1 (~5.0 mg) in toluene-d₈ (0.7 mL) in a Schlenk tube under argon. The sample was freeze-thawed three times to remove any traces of oxygen and transferred into an NMR tube. ¹H NMR spectra were collected at with 300 MHz spectrometer at 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, and 100 ºC. No clear coalescence of the diagnostic peaks was observed at the tested temperature range.

5.5.5 Exchange spectroscopy measurements (EXSY)
The sample was prepared by dissolving stable isomers (R,P,Sa/Ra)-1 (~10.0 mg) in toluene-d₈ (0.7 mL) in a Schlenk tube under argon. The sample was freeze-thawed three times to remove any traces of oxygen and transferred into an NMR tube. One-dimensional phase-sensitive ¹H-¹H nuclear Overhauser enhancement spectra (1D-NOESY) for NMR exchange experiments were collected at 500 MHz by exciting the sample with an impulse with frequency range corresponding to the absorption at δ 7.78 ppm and using the following acquisition parameters: π/2 pulse width, 8.33 µs; spectral width, 6.000 Hz; data size, 32 K; recycling delay, 4 s; number of transients, 32; acquisition time, 2.048 s; steady-state, 8; scans, 64. The measurements were conducted at 39.17, 44.85, 49.30, 54.43, and 60.86 ºC (respectively, 312.32, 318.00,
322.45, 327.58, 334.01 K) consisting of an arrayed cluster of mixing times (t_m = 0.10, 0.20, 0.30, 0.40, 0.50, 0.65, 0.80, 0.95, 1.10, 1.30, 1.50, 1.70, and 2.00 s) per temperature.\textsuperscript{69,110}

5.5.6 Irradiation experiments: characterization and monitoring by UV-vis and CD spectroscopy, determination of PSS mixtures ratios by CSP-HPLC

The irradiation experiments were performed as follows (for UV-vis absorption and CD spectra, see main text, Figure 5.13). A solution of stable isomers (\(R,P,S_a/R_a\))-1 (96\% ee, toluene, 5.8\(\times\)10\(^{-5}\) M) was transferred in a fluorescence quartz cuvette with a magnetic stirrer and degassed with argon under stirring for 10 min. The forward and backward irradiation process from the stable isomer towards the metastable isomer was monitored by UV-vis absorption spectroscopy in a time-course measurement (wavelength range 300–650 nm, scan periods of 20 s). After starting the acquisition, the sample was irradiated under stirring with the proper LED source perpendicularly to the analysis path of the spectrophotometer (5 min at 365 nm, 10 min at 420 nm). To ensure that the PSS was reached, irradiations were continued until no further changes in the absorption spectra were observed; five cycles of forward and backward irradiation were performed sequentially on the same sample. A gradual decrease of the absorbance over multiple irradiation cycles was observed, suggesting switching fatigue suffered by 1 (Figure 5.14).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{irradiation_cycles.png}
\caption{Irradiation cycles of (\(R\))-1 (toluene, \(\sim\)6.0\(\times\)10\(^{-5}\) M) towards opposite PSS mixtures (red: 365 nm, 4 min; blue: 420 nm, 15 min).}
\end{figure}

The same experiment was subsequently performed on a solution of (\(R\))-1 (toluene, \(\sim\)4.0\(\times\)10\(^{-5}\) M) containing a substoichiometric amount of TEMPO (\(\sim\)10\(^{-5}\) M), which resulted in no evidence of degradation even after six irradiation cycles (see Figure 5.13). CD spectra were recorded for the starting solution of stable isomers (\(R,P,S_a/R_a\))-1 (96\% ee, toluene, 5.8\(\times\)10\(^{-5}\) M) and after reaching the PSS at 365 nm and 420 nm (mixture of stable isomers (\(R,P,S_a/R_a\))-1 and metastable isomers (\(R,M,R_a/S_a\))-1; for ratios vide infra, first irradiation cycle).

