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Dynamic control over catalytic function using responsive bithiourea catalysts†

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Two novel bithiourea molecular motor-based catalysts were designed and their dynamic control of activity and stereoselectivity in the Henry reaction using heat and light as external stimuli was investigated. Enantioselective organocatalysis studies established that a basic functional group is not required within the catalyst core to effect efficient dual stereocontrol, illustrating novel stimuli responsive organocatalysts.

Introduction

Bithiourea catalysts have been shown to accelerate various asymmetric chemical transformations, such as the Mannich,¹ Henry,^{2,3} aza-Henry,⁴ Morita–Baylis–Hillman,^{3,5–7} Friedel–Crafts,⁸ and Diels–Alder reactions.^{9–12} Although such catalytic diversity has been reported for the bithiourea catalysts^{2,7,13–17} stimuli responsive versions with which control of activity or selectivity might be achieved are rare, *i.e.* an elegant redox-configurable bisurea catalyst reported by Canary *et al.* is a notable exception.^{18–20} In fact, the control of the function activity/selectivity of chiral catalysts through conformational changes induced by external stimuli, reflecting allosteric enzymatic regulation found in Nature, is a contemporary challenge in chemistry.^{21–26} In this context, it was shown by our group that first generation molecular motors²⁷ provide a unique platform to achieve this goal, as their two accessible *cis* states^{28–30} allow for dual stereocontrol, in which either enantiomer of the product may be accessed on demand.

The dynamic responsive behavior of a motor-based catalyst is depicted in Scheme 1 and illustrates that upon irradiation of the catalyst in its initial *trans* state, (R,R) -(*P,P*)-*trans*, an unstable *cis* isomer is obtained, (R,R) -(*M,M*)-*cis*, in which the two distant active moieties (A and B in Scheme 1) are brought into proximity, resulting in the potential for cooperation between the two catalytic functional groups and ideally a more active and selective catalyst. Upon heating of (R,R) -(*P,P*)-*cis* a

Scheme 1 Design of a dynamic bifunctional responsive organocatalyst based on a molecular motor. A, B = catalytic units (e.g. thiourea, pyridine, etc.).

thermal helix inversion occurs generating stable (R,R) -(*P,P*)-*cis*; in this isomer the two catalytic functional groups remain close in space, but the helicity of the motor core has been inverted, providing a pseudoenantiomeric catalytic environment. Through a judicious choice of irradiation wavelength and temperature the two pseudoenantiomeric catalytically active *cis* states can be accessed on demand allowing dynamic control of activity and stereoselectivity.

We have previously reported two stimuli-responsive organocatalysts based on a first generation molecular motor core. In

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the initial design the upper half of the motor core was functionalized with a 2-aminopyridine moiety, while the lower half bore a thiourea group. A further structural feature was the use of an aryl spacer inserted between the catalytically active groups A and B and the motor core. This catalyst exhibited remarkable dual stereocontrol in the thio-Michael reaction.²⁸ Subsequently it was shown that the attachment of the active moieties directly to the motor core (*i.e.* removing the aryl spacer) not only allowed for a more expedient synthesis but also resulted in a higher catalyst efficiency, as demonstrated in the Henry reaction between nitromethane and various trifluoromethyl ketones.²⁹

The Henry reaction, or nitroaldol reaction, was first reported in 1895³¹ and remains a highly valuable method for carbon–carbon bond formation to date.^{32,33} The β -nitro alcohols formed in this transformation provide rapid access to important β -amino alcohols and as such this transformation has been used extensively in the synthesis of pharmaceuticals and bioactive molecules.^{34–38} In 1992 Shibasaki and co-workers reported the asymmetric Henry reaction for the first time using a heterobimetallic catalyst, accessing chiral β -nitro alcohols in an enantioenriched form.³⁹ Two years later, organocatalysis was employed in the asymmetric Henry reaction using enantiopure guanidinium catalysts.⁴⁰ While our own studies have established that dynamic control of enantioselectivity in the Henry reaction may be achieved using a bifunctional molecular motor catalyst²⁹ containing 2-aminopyridine and thiourea moieties, we were interested to understand whether the incorporation of the basic functionality into the motor core, which makes the synthesis more complicated, is required for efficient activity and stereocontrol. Furthermore, such studies may provide an important insight into the nature of the catalytic site and the role of a base in the enantiodetermining step.

Considering our previous observations on the relationship between the catalyst structure and activity, in the current design the thiourea moieties are directly attached to the motor core (Fig. 1). Since the structure requires two identical catalytic moieties, rather than differential functionalization of the upper and lower halves of the motor core, the synthesis of the motor-based chiral catalyst is considerably simplified.

Encouraged to further probe the role of the catalyst structure in activity and stereocontrol we drew our attention on recent work by Cheng^{41,42} and coworkers. These authors

showed that a catalyst containing an aliphatic thiourea is more active than its aromatic analogue based on the common 3,5-bis(trifluoromethyl)phenyl group,⁴³ and provides higher enantioselectivities in Michael addition reactions. We thus initiated the synthesis of aliphatic and aromatic bithioureas **1** and **2** and investigated their use as stimuli responsive catalysts for the Henry reaction in the presence of an external base.

