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Enantiospecific Photochemical Transformations under Elevated Pressure

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Abstract: Enantiospecific axial-to-point chiral transfer in light-induced transformations was efficient under elevated pressure at high temperatures. Model photoreactions with atropisomeric compounds showed higher enantioselectivity in the photoproducts under elevated pressure. The *ee* values in the photoproducts were rationalized based on the increased stability of optically pure atropisomeric compounds at elevated pressure, even at high temperatures.

Keywords: asymmetric synthesis · atropisomerism · enantioselectivity · photochemistry · pressure effects · Non-biaryl atropisomers

Introduction

Chiral motifs in nature play a central role in many vital chemical and biological processes. Recognizing the importance of chiral compounds, chemists have focused their attention on controlling chirality during synthetic chemical transformations. One of the main classes of compounds that has gained considerable attention in recent years for the development of new and effective asymmetric synthetic procedures[1] is atropisomeric compounds, which possess axial chirality that originates from restricted bond rotation.[2–8] One of the inherent issues with atropisomeric molecules is their propensity to racemize at elevated temperature.[9] Hence, in spite of being an effective chiral scaffold at room temperature, axially chiral molecules can easily lose their original absolute configuration, which is a significant limitation to their use in chemical transformations that require high reaction temperatures.[10]

For atropisomeric compounds, the interconversion between left- and right-handed structural forms can be manipulated by external stimuli, such as temperature, which influence the extent of hindered single-bond rotation.[11] Whereas point chiral compounds (in which the chiral center is defined on a tetrahedral carbon atom or on another atom) retain their absolute configuration, racemization is an inherent characteristic of atropisomeric compounds at elevated temperature.[9] Uncovering the intricacies[12–17] that are involved in this racemization process is indispensable for understanding the stereochemical influence of atropisomeric compounds on asymmetric chemical transformations.[9] Pressure, volume, and temperature constitute a triumvirate of parameters that can be empirically exploited to study the dynamics of natural phenomena.[18–25] Variation of one of these parameters provides an opportunity to understand and investigate dynamic chemical processes that are influenced by a change in physical conditions. For isochoric processes, pressure and temperature are interchangeably used to compute thermodynamic and kinetic parameters.[24–25]

Recently, we have been exploring[26–31] the use of non-biaryl axially chiral chromophores to achieve stereoselectivity during photoreactions (6π-photocyclization,[26–31] photochemical H-abstraction,[26–31] [2+2]-photocycloaddition[26–31] and 4π-photochemical ring closure[26–31]) in solution and have achieved high enantioselectivity (>90% *ee*) in the photoproducts. In those studies, we showed that effective chiral transfer was dependent on the reaction temperature.[26–31] To evaluate the potential of axially chiral chromophores for application in reactions that require elevated temperature, it became critical to also investigate the effect of pressure, because pressure and volume affect one another when the temperature is kept constant.[24–25] Herein, we have performed detailed investigations on axial-to-point chiral transfer during photochemical transformations (Scheme 1) under elevated pressure. Our results indicate that elevated pressure inhibits/suppresses the racemization of non-biaryl atropisomeric chromophores, thereby leading to enhanced enantiomeric excess (*ee*) in the photoproducts. To show the general applicability of pressure in the stabilization of axial chirality, as well as its use in enantiospecific photoreactions, we have comparatively investigated three different atropisomeric systems, that is, α-oxoamide **1a**, 2-pyridone **1b**, and acrylanilides **1c**–**1e** (Scheme 1).