Chiral HPLC analysis of each irradiation stages of (\(R,P,S_a/R_a\))-1 afforded the composition of each PSS mixture (365 nm and 420 nm, first irradiation cycles) in toluene. Quantitative analysis was achieved by setting the PDA detector of the HPCL at the isosbestic point \(\lambda = 368\) nm as previously determined by the UV-vis abs. analysis. Analysis was performed on CSP-HPLC: Chiralpak AD-H, heptane:2-propanol = 85:15, flow rate = 0.5 mL/min, column temperature = 40 °C, \(R_t\): 15.5 min for metastable isomers (\(R,M,R_a/S_a\))-1 (broad peak spread over 1-3 min, depending on sample concentration), 18.4 min for stable isomers (\(R,P,S_a/R_a\))-1. Similarly, analysis of solutions of (\(S,M,R_a/S_a\))-1 was performed on CSP-HPLC with identical conditions: Chiralpak AD-H, heptane:2-propanol = 85:15, flow rate = 0.5 mL/min, column temperature = 40 °C, \(R_t\): 12.7 min for stable isomers (\(S,M,R_a/S_a\))-1, 28 min for metastable isomers (\(S,P,S_a/R_a\))-1 (very broad peak spread over 5-10 min, depending on sample concentration). HPLC analysis of the irradiated mixture displayed the appearance of a new eluted band having a PDA profile consistent
with the data obtained by UV-vis abs spectroscopy. Notably, the profile of new eluted band is symmetric and very large, stretched over the span of ca. 10 min during the analytical HPLC run. Minor decomposition suggested by emerging unidentified peaks was observed by HPLC analysis after irradiation of the samples for prolonged time both at 365 and 420 nm.

Note: due to the low barrier for rotation of the biaryl core, no separation of the atropisomers was observed by HPLC analysis. Each pair of atropisomers (e.g. \((R,P,S_a)\)-1 and \((R,P,R_a)\)-1), is eluted as a single symmetrical peak in the chromatogram. Attempts to lower the temperature of the column (down to 0 °C) in order to achieve Dynamic HPLC and allowing the investigation of possible stereomutation processes did not lead to any change in the shape of the chromatograms. See EXSY experiments for determination of energy barrier of biaryl inversion.

Stable isomers \((R,P,S_a/R_a)\)-1, 96% ee

![chromatogram](image)

<table>
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<th>Area%</th>
</tr>
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<td>98.054</td>
</tr>
<tr>
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</tbody>
</table>

\[\text{PSS}_{365} \text{ mixture of stable isomers } (R,P,S_a/R_a)\text{-1} : \text{metastable isomers } (R,M,R_a/S_a)\text{-1} = 17 : 83\]

![chromatogram](image)

<table>
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</table>

\[\text{PSS}_{420} \text{ mixture of stable isomers } (R,P,S_a/R_a)\text{-1} : \text{metastable isomers } (R,M,R_a/S_a)\text{-1} = 50 : 50\]
5.5.7 Irradiation experiments: monitoring of isomerization, characterization of metastable isomers

\((R,M,R_1/S_1)-1\) by \(^1\)H NMR

\((R,P,S_1/R_1)-1\) (~5.0 mg) was dissolved in toluene-\(d_8\) (0.7 mL). The sample was placed in an NMR tube and irradiated (365 nm) at a distance of 3 cm from the center of the lamp for 30 min, with periodic mixing of the solution to facilitate diffusion. \(^1\)H NMR spectra of the sample were taken before, during and after irradiation at rt. The irradiation was not continued after 30 min in order to avoid decomposition of the sample and emergence of secondary peaks. The relative integration of the absorptions peaks of the two isomers revealed a photostationary state ratio in toluene-\(d_8\) at 365 nm of stable isomers \((R,P,S_1/R_1)-1\) : metastable isomers \((R,M,R_1/S_1)-1\) = 35:65. \(^1\)H and COSY NMR spectra of PSS\(_{365}\) mixtures are displayed in Figure 5.15. For stacked \(^1\)H NMR spectra of the solution before and after irradiation with assignment of distinctive absorptions, see Figure 5.12. For corresponding UV-vis and CD spectra, see Figure 5.13. See following section for characterization of isolated metastable state.

<table>
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</tr>
<tr>
<td>Total</td>
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</tr>
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</table>
Central-to-Helical-to-Axial-to-Central Transfer of Chirality in a Photoresponsive Catalyst

Figure 5.15. $^1$H NMR spectra (toluene-$d_8$) of stable isomers ($R,P,S,R$)-1 after 30 min of irradiation with 365 nm UV light, affording a mixture in toluene-$d_8$ of stable isomers ($R,P,S,R$)-1 : metastable isomers ($R,M,R,S$)-1 = 35 : 65 (note: overall summed quantities of atropisomers mixtures for each state).