Results and discussion

Synthesis and photoisomerization studies

Synthesis. The diamine core of catalysts **1** and **2** was prepared as previously reported²⁹ *via* McMurry coupling of a non-racemic chiral bromo-substituted ketone,⁴⁴ providing the tetra-substituted alkenes as an *E,Z* mixture of isomers. After palladium-catalysed Buchwald–Hartwig imination the *E* and *Z* isomers could be readily separated by flash column chromatography. Subsequent hydrolysis of the imines furnished the key diamine core and the thiourea moieties were subsequently introduced *via* condensation with the appropriate isothiocyanate (Scheme 2).

In order to confirm that the two novel bithiourea catalysts still possess the unique properties of molecular motors and can undergo a full 4-step unidirectional rotary cycle (Scheme 3) upon being subjected to appropriate stimuli, extensive UV-Vis, CD and NMR studies were performed.

UV-Vis studies. The photoisomerization process from (*P,P*)-*trans*-**1** (*trans*-stable-**1**) to (*M,M*)-*cis*-**1** (*cis*-unstable-**1**) with 312 nm light was followed by UV-Vis spectroscopy (Fig. 2a). An isosbestic point was observed at $\lambda = 330$ nm along with a bathochromic shift of the absorption maximum, characteristic of the unstable *cis* form of first generation motors.²⁷

Fig. 1 Novel bithiourea responsive catalysts **1** and **2** (only the *cis*-stable forms of the catalysts are depicted).

Scheme 2 Synthesis of aliphatic and aromatic bithiourea catalysts **1** and **2**.

Scheme 3 Unidirectional rotary cycle of catalysts **1** and **2**.

Fig. 2 The photoisomerization process was followed at 312 nm in THF at $-20\text{ }^{\circ}\text{C}$ by UV-Vis spectroscopy: (a) from (P,P) -*trans*-**1** to (M,M) -*cis*-**1**; (b) (P,P) -*cis*-**1** to (M,M) -*trans*-**1**.

The thermal helix inversion of *cis*-unstable-**1** to *cis*-stable-**1** was followed by UV-Vis spectroscopy by monitoring the absorption changes at 365 nm over five temperatures (35, 40, 50, 55 and $60\text{ }^{\circ}\text{C}$) in THF (Fig. 3a). Using the Eyring equation, the Gibbs free energy was calculated to be 100 kJ mol^{-1} at $20\text{ }^{\circ}\text{C}$ corresponding to a half-life of 30 h, and at $-17\text{ }^{\circ}\text{C}$ the calculated Gibbs energy was 95 kJ mol^{-1} corresponding to a half-life of 543 h (22 d). These values were highly promising for promoting dual stereocontrol, where the *cis*-unstable isomer must be sufficiently stable at the reaction temperature; any thermal helix inversion during catalysis with *cis*-unstable-**1** will lead to an erosion of the enantiomeric ratio (er).

The photoisomerization from (P,P) -*cis*-**1** (*cis*-stable-**1**) to (M,M) -*trans*-**1** (*trans*-unstable-**1**) was followed by UV-Vis spectroscopy (Fig. 2b). The changes in UV-Vis absorption spectra upon photoirradiation at 312 nm were monitored, showing the expected red shift in the absorption (characteristic of unstable motor isomers) along with a clear isosbestic point at $\lambda = 330\text{ nm}$.

The thermal helix inversion of *trans*-unstable-**1** to *trans*-stable-**1** was followed by UV-Vis spectroscopy by absorption changes at 355 nm over five temperatures (-20 , -15 , -10 , -5 and $0\text{ }^{\circ}\text{C}$) in THF (Fig. 3b). Using the Eyring equation, the Gibbs free energy was calculated to be 82 kJ mol^{-1} corresponding to a half-life of one min at $20\text{ }^{\circ}\text{C}$, and at $-17\text{ }^{\circ}\text{C}$ a half-life of 2 h was calculated. While it is important to note that the short half-lives observed for this process prohibit the use of *trans*-unstable-**1** as a catalyst, the spatial separation of the catalytic functional groups is already expected to preclude cooperative catalysis. Furthermore, the low Gibbs free energy for the thermal helix inversion means that irradiation of *cis*-stable-**1** with 312 nm leads to the generation of *cis*-unstable-**1** (via *trans*-unstable-**1** and *trans*-stable-**1**). In this way the two pseudoenantiomeric *cis* states can be interconverted simply through the application of heat (*cis*-unstable-**1** to *cis*-stable-**1**) and irradiation (*cis*-stable-**1** to *cis*-unstable-**1**).