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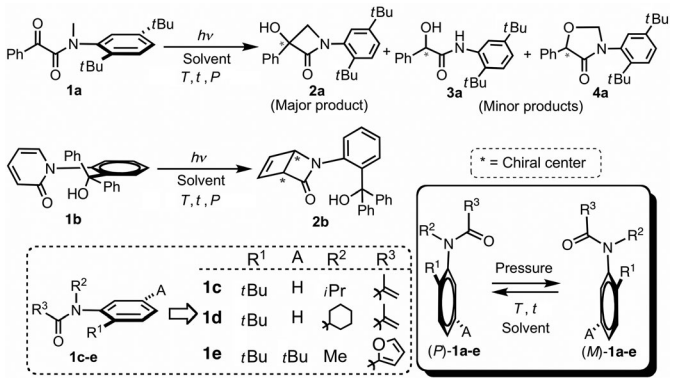

Scheme 1. Optically pure atropisomers **1a**–**1e**, which were evaluated for enantiospecific photoreactions and racemization at elevated pressure.

Table 1. Enantiospecific photochemical reactions of α-oxoamide **1a** and 2-pyridone **1b** under different pressures in MeCN at 70 °C.[a]

Entry	Compound[b]	*t* [h]	*ee* [%] (photoproduct)[c] 0.1 MPa	20 MPa	100 MPa
1	(−)-**1a**	2	17 (A)	29 (A)	–
2	(+)-**1a**	2	16 (B)	30 (B)	–
3	(−)-**1b**	1	4 (B)	18 (B)	27 (B)

[a] The samples were placed inside a pressure cell that was equipped with sapphire windows. Irradiation was performed by using an optical fiber that contained a light source from a Xe lamp. The values are an average of two runs and carry an error of ±20%, owing to experimental limitations of handling the samples at elevated pressure and temperature in the cell. [b] (+) and (−) denote the sign of the optical rotation of the reactant. [c] A and B refer to the elution order of the enantiomers during HPLC analysis on a chiral stationary phase.

Results and Discussion

Optically pure atropisomeric compounds **1a**–**1e** were synthesized according to literature procedures.[26–31] The optical purity of these samples was verified by HPLC analysis on a chiral stationary phase, the sign/magnitude of the optical rotation, and by the sign of the Cotton effect. Photochemical transformation under high pressures and the racemization kinetics of optically pure isomers of compounds **1** were investigated in spectrophotometric-grade solvents at a given temperature and pressure in a custom-built high-pressure vessel.[24–25] This high-pressure vessel was fitted with three optical windows that were made of sapphire or diamond, with an effective aperture of 9 mm or 3 mm (i.d.), respectively. Sapphire windows were used for the photoirradiation and UV/Vis and fluorescence spectroscopy experiments, whilst birefringence-free diamond windows were used for circular dichroism (CD) spectroscopy. A quartz inner cell with inner dimensions of 3 mm (W) × 2 mm (D) × 7 mm (H) was connected to a short flexible Teflon tube to adjust the volume change under pressure. This quartz cell was filled with a solution of the sample at a known concentration. The top end of the Teflon tube was stoppered and the whole cell was placed inside the pressure vessel. The vessel was fixed inside the sample chamber of the spectrometer at a set hydrostatic pressure and temperature. The samples were irradiated by using a fiber optics cable, which delivered light from a Xe light source that was equipped with a 300-(±10) nm band-pass filter. Because we had already established the temperature-dependent photoreaction of optically pure atropisomers of α-oxoamide **1a**, which underwent enantiospecific Norrish–Yang cyclization,[28] and 2-pyridone **1b**, which underwent enantiospecific 4π-ring closure[30] (Scheme 1), we selected these systems to investigate the effect of elevated pressure on photochemical transformations at high reaction temperatures (Scheme 1).