5.5.8 Isolation of metastable isomers ($R,M,R,S$)-1 by preparative HPLC and characterization by NMR spectroscopy.

A Schlenk tube equipped with a stirring bar was charged with stable isomers ($R,P,S,R$)-1 (21 mg, 0.05 mmol). The Schlenk tube was connected to a vacuum/nitrogen line and evacuated and backfilled three times. Dry Et$_2$O (15 mL) was added and the solution was purged with Argon under stirring for 10 min at -20°C. The solution was irradiated with 365 nm light to PSS over 30 min under stirring at rt. A jet of air on the outer surface of the Schlenk tube was used to avoid heating from the UV-light source during the irradiation (a yellow precipitate was otherwise observed). The solvent was evaporated under reduced pressure and the residue was re-dissolved in heptane:2-propanol = 85:15 (1.5 mL). Separation of the metastable isomers (~4 mg) was achieved by CSP-HPLC: Chiralpak AD-H, heptane:2-propanol = 90:10, flow rate = 0.5 mL/min, column temperature = 40°C, injection volume per run = 100 µL, Rt: 21.3 min for metastable isomers ($R,M,R,S$)-1, 27.7 min for stable isomers ($R,P,S,R$)-1.

Stable isomers ($R,P,R,S$)-1: $^1$H NMR (400 MHz, toluene-$d_8$, 67:33 mix. of two atropoisomers) δ 7.78 (d, J = 7.8 Hz, 0.8H), 7.72–7.68 (m, 0.4H), 7.44–7.38 (m, 0.8H), 7.31 (dd, J = 15.5, 7.4 Hz, 0.4H), 7.17 (dd, J = 7.5, 2.0 Hz, 0.8H), 7.14–6.93 (m, 7.4H), 6.90 (dd, J = 7.5, 1.7 Hz, 0.4H), 6.83–6.78 (m, 0.6H), 6.73 (t, J = 7.6 Hz, 0.6H), 6.61–6.54 (m, 0.4H), 6.53–6.40 (m, 2H), 6.18 (t, J = 7.4 Hz, 0.4H), 6.13 (dd, J = 7.7, 1.6 Hz,0.6H), 5.69 (br s, 0.6H), 4.73 (br s, 0.4H), 4.62 (br s, 0.6H), 4.31 (br s, 0.4H), 3.94 (app. sext, J = 7.2 Hz, 0.6H), 3.85 (app. sext, J = 7.1 Hz, 0.4H), 3.35–3.25 (m, 0.4H), 2.39–2.26 (m, 1.2H), 2.24–2.13 (m, 0.8H), 2.03–1.91 (m, 0.4H), 1.33 (d, J = 6.9 Hz, 1.8H), 1.22 (d, J = 7.0 Hz, 1.2H), 1.13–0.96 (m, 1H); note: a total amount of ca. 7.4H is expected to be hidden underneath the solvent signals of toluene-$d_8$.