Fig. 3 (a) Thermal isomerization from (M,M) -*cis*-**1** to (P,P) -*cis*-**1** in THF, followed by absorption changes in the UV-Vis spectrum at 365 nm, at five different temperatures (60 , 55 , 50 , 40 and $35\text{ }^{\circ}\text{C}$). By analysis of these data using the Eyring equation the following data have been calculated: $k^{20\text{ }^{\circ}\text{C}}\text{ (s}^{-1}\text{)} = 9.02 \times 10^{-6}$, $t_{1/2} = 30\text{ h}$, $\Delta H^{\ddagger} = 64.5\text{ kJ mol}^{-1}$, $\Delta G^{\ddagger}_{20\text{ }^{\circ}\text{C}} = 100.2\text{ kJ mol}^{-1}$, $\Delta S^{\ddagger} = -122.0\text{ J K}^{-1}\text{ mol}^{-1}$; (b) thermal isomerization from (M,M) -*trans*-**1** to (P,P) -*trans*-**1** in THF, followed by absorption changes in the UV-Vis spectrum at 355 nm, at five different temperatures (-20 , -15 , -10 , -5 and $0\text{ }^{\circ}\text{C}$). By analysis of these data using the Eyring equation following data have been calculated: $k^{20\text{ }^{\circ}\text{C}}\text{ (s}^{-1}\text{)} = 1.6 \times 10^{-2}$, $t_{1/2} = 1\text{ min}$, $\Delta H^{\ddagger} = 73.7\text{ kJ mol}^{-1}$, $\Delta G^{\ddagger}_{20\text{ }^{\circ}\text{C}} = 82.0\text{ kJ mol}^{-1}$, $\Delta S^{\ddagger} = -28.3\text{ J K}^{-1}\text{ mol}^{-1}$; (c) thermal isomerization from *cis*-unstable **2** to *cis*-stable **2** in THF, followed by absorption changes in the UV-Vis spectrum at 365 nm, at five different temperatures (60 , 55 , 50 , 45 and $40\text{ }^{\circ}\text{C}$). By analysis of these data using the Eyring equation following data have been calculated: $k^{20\text{ }^{\circ}\text{C}}\text{ (s}^{-1}\text{)} = 3.5 \times 10^{-4}$, $t_{1/2} = 1\text{ min}$, $\Delta H^{\ddagger} = 89.2\text{ kJ mol}^{-1}$, $\Delta G^{\ddagger}_{20\text{ }^{\circ}\text{C}} = 102.4\text{ kJ mol}^{-1}$, $\Delta S^{\ddagger} = -45.0\text{ J K}^{-1}\text{ mol}^{-1}$. The rate constants k of the first order decay at different temperatures were obtained using the equation $A = A_0 e^{-kT}$ (A and A_0 are the absorbance at different times t).

Analogous UV-Vis studies were performed for catalyst 2: *cis*-unstable-2 was obtained by irradiation of *cis*-stable-2 at 4 °C (via *trans*-unstable-2 and *trans*-stable-2). The thermal helix inversion of *cis*-unstable-2 to *cis*-stable 2 was followed by UV-Vis spectroscopy by absorption changes at 365 nm over five temperatures (40, 45, 50, 55 and 60 °C) in THF (Fig. 3c). Using the Eyring equation, the Gibbs free energy was calculated to be 102.4 kJ mol⁻¹ corresponding to a half-life of 80.2 h at 20 °C, and 755 d at -17 °C. Due to these long half-lives, *cis*-unstable-2 possesses sufficient conformational stability to function as a selective catalyst even at ambient temperatures.

CD studies. CD spectroscopy was used to further characterize the unidirectional rotary cycle of catalyst 1, where the expected change in helicity was observed with each step (Fig. 4).

¹H NMR spectroscopy studies. The photoisomerization processes were followed for both catalysts 1 and 2 with ¹H NMR spectroscopy. By irradiation of a solution of *trans*-stable-1 in THF-*d*₈ and following the photoisomerization by ¹H NMR spectroscopy it was possible to accurately determine the PSS for this isomerization. The PSS ratio was 92:8 in favor of *cis*-unstable-1. This high PSS ratio in favor of *cis*-unstable-1 is highly promising for use in catalysis.

After reaching the PSS, the sample was heated to 60 °C for 24 h, facilitating thermal helix inversion: complete conversion of *cis*-unstable-1 to *cis*-stable-1 was observed by ¹H NMR spectroscopy (Fig. 5).

Similar studies for catalyst 2 were conducted: exposure of stable-*cis*-2 to 312 nm light at 4 °C gave direct access to the PSS mixture of stable *trans*-2/unstable-*cis*-2 (Fig. 6), where this process involves an NMR-undetected isomerisation to *trans*-unstable-2, followed by rapid thermal helix inversion to *trans*-

Fig. 5 ¹H NMR spectrum of stable *trans*-1 in THF-*d*₈ and spectral changes after irradiation with 312 nm for 2 h giving predominately unstable *cis*-1. Subsequent heating at 60 °C for 24 h induces thermal isomerization to stable *cis*-1 (insert: zoomed ¹H NMR spectra in the aliphatic region around representative peak of H_b).

Fig. 6 ¹H NMR spectrum of stable *cis*-2 in DCM-*d*₂ and spectral changes after irradiation with 312 nm giving the PSS mixture of *trans*-stable-2/*cis*-unstable-2. (insert: zoomed ¹H NMR spectra in the aliphatic region around representative peak of H_a).

Fig. 4 CD spectra of compound 1 before and after each isomerisation process of the four-step unidirectional rotary cycle: (a) CD spectral changes of catalyst 1 (6×10^{-6} M) upon irradiation of (*P,P*)-*trans* catalyst 1 at 312 nm in THF at 20 °C. (b) CD spectral changes during thermal helix inversion of (*M,M*)-*cis*-1 upon heating in THF at 20 °C. (c) CD spectral changes of catalyst 1 (7.7×10^{-5} M) upon irradiation of (*P,P*)-*cis*-1 at 312 nm in THF at -78 °C. (d) CD spectral changes during thermal helix inversion of (*M,M*)-*trans*-1 upon heating in THF at -78 °C.

stable-2, which under irradiation undergoes photoisomerisation to *cis*-unstable-2. The PSS ratio was 85:15 in favor of *cis*-unstable-1. These observations confirm that practically the *cis*-unstable and *cis*-stable states can be accessed simply by irradiation at 312 nm under ambient conditions (favouring the *cis*-unstable-2) or heating to 60 °C (favouring the *cis*-stable-2).