The photoreactions of optically pure compounds **1a** and **1b** were investigated in MeCN at 70 °C under different pressures, that is, 0.1–100 MPa (Table 1). Photoirradiation of compound **1a** in $CHCl_3$ gave compound **2a** as the exclusive photoproduct. Because we had planned to evaluate axial chiral transfer at high temperatures (about 70 °C), the use of $CHCl_3$ as a solvent was ruled out and MeCN was chosen as the solvent of choice. The photoreaction of compound **1a** was expected to yield three different photoproducts, compounds **2a**–**4a**. In MeCN, at 70 °C and 0.1 MPa, photoirradiation of compound **1a** gave β-lactam **2a** as the major photoproduct (**2a**/**3a**/**4a**, 70:28:2). Photoirradiation of optically pure 2-pyridone **1b** at 70 °C and 0.1 MPa gave bicyclic β-lactam **2b** as the major photoproduct. HPLC analysis of the photoreaction mixture on a chiral stationary phase revealed the *ee* values for the photoproducts. At 70 °C and 0.1 MPa, the *ee* values of photoproducts **2a** and **2b** were 16% and 4%, respectively (Table 1). On the other hand, the photoirradiation of compounds **1a** and **1b** at 20 MPa gave *ee* values of 30% and 18% in the corresponding photoproducts (**2a** and **2b**, respectively). Further increasing the pressure to 100 MPa in the photoirradiation of compound **1b** resulted in an *ee* value of 27% in the photoproduct (**2b**, Table 1; entry 3). The clear increase in *ee* value upon increasing the pressure during these photochemical transformations was quite striking (Table 1).

Upon inspection of the *ee* values in Table 1, it was clear that a moderate increase in pressure from 0.1 MPa to 20 MPa had a significant effect on axial-to-point chiral transfer during these photochemical transformations. It is likely that, at elevated pressure, the rate of racemization of optically pure atropisomers is slow, which is reflected in the enhanced *ee* values in the photoproduct. To confirm this conjecture, we investigated the effect of pressure on the racemization of optically pure atropisomeric α-oxoamide **1a** and 2-pyridone **1b** at elevated temperature. In addition, to determine whether the effect of pressure on inhibition/suppression of the racemization of atropisomeric compounds was a general phenomenon, we also evaluated the rates of racemization for optically pure atropisomeric acrylanilides **1c**–**1e**.

For a qualitative discussion of the effect of pressure on racemization, it is important to calculate the activation volume ($\Delta V^{\neq}_{rac}$) for the racemization processes (Eqs. 1 and 2),[32] that is, the difference between the partial molar volume of the transition state and the sum of the partial volumes of the reactant(s) at a given temperature and pressure.

The value of activation volume is obtained at equilibrium, when the internal force of the substrate equalizes the applied pressure. Because the rate constant depends on both temperature and pressure, at any given temperature (T in Kelvin), the effect of pressure (P in MPa) on the racemization rate constant (k_{rac}) is given by Equations (1) to (5),[24–25] where $\tau_{1/2}$ is the half-life of racemization, R is the gas constant (8.314 $cm^3 MPa K^{-1} mol^{-1}$), C is a constant, $[P]_0$ is the initial concentration of the P isomer, $x=[P_0-([P],[M])]$, ($[P]$,$[M]$) represents the concentration of the racemate at time t, k_B is the Boltzmann constant, and h is Planck's constant.

$$\Delta V^{\ddagger}_{rac} = -RT(\partial \ln k_{rac}/\partial P)_T \quad (1)$$

$$(\ln k_{rac})_T = -(\Delta V^{\ddagger}_{rac}/RT)P + C \quad (2)$$

$$\ln[[P]_0/([P]_0-x)] = \ln[([P]+[M])/([P]-[M])] = k_{rac}t \quad (3)$$

$$\tau_{1/2} = \ln 2/k_{rac} \quad (4)$$

$$(\ln k_{rac}/T) = \Delta S^{\ddagger}_{rac}/R - \Delta H^{\ddagger}_{rac}/RT + \ln(k_B/h) \quad (5)$$

A point to note is that, enantiomerization is a microscopic phenomenon, whereas racemization is a macroscopic phenomenon; thus, it is important to appreciate the relationship between these processes, that is, $k_{rac}=2\times k_{enant}$, where k_{enant} is the rate constant of enantiomerization.[9]