Metastable isomers ($R,M,R,S$)-1: $^1$H NMR (400 MHz, toluene-$d_8$, 55:45 mixture of two atropoisomers) δ 7.69 (d, J = 7.8 Hz, 1.3H), 7.54 (d, J = 7.8 Hz, 1.1H), 7.32 (d, J = 7.6 Hz, 4H), 7.16–7.14 (m, 2H), 7.05–6.93 (m, 7H), 6.83 (t, 1.4H), 6.72 (dd, J = 7.3, 2.0 Hz, 0.8H), 6.63 (t, 0.9H), 6.57–6.43 (m, 4.5H), 6.37–6.32 (m, 2H), 6.25 (t, J = 7.5, 1.2 Hz, 1.3H), 5.13 (s, 1H), 4.33 (s, 1H), 3.82 (p, J = 6.7 Hz, 1H), 3.42 (s, 0.8H), 2.73--
2.59 (m, 2.3H), 2.48-2.31 (m, 2.9H), 2.27 (d, J = 8.9 Hz, 0.91H), 1.66-1.58 (m, 3H), 1.49 –1.34 (m, 4H), 1.29 (d, J = 6.7, 3H), 1.29 (d, J = 6.7, 4H), 1.06-0.91 (m, 4H); note: due to the presence of two atropisomers in an apparent ~55:45 ratio and presence of several overlapped absorption peaks, the integrals of the signals corresponding to the absorption peaks of the products do not indicate the absolute values but merely the experimental relative ratio: $^{13}$C NMR (100 MHz, toluene-d$_8$, 55:45 mixture of two atropisomers) $\delta$ 156.3, 156.0, 155.1, 155.0, 148.7, 146.3, 144.2, 143.1, 142.6, 142.2, 142.1, 141.7, 141.1, 136.7, 136.5, 129.6, 129.4, 129.3, 129.2, 129.1, 128.9, 128.9, 128.1, 127.9, 127.9, 126.6, 126.0, 126.0, 123.9, 123.8, 122.9, 122.5, 122.1, 121.6, 121.5, 121.4, 120.8, 119.9, 118.3, 36.7, 35.0, 34.5, 34.5, 32.7, 29.9, 29.6; note: due to the limited amount of isolated compound, the intensity of the signals corresponding to the product peaks were affected by the strong intensity of the absorption peaks of the solvent residue of toluene-d$_8$ and multiple unidentified peaks of the product are likely to be hidden underneath the solvent peaks. Analysis was performed on CSP-HPLC: Chiralpak AD-H, heptane:2-propanol = 85:15, flow rate = 0.5 mL/min, column temperature = 40 °C, Rt: 15.5 min for metastable isomers (R,M,R/S,S)-1.

5.5.9 General procedure for enantioselective additions of dialkylzinc to aldehydes

General procedure for the catalyzed addition of dialkylzinc to aldehydes with stable isomers (R,P,S/R,S)-1 (main manuscript, Table 5.1, odd number entries 1-13)

A Schlenk tube equipped with a stirring bar was charged with (R,P,S/R,S)-1 (5.21 mg, 0.013 mmol, 0.1 equiv). The Schlenk tube was connected to a vacuum/nitrogen line, evacuated and backfilled three times. Dry toluene (0.5 mL) was added and the solution was stirred at 0 °C for 5 min. A solution of dialkylzinc (Et$_2$Zn, 1.0 M in hexane; i-Pr$_2$Zn, 1.0 M in toluene; 0.375 mL, 0.375 mmol, 3 equiv) was added dropwise at this temperature and the solution was stirred over 10 min. The selected aldehyde 11 (0.125 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 7 d. The progress of the reaction was monitored by GC-MS analysis by withdrawing aliquots and quenching in an Et$_2$O:MeOH = 3:1 solution. Aq. 1M HCl (3 mL) was added at 0 °C and the aqueous layer was extracted with Et$_2$O (3 x 3 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO$_4$ and filtered. After removal of the solvent, the crude mixture was analyzed by $^1$H NMR spectroscopy to measure conversion and selectivity (1,2-addition vs. reduction products). The residue was then purified by quick column chromatography (SiO$_2$, pentane:Et$_2$O = 10:1 to 5:1) to yield the secondary alcohols 12 as colorless liquids. The mixture was further eluted (pentane:Et$_2$O = 2:1) to recover 1. The ee values of the secondary alcohols were determined by Chiral HPLC or Chiral GC analysis. The absolute configuration of major enantiomer of the alcohols 12 was assigned as (R) by comparison of the sign of the optical rotation with reported data.$^{103,113,114}$

General procedure for the catalyzed addition of dialkylzinc to aldehydes with irradiated mixture of (R,P,S/R,R)-1 (Table 5.2, even number entries 2-14)

A Schlenk tube equipped with a stirring bar was charged with (R,P,S/R,R)-1 (5.21 mg, 0.013 mmol, 0.1 equiv), connected to a vacuum/nitrogen line, evacuated and backfilled three times. Dry Et$_2$O (15 mL) was added and the solution was purged with nitrogen under stirring for 10 min at -20°C. The solution was irradiated with 365 nm UV-light to PSS over 30 min under stirring at rt (PSS ratio was measured by HPLC analysis after irradiation). A jet of air on the outer surface of the Schlenk tube was used to avoid heating from the UV-light source during the irradiation. The ether was evaporated under reduced pressure and the residue was re-dissolved in dry toluene (0.5 mL). The solution was stirred at 0 °C for 5 min. The procedure follows with addition of dialkylzinc and aldehyde, stirring over 7 d, work up, purification and analysis according to the methodology described above. The absolute configuration of major enantiomer of the alcohols 12 was assigned as (S) by comparison of the sign of the optical rotation with reported data.$^{103,113,114}$
**Procedure for the addition of diethylzinc to benzaldehyde without** \((R,P,R_a/S_a)-1\) (entry 15, Table 5.1).