Catalytic studies

With the new catalysts 1 and 2 in hand, the activity and selectivity of each of their interconvertible states were tested in the Henry reaction. Key to these studies was establishing whether

the use of an external base, as opposed to incorporation of the base into the bifunctional catalyst, would effect catalytic activity and stereocontrol. Thus, initial studies focused on the effect of the external base on the reaction.

The Henry reaction between 4-nitrobenzaldehyde and nitromethane using 5 mol% of catalyst **1** in its *cis*-stable form was investigated, using various amounts of DABCO as the external base (Table 1). We were pleased to observe significant enantioselectivity with as little as 5 mol% base, establishing that high stereocontrol can be achieved without the base being incorporated into the catalyst. It was observed that the amount of the added base did not have a significant influence on the stereoselectivity, but did effect the reactivity, where 20 mol% DABCO was required to achieve synthetically useful yields over a reaction time of two days. Subsequently, catalyst **1**, in its *cis*-stable state, was tested with different bases in the Henry reaction, in the hope of improving the asymmetric induction (Table 2). Little improvement in asymmetric control was observed upon using a variety of amine bases, although triethylamine did provide a somewhat higher enantioselectivity. Attempts to vary the solvent of the reaction were thwarted by issues of catalyst solubility. Surprisingly, catalyst **2** did not induce asymmetric induction in any of the tested conditions (Table 3), providing

Table 1 Screening the amount of added base for the Henry reaction using *cis*-stable catalyst **1**

Entry	Base	Base mol%	Yield ^a %	er ^b
1	DABCO	5	74	74 : 26 (<i>R</i>)
2	DABCO	10	85	74 : 26 (<i>R</i>)
3	DABCO	20	97	73 : 27 (<i>R</i>)

^a Yields of isolated products after flash chromatography. ^b Determined by CSP HPLC analysis.

Table 2 Screening various bases for the Henry reaction of nitromethane with *p*-nitrobenzaldehyde using *cis*-stable catalyst **1**

Entry	Base	Yield ^a /%	er ^b
1	Et ₃ N	88	83 : 17 (<i>R</i>)
2	DABCO	70	73 : 27 (<i>R</i>)
3	Hünigs base	90	74 : 26 (<i>R</i>)
4	DMAP	91	72 : 28 (<i>R</i>)

^a Yields of isolated products after flash chromatography. ^b Determined by CSP HPLC analysis.

Table 3 Screening the conditions using *cis*-stable catalyst **2** in the Henry reaction of nitromethane with *p*-nitrobenzaldehyde

Entry	Base	Solvent	Time/h	er ^a
1	Et ₃ N	DCM	16	50 : 50
2	Hünigs base	THF	16	50 : 50
3	Et ₃ N	THF	16	50 : 50
4	Hünigs base	Toluene	16	50 : 50
5	DABCO	Toluene	16	50 : 50

^a Determined by CSP HPLC analysis.

the β -nitro alcohol in the racemic form. The poor performance of catalyst **2** compared to **1** might be explained by the lower acidity of catalyst **2**, that results in less tight substrate–catalyst transition states. It may also be attributed to reduced aromatic interactions between the catalyst and the substrate.

The scope of the reaction was investigated across four different aromatic aldehydes and ketones using a variety of bases (Table 4). While both catalysts provided the corresponding β -nitro alcohol products in excellent yields, asymmetric induction was markedly different between the two catalysts. Catalyst **1** provided moderate levels of enantioselectivity using a variety of bases (with the choice of base having little influence). The use of catalyst **2**, however, led to racemic products in all cases. In order to check if the newly synthesized bithiourea **1** indeed functions as a responsive catalyst, experiments were performed with various isomers of catalyst **1** (Table 6). It was evident from the screening of various substrates with both *cis* forms of catalyst **1**, that indeed dual stereocontrol of the Henry reaction was achieved (Table 6, entries 1–13). In all cases the opposite enantiomers of the β -nitro alcohol product were obtained using the *cis*-stable and *cis*-unstable forms of the catalyst. Using the *trans* state of the catalyst, in which the thiourea groups are far apart, resulted in lower activity of the catalyst and in no stereoselectivity (Table 6, entries 1, 2, 8 and 11). This suggests that the cooperativity between the thiourea groups is crucial for both activity and the induction of stereoselectivity.

Just like the previously reported bifunctional DMAP-thiourea catalyst,²⁹ the enantioselectivities obtained with the *cis*-unstable form of catalyst **1** were slightly higher than those obtained with the *cis*-stable form, resulting from differences in the structure of the two pseudoenantiomeric *cis* forms of the catalyst. Furthermore, the results obtained using the *cis* states of the bithiourea catalyst with the addition of an external base (Table 6, entries 12 and 13) were comparable to the results obtained with the bifunctional motor catalyst reported previously²⁹ (almost identical er), clearly showing that the base does not need to be a part of the catalyst to achieve efficient responsive catalysis. These results indicate that the molecular

Table 4 Screening various aromatic substrates for the Henry reaction using stable *cis* 1 and 2 as catalysts^{a,b}