Racemization studies of optically pure isomers of compounds **1a–1e** were performed by using CD spectroscopy in spectrophotometric-grade solvents at a given temperature and pressure in the custom-built high-pressure vessel.[24–25] To correlate the effects of pressure, temperature, and volume on the racemization process, two sets of experiments were performed (Figure 1, Figure 2, and Figure 3). In the first set of experiments (Table 2, Figure 2), the pressure was kept constant at 0.1 MPa and the temperature was varied to determine the racemization rate constant (k_{rac}), the activation free energy of racemization ($\Delta G^{\ddagger}_{rac}$),[33] the activation enthalpy ($\Delta H^{\ddagger}_{rac}$), and the activation entropy ($\Delta S^{\ddagger}_{rac}$). In the second set of experiments (Table 2, Figure 1, Figure 2, and Figure 4), the temperature was kept constant and the pressure was varied to determine the activation volume ($\Delta V^{\ddagger}_{rac}$), the racemization rate constant (k_{rac}), and the activation energy for racemization ($\Delta G^{\ddagger}_{rac}$).[33]

The racemization of optically pure non-biaryl atropisomeric compounds was monitored by CD spectroscopy at elevated temperatures at different pressures (Table 2 and Table 3). To study the influence of solvent on the racemization process, racemization studies were carried out in various solvents. At pressures as high as 50 MPa, some of the solutions became cloudy. This result indicates that, under high pressures, the compounds precipitated/crystallized, thereby making the solution cloudy. This precipitation/crystallization presumably depended on the solubility of the given compound and any physical interactions between the solute and the solvent. Apart from the solvents listed in Table 3, other solvents were not suitable for high-pressure measurements, owing to microcrystallization/cloudiness of the sample at these pressures. To enhance the racemization rate, we performed our studies at elevated temperatures and pressures in the range 0.1–20 MPa. CD measurements on the pressurized samples (10 MPa and 20 MPa) were recorded at 343 K (Table 3).