The Schlenk tube was connected to a vacuum/nitrogen line, then evacuated and backfilled three times. Dry toluene (0.5 mL) and a solution of diethylzinc (1.0 M in hexanes, 0.375 mL, 0.375 mmol, 3 equiv) were added dropwise at 0 °C. After stirring for 5 min, benzaldehyde 11a (13 mg, 0.125 mmol, 13 µL, 1 equiv) was added dropwise to the solution. The procedure follows with work up, purification and analysis according to the methodology described above. The isolated yield was not determined.

**General procedure for preparation of racemic mixtures of secondary alcohols for Chiral HPLC and GC analysis**

The Schlenk tube was connected to a vacuum/nitrogen line, evacuated and backfilled three times and charged with dry Et₂O (2 mL) and aldehyde 11 (0.5 mmol, 1 equiv). The solution was cooled to 0 °C. A solution of ethyl magnesium bromide (3.0 M in Et₂O, 0.22 mL, 0.65 mmol, 1.3 equiv) was added dropwise and the reaction mixture was stirred for 1 h. Aq. 1M HCl (3 mL) was added and the aqueous layer was extracted with Et₂O (3 x 3 mL). The combined organic layer was washed with brine, dried over anhydrous MgSO₄ and filtered. After removal of the solvent, the residue was then purified by a quick column chromatography (SiO₂, pentane:Et₂O = 10:1 to 5:1) to yield the secondary alcohols 12 as colorless liquids.

**Catalytic tests with tetrabutylammonium bromide and related comments**

Song and co-workers demonstrated the significant synergistic effect of achiral quaternary ammonium salts on chiral phosphoramidate catalyzed asymmetric additions of diethylzinc to aldehydes, allowing to maintain high catalytic efficiency in the presence of 10 mol% of Bu₄NBr and only 0.5 mol% of chiral phosphoramidate. In an attempt to improve catalytic activity, screening of variable loading amount of stable isomers \((R,P,S_a/R_a)-1\) (1, 3 and 10 mol%) in presence of 10 mol% of Bu₄NBr resulted in a dramatic increase of the reaction rate and selectivity, with full conversion reached within 16 h (Table 5.6). However, the enantioselectivity was completely lost. By comparison with the reaction performed in the presence of only the ammonium salt (entry 15), it clearly shows how this additive could be responsible for a competing fast background reaction with loss of control from the chiral ligand \((R,P,S_a/R_a)-1\).

**Table 5.6. Catalysis test for synergistic effect of achiral quaternary ammonium salts with \((R)-1\) in enantioselective addition of diethylzinc to benzaldehyde.**

<table>
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<tr>
<th>Entry a</th>
<th>Loading of ((R)-1) (mol%)</th>
<th>Conv. of 11a (%) b</th>
<th>Yield of 12 (%) c</th>
<th>ee of 12 (%) c</th>
<th>12:13 b</th>
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</thead>
<tbody>
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<td>1 c</td>
<td>1</td>
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<td>N.D.</td>
<td>&lt;5 (±)-12a</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>2 c</td>
<td>3</td>
<td>&gt;95</td>
<td>N.D.</td>
<td>&lt;5 (±)-12a</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>3 c</td>
<td>10</td>
<td>&gt;95</td>
<td>N.D.</td>
<td>&lt;5 (±)-12a</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>4 c</td>
<td>0</td>
<td>&gt;95</td>
<td>N.D.</td>
<td>N.A.</td>
<td>&gt;98:2</td>
</tr>
</tbody>
</table>

**General reaction conditions: \((R,P,S_a/R_a)-1\) (loading reported in table) and NBu₄Br (4.03 mg, 0.013 mmol) in 0.5 mL of dry toluene cooled at 0 °C; 0.375 mmol of R₂Zn (Et₂Zn, 1.0 M sol. in hexane; iPr₂Zn, 1.0 M sol. in toluene) added dropwise and stirred over 10 min; 0.125 mmol of 11 added to mixture. Reaction mixture stirred for 7 days at 0 °C. Conversion monitored by GC-MS analysis. b Determined by GC-MS and 1H NMR analysis of crude after quenching. c Isolated yield. d Full conversion reached after 16 h. Abbreviations: N.A., Not Applicable; N.D., Not Determined.
General procedure for the catalyzed addition of diethylzinc to benzaldehyde with \((R,P,S_1/R_2)-1\) and tetrabutylammonium bromide (entries 16-18, Table 5.4)