<i>cis</i>-stable 1 DABCO: 78%, 74 : 26 <i>e.r.</i> (<i>R</i>) Hünigs base: 90%, 74 : 26 <i>e.r.</i> (<i>R</i>) DMAP: 91%, 72 : 28 <i>e.r.</i> (<i>R</i>)	<i>cis</i>-stable 1 DABCO: 77%, 69 : 31 <i>e.r.</i> (<i>R</i>) Hünigs base: 25%, 65 : 35 <i>e.r.</i> (<i>R</i>) Et₃N: 70%, 62 : 38 <i>e.r.</i> (<i>R</i>)	<i>cis</i>-stable 1 DABCO: 47%, 21 : 79 <i>e.r.</i> (<i>S</i>) Hünigs base: 95%, 20 : 80 <i>e.r.</i> (<i>S</i>) Et₃N: 90%, 23 : 77 <i>e.r.</i> (<i>S</i>)	<i>cis</i>-stable 1 DABCO: 47%, 31 : 69 <i>e.r.</i> (<i>R</i>) Hünigs base: 72%, 28 : 72 <i>e.r.</i> (<i>R</i>) Et₃N: 45%, 22 : 78 <i>e.r.</i> (<i>R</i>)
<i>cis</i>-stable 2 DABCO: 74%, 50 : 50 <i>e.r.</i>		<i>cis</i>-stable 2 Et₃N: 86%, 48 : 52 <i>e.r.</i>	<i>cis</i>-stable 2 Et₃N: 70%, 47 : 53 <i>e.r.</i>

^a Yields of isolated products after flash chromatography. ^b Determined by CSP HPLC analysis. *er* are reported according to the elution order of *R* and *S* enantiomers in chiral HPLC.

Table 5 Results of the Henry reaction of nitromethane with hexanal with catalysts 1 and 2

Entry	Catalyst	<i>er</i> ^b	Conversion ^c /%
1	<i>cis</i> -Stable 1	62 : 38 (<i>R</i>)	84
2	<i>cis</i> -Unstable 1	33 : 67 (<i>S</i>)	85
3	<i>trans</i> -Stable 1	51 : 49	~95 ^a
4	<i>cis</i> -Stable 2	56 : 44 (<i>R</i>)	>95
5	<i>cis</i> -Unstable 2	44 : 56 (<i>S</i>)	>95

^a Reactions were performed on a 0.1 mmol scale, except entry 3, which was performed on a 0.05 mmol scale. ^b Determined by CSP HPLC analysis. ^c Conversions were determined from the ¹H-NMR spectrum of the crude reaction mixture.

motor-based bishiourea catalysts, with their considerably simplified synthesis, are as effective in the asymmetric Henry reaction as their bifunctional structural analogues.

We also investigated an aliphatic substrate (*n*-hexanal) in order to further establish the effect of the substrate structure on catalyst activity and selectivity (Table 5). Bishiourea catalyst 1 was able to effect asymmetric induction with hexanal and exhibited dual stereocontrol, as exemplified by the opposite enantiomeric ratios observed for *cis*-stable-1 and *cis*-unstable-1 (Table 5). The enantioselectivities were slightly lower than those for the corresponding aromatic substrates, which can perhaps be attributed to decreased aromatic interactions between the substrate and the catalyst. Interestingly, here some minor levels of stereocontrol were observed for aliphatic catalyst 2.

Table 6 Results of the Henry reaction with various aromatic substrates using different isomers of catalyst 1

Entry	Substrate	Catalyst	Time/d	Isolated yield ^b %	<i>er</i> ^c
1	R ¹ = NO ₂ , R ² = H	<i>trans</i> -Stable-1	2	95 ^a	47 : 53
2	R ¹ = NO ₂ , R ² = H	<i>trans</i> -Stable-1	1	25 ^a	49 : 51
3	R ¹ = NO ₂ , R ² = H	<i>cis</i> -Stable-1	2	90	74 : 26 (<i>R</i>)
4	R ¹ = NO ₂ , R ² = H	<i>cis</i> -Stable-1	1	90	74 : 26 (<i>R</i>)
5	R ¹ = NO ₂ , R ² = H	<i>cis</i> -Unstable-1	2	92	18 : 82 (<i>S</i>)
6	R ¹ = H, R ² = H	<i>cis</i> -Stable-1	2	22	64 : 36 (<i>R</i>)
7	R ¹ = H, R ² = H	<i>cis</i> -Unstable-1	2	28	30 : 70 (<i>S</i>)
8	R ¹ = H, R ² = COOEt	<i>trans</i> -Stable-1	2	80 ^a	51 : 49
9	R ¹ = H, R ² = COOEt	<i>cis</i> -Stable-1	2	72	28 : 72 (<i>R</i>)
10	R ¹ = H, R ² = COOEt	<i>cis</i> -Unstable-1	2	96	88 : 12 (<i>S</i>)
11	R ¹ = H, R ² = CF ₃	<i>trans</i> -Stable-1	1	30	50 : 50
12	R ¹ = H, R ² = CF ₃	<i>cis</i> -Stable-1	2	97	20 : 80 (<i>S</i>)
13	R ¹ = H, R ² = CF ₃	<i>cis</i> -Unstable-1	2	82	81 : 19 (<i>R</i>)

^a Reactions were performed on a 0.1 mmol scale, except entries 1, 2 and 8 which were performed on a 0.05 mmol scale. ^b Yields of isolated products after flash chromatography. ^c Determined by CSP HPLC analysis. *er* are reported according to the elution order of *R* and *S* enantiomers in chiral HPLC.