A Schlenk tube equipped with a stirring bar was charged with stable isomers \((R,P,S_1/R_2)-1\) (catalyst loading ranging from 0.01 eq to 0.1 eq: a) 0.52 mg, 0.001 mmol, 0.01 eq; b) 1.56 mg, 0.0038 mmol, 0.03 eq; c) 5.21 mg, 0.013 mmol, 0.1 equiv) and tetrabutylammonium bromide (4.03 mg, 0.013 mmol, 0.1 equiv). The Schlenk tube was connected to a vacuum/nitrogen line, evacuated and backfilled three times. Dry toluene (0.5 mL) was added and the solution was stirred at 0 °C for 5 min. The procedure follows with addition of dialkylzinc and aldehyde, stirring over 16 h, work up, purification and analysis according to the methodology described above. Racemic product was obtained in all cases.

Catalyst recovery and analysis after catalytic reaction

After isolation of the secondary alcohols by column chromatography, the residue was further eluted (pentane:Et₂O = 2:1) to recover the catalyst \((R)-1\). Under the reaction conditions no decomposition, racemization or significant thermal relaxation of the recovered catalyst (90% average catalyst recovery) was observed, as determined by \(^1\)H NMR and chiral HPLC analysis.

5.5.10 Characterization data for compounds 12a-12f

1-Phenylpropanol (12a, entries 1-2 in Table 5.4)

Reaction conducted with non-irradiated \((R)-1\) (entry 1 in Table 5.4): \(12a:13a = 93:7, 86\%\) yield, 68\% ee \((R)\).

Reaction conducted with irradiated mixture (365 nm) of \((R)-1\) (entry 2 in Table 5.4): \(12a:13a = 93:7, 87\%\) yield, 45\% ee \((S)\).

Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiracel OD-H, heptane:2-propanol = 90:10, flow rate = 0.5 mL/min, column temperature = 40 °C, R\(_s\): 10.7 min for \((R)\), 11.2 min for \((S)\). \([\alpha]_{D}^{20} = +14.8\) (c 1.00, CHCl\(_3\)) for 68\% ee \((R)\) [Lit.\(^{103}\) \([\alpha]_{D}^{20} = +20.3\) (c 1.00, CHCl\(_3\)) for 93\% ee \((R)\)]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.46, 7.22\) (m, 1H), \(4.62\) (t, \(J = 6.6\) Hz, 0H), \(1.96-1.68\) (m, 1H), 0.95 (t, \(J = 7.4\) Hz, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 144.5, 128.3, 127.4, 125.9, 75.9, 31.8, 10.1\); HRMS (ESI, m/z): calcd for C\(_9\)H\(_{11}\):[M-H₂O]+: 119.0855, found: 119.0852.

1-(4-Chlorophenyl)propanol (12b)

Reaction conducted with non-irradiated \((R)-1\) (entry 3 in Table 5.4): \(12b:13b = 81:19, 80\%\) yield, 35\% ee \((R)\).

Reaction conducted with irradiated mixture (365 nm) of \((R)-1\) (entry 4 in Table 5.4): \(12b:13b = 81:19, 80\%\) yield, 24\% ee \((S)\).

Colorless oil. The ee value was determined by Chiral GC: CP-Chirasil-Dex-CB, 25m x 0.25mm, He-flow 1.0 mL/min, column temperature: 40 °C, gradient 10 °C/min to 140 °C, hold 140 °C, R\(_r\): 26.3 min for \((R)\), 28.1 min for \((S)\). \([\alpha]_{D}^{20} = +16.8\) (c 1.00, CHCl\(_3\)) for 26\% ee \((R)\) [Lit.\(^{113}\) \([\alpha]_{D}^{20} = +22.0\) (c 0.52, CHCl\(_3\)) for 68\% ee \((R)\)]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.40, 7.19\) (m, 1H), \(4.58\) (t, \(J = 6.6\) Hz, 0H), 4.63 (t, \(J = 6.6\) Hz, 0H), 1.96-1.68 (m, 1H), 0.95 (t, \(J = 7.4\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 143.0, 133.1, 128.5, 127.3, 75.3, 31.9, 10.0\); HRMS (ESI, m/z): calcd for C\(_9\)H\(_{10}\)Cl: [M-H₂O]+: 153.0466, found: 153.0466.