Conclusion

Novel molecular motor-based bithiourea organocatalysts **1** and **2** were prepared, and studied with respect to activity and stereocontrol in the asymmetric Henry reaction. Catalyst **1** exhibited good activity and dual stereocontrol, as shown by inversion in enantioselectivity upon catalysis with the interconvertible pseudoenantiomeric *cis* isomers. We have shown that the catalyst structure plays a key role in asymmetric induction, where the corresponding aliphatic bithiourea catalyst **2** exhibits no evidence of enantioselectivity. To the best of our knowledge, this is the first reported case of a responsive bithiourea catalyst and clearly establishes that a basic functional group is not required to be integrated within the catalyst structure when compared to the structurally analogous bifunctional catalysts.²⁹ Being able to harness the valuable bithiourea motif represents an important advance in dynamic stimuli responsive catalysis.

Experimental section

General information

Solvents and commercial starting materials were used as received (from Sigma Aldrich or Acros Organics). Technical grade solvents were used for extraction and chromatography. Merck silica gel 60 (230–400 mesh ASTM) was used in flash chromatography. UV-Vis measurements were performed on a Jasco V-630 spectrophotometer. CD measurements were performed on a Jasco J-815 CD spectrophotometer. UV irradiation experiments were carried out using a Spectroline model ENG-280C/FE lamp. NMR spectra were obtained using Varian Mercury Plus-400 (400 MHz) and Varian Inova-500 (500 MHz) spectrometers at 298 K. Chemical shift values (δ) are reported in parts per million (ppm) with the solvent resonance as the internal standard (CD₂Cl₂: δ 5.32 for ¹H, δ 53.8 for ¹³C, THF-*d*₈: δ 1.72 and 3.58 for ¹H, δ 67.2 and 35.2 for ¹³C). The following abbreviations are used to indicate signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or dd (doublet of doublets). Enantiomeric ratios were determined by HPLC analysis using a Shimadzu LC 10ADVP HPLC equipped with a Shimadzu SPD10AVP diode array detector and chiral columns as indicated. Sample injections were made using an HP 6890 Series auto sample injector. Exact mass spectra were recorded on an LTQ Orbitrap XL (ESI+) or on a DART Xevo G2 Qtof. Optical rotations were measured in CHCl₃ on a PerkinElmer 241 MC polarimeter with a 10 cm cell (concentration *c* given in g mL^{−1}) at 20 °C. All reactions requiring an inert atmosphere were carried out under a nitrogen atmosphere using oven dried glassware and standard Schlenk techniques. Dichloromethane and toluene were used from the solvent purification system using an Mbraun SPS-800 column. THF was distilled over sodium under a nitrogen atmosphere prior to use. Melting points were determined using a Büchi Melting Point B-545.

Synthesis

1,1'-((2*R*,2'*R*,*Z*)-2,2',4,4',7,7'-Hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) or (*cis*-stable **1).** A *cis* bis-amine motor^{29,44} (250 mg) was dissolved in dry THF (34 mL) and the solution was cooled down to 0 °C in an ice bath. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (430 mg) was added to the reaction mixture. It was allowed to warm up to room temperature and left to stir overnight. The solvent was evaporated and the crude product was purified by silica gel chromatography by using first pentane/CH₂Cl₂ = 5/95 as the eluent and then increasing the polarity of the eluent to pure CH₂Cl₂. Compound *cis*-stable **1** (584 mg, 96%) was obtained as a white solid. Mp: 200 °C (dec.). [α]_D²⁰ = +216 (*c* = 0.1 in THF). ¹H NMR (400 MHz, THF-*d*₈) δ 9.20–8.90 (m, 4H), 8.06 (d, *J* = 6.2 Hz, 4H), 7.66 (s, 2H), 7.07 (s, 2H), 3.49–3.40 (m, 2H), 3.12 (dd, *J* = 15.2, 6.2 Hz, 2H), 2.58–2.50 (m, 2H), 2.23 (s, 6H), 1.51 (s, 6H), 1.09 (d, *J* = 6.4 Hz, 6H). ¹³C NMR (400 MHz, THF-*d*₈) δ 181.7, 143.8, 142.8, 135.6, 132.5, 131.8, 129.6, 129.5, 128.3, 126.7, 125.2, 120.2, 118.2, 42.3, 39.1, 20.4, 18.13, 18.12. HRMS (APCI+, *m/z*): calc. C₄₂H₃₇F₁₂N₄S₂ [*M* + *H*]⁺: 889.2200, found 889.2202.