1-p-Tolylpropanol (12c)

Reaction conducted with non-irradiated \((R)-1\) (entry 5 in Table 5.4): \(12c:13c = 89:11, 87\%\) yield, 40\% ee \((R)\).

Reaction conducted with irradiated mixture (365 nm) of \((R)-1\) (entry 6 in Table 5.4): \(12c:13c = 88:12, 86\%\) yield, 42\% ee \((S)\).
Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiralcel OB-H, heptane:2-propanol = 98:2, flow rate = 0.5 mL/min, column temperature = 40 °C, R: 18.6 min for (R), 22.8 min for (S). [\text{ee}^R]_D = +14.5 (c 1.00, CHCl₃) for 40% ee (R) [Lit.]² [\text{ee}^R]_D = +37.2 (c 1.00, CHCl₃) for 85% ee (R). \text{H NMR (400 MHz, CDCl₃) δ 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 4.56 (t, J = 6.6 Hz, 1H), 2.35 (s, 3H), 1.90–1.62 (m, 3H), 0.91 (t, J = 7.4 Hz, 3H);} \text{^{11}C NMR (100 MHz, CDCl₃) δ 141.6, 137.1, 129.1, 125.9, 75.9, 31.8, 21.1, 10.2;} \text{HRMS (ESI, m/z): calcd for C₁₀H₁₃ [M-H₂O]⁺: 133.1012, found: 133.1013.}

1-(4-Methoxyphenyl)propanol (12d)

Reaction conducted with non-irradiated (R)-1 (entry 7 in Table 5.4): \text{12d:13d = 62.38, 37% yield, 40% ee (R).}

Reaction conducted with irradiated mixture (365 nm) of (R)-1 (entry 8 in Table 5.4): \text{12d:13d = 97.3, 76% yield, 55% ee (S).}

Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiralcel OD-H, heptane:2-propanol = 98:2, flow rate = 0.5 mL/min, column temperature = 40 °C, R: 38.9 min for (R), 46.2 min for (S). [\text{ee}^R]_D = +30.8 (c 1.00, CHCl₃) for 40% ee (R) [Lit.]² [\text{ee}^R]_D = +22.7 (c 0.59, CHCl₃) for 50% ee (R). \text{H NMR (300 MHz, CDCl₃) δ 7.39–7.19 (m, 3H), 6.97 (t, 1H), 6.89 (d, J = 8.2 Hz, 1H), 4.79 (t, J = 6.7 Hz, 1H), 3.86 (s, 3H), 1.91–1.75 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H);} \text{^{11}C NMR (75 MHz, CDCl₃) δ 156.6, 132.3, 128.2, 127.1, 120.7, 110.5, 72.5, 55.3, 55.2, 30.12, 10.5; HRMS (ESI, m/z): calcd for C₁₀H₁₃O [M-H₂O]⁺: 149.0961, found: 149.0958.}

1-o-Tolylpropanol (12e)

Reaction conducted with non-irradiated (R)-1 (entry 9 in Table 5.4): \text{12e:13e = 63.37, 58% yield, 48% ee (R).}

Reaction conducted with irradiated mixture (365 nm) of (R)-1 (entry 10 in Table 5.4): \text{12d:13d = 85.15, 79% yield, 50% ee (S).}

Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiralpak AD-H, heptane:2-propanol = 99:1, flow rate = 1.0 mL/min, column temperature = 40 °C, R: 15.5 min for (R), 17.8 min for (S). [\text{ee}^R]_D = +51.9 (c 1.00, CHCl₃) for 48% ee (R) [Lit.]² [\text{ee}^R]_D = +40.3 (c 0.51, CHCl₃) for 73% ee (R). \text{H NMR (300 MHz, CDCl₃) δ 7.46 (d, J = 7.5 Hz, 1H), 7.25–7.10 (m, 3H), 4.87 (t, J = 6.4 Hz, 1H), 2.35 (s, 3H), 1.87–1.65 (m, 4H), 0.99 (t, J = 7.4 Hz, 3H);} \text{^{11}C NMR (75 MHz, CDCl₃) δ 156.6, 132.3, 128.2, 127.1, 120.7, 110.5, 72.5, 55.2, 30.1, 10.5; HRMS (ESI, m/z): calcd for C₁₀H₁₃O [M-H₂O]⁺: 133.1009.}