1,1'-((2*R*,2'*R*,*E*)-2,2',4,4',7,7'-Hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) or (*trans*-stable **1).** Under a N₂ atmosphere, a *trans*-bisamine motor (20 mg) was dissolved in dry THF (2 mL) and cooled down to 0 °C in an ice bath. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (34 mg) was added to the reaction mixture. It was allowed to warm up to room temperature and left to stir overnight. The solvent was evaporated and the crude product was purified by silica gel chromatography by using first SiO₂, pentane/CH₂Cl₂ = 5/95 as the eluent and then increasing the polarity of the eluent to pure CH₂Cl₂. Compound *trans*-stable **1** (39 mg, 79%) was obtained as a white solid. Mp: 152 °C. [α]_D²⁰ = +28 (*c* = 0.1 in THF). ¹H NMR (500 MHz, CD₂Cl₂) δ 8.20 (s, 2H), 8.10 (s, 4H), 7.74 (s, 2H), 7.72 (s, 2H), 7.07 (s, 2H), 2.95–2.81 (m, 2H), 2.69 (dd, *J* = 14.9, 5.7 Hz, 2H), 2.43 (s, 6H), 2.32 (d, *J* = 14.9 Hz, 2H), 2.24 (s, 6H), 1.11 (d, *J* = 6.5 Hz, 6H). ¹³C NMR (400 MHz, CD₂Cl₂) δ 180.2, 143.7, 143.2, 142.0, 140.2, 133.8, 132.9, 132.1, 131.8, 131.4, 131.1, 129.0, 127.1, 124.5, 124.28, 124.26, 121.7, 119.0, 46.6, 42.5, 38.7, 18.8, 18.6, 17.9. HRMS (APCI+, *m/z*): calc. C₄₂H₃₇F₁₂N₄S₂ [*M* + *H*]⁺: 889.2200, found 889.2205.

1,1'-((2*R*,2'*R*,*Z*)-2,2',4,4',7,7'-Hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diyl)bis(3-(2,2,2-trifluoroethyl)thiourea) or (*cis*-stable **2).** Under a N₂ atmosphere, a *cis*-bisamine motor (40 mg) was dissolved in dry THF (5 mL) and the solution was cooled down to 0 °C in an ice bath. 1,1,1-Trifluoro-2-isothiocyanatoethane (36 mg) was added to the reaction mixture. It was allowed to warm up to room temperature and left to stir overnight. The solvent was evaporated and the crude product was purified by GRACE automatic column chromatography using pentane/dimethyl ether as the eluent and increasing the polarity of the eluent to pure dimethyl ether. Compound **2** (78 mg, 94%) was obtained as a pale yellow solid. Mp:

decomposition starts at 176 °C. $[\alpha]_{\text{D}}^{20} = +20$ ($c = 0.1$ in THF). ^1H NMR (400 MHz, CD_3Cl) δ 9.18 (s, 2H), 6.89 (s, 2H), 5.83 (s, 2H), 4.70–4.51 (m, 2H), 4.51–4.25 (m, 2H), 3.40 (m, 2H), 3.12 (dd, $J = 15.2, 6.2$ Hz, 2H), 2.48 (d, $J = 15.3$ Hz, 2H), 2.25 (s, 6H), 1.36 (s, 6H), 1.10 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (400 MHz, CD_2Cl_2) δ 181.9, 144.8, 142.9, 141.3, 132.3, 130.3, 126.9, 125.5, 122.8, 46.0, 41.6, 38.7, 20.2, 18.3, 16.3. HRMS (APCI+, m/z): calc. $\text{C}_{30}\text{H}_{35}\text{F}_6\text{N}_4\text{S}_2$ $[\text{M} + \text{H}]^+$: 629.2100, found 629.2102.

CD spectroscopy experiments

The samples were irradiated with UV light ($\lambda = 312$ nm), while mounted on the sample holder of the CD spectrometer, until the PSS was reached. CD spectra were taken before and after irradiation.

UV-Vis spectroscopy experiments

The samples were irradiated with UV light ($\lambda = 312$ nm), while mounted on the sample holder of the UV-Vis spectrometer, until the PSS was reached. For the thermal helix inversion studies a high-pass filter was mounted in front of the UV lamp in order to cut off light with a wavelength lower than 340 nm. This minimizes the photochemical isomerization. Consequently, the holder was heated up to the appropriate temperature and the changes in the absorption were monitored over time. From the data, the rate constants (k) for the thermal helix inversion steps and the Eyring plots were obtained.

^1H NMR studies of the rotary cycle

The PSS were determined by tracking the absorption shifts in time during irradiation. The sample dissolved in a deuterated solvent was irradiated in a NMR tube at 4 °C and ^1H NMR spectra were taken after distinct intervals of time until no more changes were observed.

General procedure for the catalytic reactions

Into a vial with a magnetic stirring bar the catalyst was added (0.005 mmol, *cis*-stable **1**, *cis*-stable **2**, *trans*-stable **1**, *cis*-unstable **1***). The substrate was added (0.1 mmol) (*via* an automatic micro syringe if a liquid). Dry THF (0.1 mL) was added next and the reaction mixtures were cooled down in an ice bath. The base was added fast (0.02 mmol) *via* an automatic microsyringe and the vials were cooled to –17 °C and stirred for 30 min. Nitromethane (1 mmol, 54.16 μL), precooled to –17 °C was added *via* a microsyringe. The reaction mixture was left to stir for 16 h at –17 °C. After completion, the reaction mixture was quenched with saturated aq. solution of NH_4Cl , extracted with ethyl acetate, washed with water and brine and dried over MgSO_4 . The solvent was evaporated and the crude product was purified by column chromatography (benzaldehyde and 4-nitrobenzaldehyde, hexane/ $\text{EtOAc} = 5 : 2$, 2,2,2-trifluoro-1-phenylethan-1-one *via* automatic GRACE column chromatography with solvent gradient from 5% to 10%, then 100% of ether in pentane, ethyl 2-oxo-2-phenylacetate product, hexane : $\text{EtOAc} = 9 : 1$). The analytical data of

the obtained products are in agreement with the published results.^{45–51}

*The *cis*-unstable **1** catalyst (PSS mixture, *cis*-unstable : *trans*-stable = 98 : 2) preparation procedure: *trans*-stable catalyst **1** was dissolved in CD_2Cl_2 and irradiated with 312 nm UV light for 2 h at 4 °C. The solution was transferred to the reaction vial and the DCM was evaporated first in a stream of nitrogen gas, and then *in vacuo*.