1-(2-Methoxyphenyl)propanol (12f)

Reaction conducted with non-irradiated (R)-1 (entry 11 in Table 5.4): \text{12f:13f = 89.11, 81% yield, 46% ee (R).}

Reaction conducted with irradiated mixture (365 nm) of (R)-1 (entry 12 in Table 5.4): \text{12f:13f = 83.17, 72% yield, 31% ee (S).}

Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiralpak AD-H, heptane:2-propanol = 99:1, flow rate = 1.0 mL/min, column temperature = 40 °C, R: 25.1 min for (R), 26.7 min for (S). [\text{ee}^R]_D = +18.1 (c 1.00, CHCl₃) for 46% ee (R) [Lit.]² [\text{ee}^R]_D = +13.2 (c 0.50, CHCl₃) for 67% ee (R). \text{H NMR (300 MHz, CDCl₃) δ 7.36–7.17 (m, 3H), 6.96 (t, 1H), 6.89 (d, J = 8.2 Hz, 1H), 4.79 (t, J = 6.7 Hz, 1H), 3.85 (s, 3H), 1.88–1.76 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H);} \text{^{11}C NMR (75 MHz, CDCl₃) δ 142.7, 134.6, 130.3, 127.1, 126.2, 125.2, 72.1, 30.9, 19.1, 10.4; HRMS (ESI, m/z): calcd for C₁₀H₁₃O [M-H₂O]⁺: 149.0961, found: 149.0960.
2-Methyl-1-phenylpropan-1-ol (12g)

Reaction conducted with non-irradiated (R)-1 (entry 13 in Table 5.4): 12g:13g = 41:59, 40% yield, racemic mixture.

Reaction conducted with irradiated mixture (365 nm) of (R)-1 (entry 14 in Table 5.4): 12g:13g = 58:42, 57% yield, racemic mixture.

Colorless oil. The ee value was determined by CSP-HPLC analysis: Chiralcel OD-H, heptane:2-propanol = 98:2, flow rate = 0.5 mL/min, column temperature = 40 °C, R; 25.1 min for (1st en.), 26.7 min for (2nd en.).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.42–7.22 (m, 5H), 4.37 (d, $J = 6.9$ Hz, 1H), 1.97 (h, $J = 6.8$ Hz, 1H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 143.6, 128.2, 128.1, 143.5, 133.1.

5.6 References

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(33) Fletcher, S. P.; Dumur, F.; Pollard, M. M.; Feringa, B. L. Science 2005, 310, 80–82.


NMR of dynamic processes http://chem.ch.hjui.ac.il/nmr/techniques/other/dynamic/dynamic.html.

It should be emphasized that compared with compound 1, the methoxy-protected precursor 9 could be obtained and isolated as variable mixtures of non-equilibrating atropisomers (see Experimental section for details). Notably no isomerization or coalescence of the NMR absorptions was observed even at temperatures up to 100 °C.


Kistemaker, J. C. M. PhD thesis, *Autonomy and Chirality in Molecular Motors*, University of Groningen,
Chapter 5

It should be noted that the quality of the commercial diethylzinc solution had a large impact on the results of the catalytic reactions, affording lower yields and selectivities as degradation of the reagent progressed.

The same reaction catalyzed by (P)-3,3'-diphenyl BINOL was reported to yield the product in 44% ee (see Ref. 95).

It should be noted that the quality of the commercial diethylzinc solution had a large impact on the results of the catalytic reactions, affording lower yields and selectivities as degradation of the reagent progressed.


(90) Hirose, T.; Kodama, K. In Comprehensive Organic Synthesis II; pp 204–266.


(101) The same reaction catalyzed by (P)-3,3'-diphenyl BINOL was reported to yield the product in 44% ee (see Ref. 95).

(102) It should be noted that the quality of the commercial diethylzinc solution had a large impact on the results of the catalytic reactions, affording lower yields and selectivities as degradation of the reagent progressed.