**The following procedures describe reactions performed with Hünig's base.

2-Nitro-1-(4-nitrophenyl)ethan-1-ol

Following the general procedure the title compound was obtained as a white wax in 90% yield and er = 74 : 26 (*R* : *S*) using (*P,P*)-*cis*-**1** as the catalyst, and in 92% yield and er = 18 : 82 favoring the (*S*)-enantiomer using the (*M,M*)-*cis*-**1** : (*P,P*)-*trans*-**1** PSS mixture (92 : 8) as the catalyst. HPLC analysis: OD-H column (220 nm), 40 °C, 0.5 mL min^{-1} method: heptane/IPA = 85/15, $t_1 = 29$ min, $t_2 = 35$ min. ^1H NMR (400 MHz, CDCl_3) δ 7.56–7.63 (m, 2H), 7.42–7.48 (m, 2H), 5.18–5.23 (m, 1H), 4.93–5.03 (m, 2H), 4.63 (s, 1H).

2-Nitro-1-phenylethan-1-ol

Following the general procedure the title compound was obtained as a white wax in 22% yield and er = 64 : 36 (*R* : *S*) using (*P,P*)-*cis*-**1** as the catalyst, and in 28% yield and er = 30 : 70 favoring the (*S*)-enantiomer using the (*M,M*)-*cis*-**1** : (*P,P*)-*trans*-**1** PSS mixture (92 : 8) as the catalyst. HPLC analysis: OD-H column (220 nm), 40 °C, 0.5 mL min^{-1} method: heptane/IPA = 85/15, $t_1 = 18$ min, $t_2 = 22$ min. ^1H NMR (400 MHz, CDCl_3) δ 7.42–7.35 (m, 5H), 5.45–5.42 (m, 1H), 4.54–4.49 (m, 1H), 4.43–4.40 (m, 1H), 2.96 (s, 1H).

1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-ol

Following the general procedure the title compound was obtained as a white wax in >95% yield and er = 20 : 80 (*R* : *S*) using (*P,P*)-*cis*-**1** as the catalyst, and in 82% yield and er = 81 : 19 favoring the (*R*)-enantiomer using the (*M,M*)-*cis*-**1** : (*P,P*)-*trans*-**1** PSS mixture (92 : 8) as the catalyst. HPLC analysis: OD-H column (220 nm), 40 °C, 0.5 mL min^{-1} method: heptane/IPA = 80/20, $t_1 = 17.7$ min, $t_2 = 22.7$ min. ^1H NMR (400 MHz, CDCl_3) δ 7.56–7.63 (m, 2H), 7.42–7.48 (m, 3H), 5.10 (d, $J = 13.8$ Hz, 1H), 5.01 (d, $J = 13.8$ Hz, 1H), 4.63 (s, 1H).

Ethyl 2-hydroxy-3-nitro-2-phenylpropanoate

Following the general procedure the title compound was obtained as a white wax in 72% yield and er = 28 : 72 (*R* : *S*) using (*P,P*)-*cis*-**1** as the catalyst, and in >95% yield and er = 88 : 12 favoring the (*R*)-enantiomer using the (*M,M*)-*cis*-**1** : (*P,P*)-*trans*-**1** PSS mixture (92 : 8) as the catalyst. HPLC analysis: OD-H column (220 nm), 40 °C, 0.5 mL min^{-1} method: heptane/IPA = 80/20, $t_1 = 12.9$ min, $t_2 = 15.6$ min. ^1H NMR (400 MHz, CDCl_3) δ 7.62–7.60 (m, 2H), 7.43–7.40 (m, 3H), 5.26 (d, $J = 14.0$ Hz, 1H), 4.68 (d, $J = 14.0$ Hz, 1H), 4.44–4.31 (m, 2H), 4.22 (s, 1H), 1.34 (t, 3H).

1-Nitroheptan-2-ol

Following the general procedure the title compound was obtained as a colorless oil in >95% conversion (determined by NMR) and er = 56:44 (*R:S*) using (*P,P*)-*cis*-2 as the catalyst, and in >95% conversion and er = 44:56 favoring the (*S*)-enantiomer using the (*M,M*)-*cis*-2:(*P,P*)-*trans*-2 PSS mixture (85:15) as the catalyst. When using (*P,P*)-*cis*-1 as the catalyst the product was obtained in 84% conversion and er = 62:38, whereas using the (*M,M*)-*cis*-1:(*P,P*)-*trans*-1 PSS mixture (92:8) as the catalyst product was obtained in 84% conversion and er = 37:63 favoring the opposite enantiomer. HPLC analysis: AD-H column (210 nm), 40 °C, 0.5 mL min⁻¹ method: heptane/IPA = 89/11, *t*₁ = 13.1 min, *t*₂ = 15.5 min. ¹H NMR (400 MHz, CDCl₃) δ 4.55–4.25 (m, 3H), 2.68 (bs, 1H), 1.60–1.15 (m, 8H), 0.9–0.7 (m, 3H).

Conflicts of interest

The authors declare no competing financial interest.

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