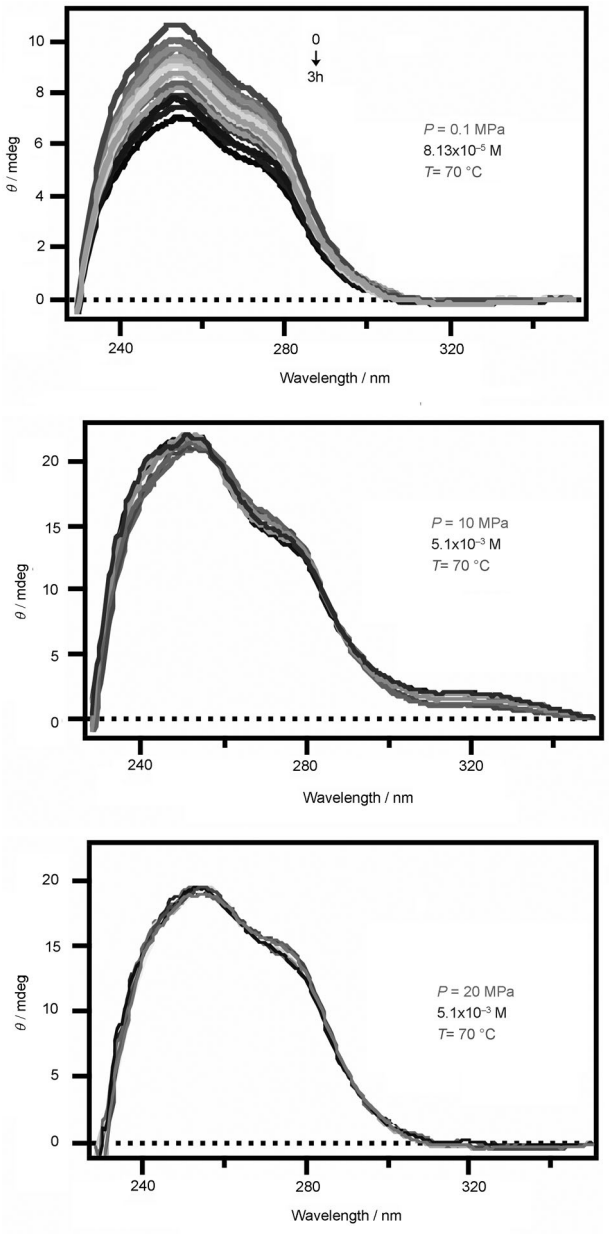

Figure 1. Racemization of optically pure acrylanilide (+)-**1c**, as monitored by CD spectroscopy at 0.1, 10, and 20 MPa in methylcyclohexane (MCH) at 343 K.

The racemization rate constant (k_{rac}) and activation free energy of racemization ($\Delta G^{\ddagger}_{rac}$)[33] were determined from the change in the intensity of the CD spectra in a given solvent at a particular temperature under constant pressure (Figure 1, Figure 2, Figure 3, Figure 4, and Table 2). For ex-

Table 2. Racemization rate constant (k_{rac})[a] and half-life of racemization ($\tau_{1/2}$) for optically pure atropisomers **1a**–**1e** at different temperatures and a pressure of 0.1 MPa.

Entry	Compound	Solvent[b]	T [K]	k_{rac} [s^{-1}][c]	$\tau_{1/2}$ [h][c]
1	**1a**	EtOH	333	1.7×10^{-5}	12
2			341	3.7×10^{-5}	5.2
3			346	7.1×10^{-5}	2.7
4		MeCN	333	2.4×10^{-5}	8.0
5			341	5.7×10^{-5}	3.4
6			348	1.5×10^{-4}	1.3
7	**1b**	EtOH	323	3.5×10^{-4}	0.55
8			333	1.0×10^{-3}	0.2
9			343	1.5×10^{-3}	0.13
10		MeCN	323	9.0×10^{-5}	2.1
11			333	3.1×10^{-4}	0.63
12			343	9.1×10^{-4}	0.21
13	**1c**	MCH	343	3.5×10^{-5}	5.5
14			348	5.6×10^{-5}	3.4
15			353	9.8×10^{-5}	2.0
16			363	2.6×10^{-4}	0.75
17		MeCN	338	1.2×10^{-5}	16
18			343	2.1×10^{-5}	9.4
19			348	3.1×10^{-5}	6.2
20	**1d**	MCH	333	1.9×10^{-5}	10
21			343	4.5×10^{-5}	4.3
22			358	3.1×10^{-4}	0.63
23	**1e**	MCH	333	3.7×10^{-5}	5.2
24			343	8.1×10^{-5}	2.4
25			353	2.1×10^{-4}	0.90
26		MeCN	338	4.3×10^{-5}	4.5
27			343	8.3×10^{-5}	2.3
28			348	1.4×10^{-4}	1.4

[a] Analysis of the racemization kinetics was performed inside a custom-built high-pressure cell with diamond windows and monitored by CD spectroscopy. All of these values carry an error of 10%. [b] [**1a**] = 9.39×10^{-5} M in EtOH and 1.16×10^{-4} M in MeCN; [**1b**] = 7.36×10^{-5} M in EtOH and 9.03×10^{-5} M in MeCN; [**1c**] = 8.13×10^{-5} M in MCH and 1.2×10^{-5} M in MeCN; [**1d**] = 1.86×10^{-5} M in MCH; [**1e**] = 2.27×10^{-4} M in MCH and 1.63×10^{-5} M in MeCN. [c] k_{rac} and $\tau_{1/2}$ were obtained from Equations (3) and (4), respectively. $\Delta G^{\ddagger}_{rac}$ values are provided in the Supporting Information.

Table 3. Racemization rate constants (k_{rac}) and half-life ($\tau_{1/2}$) of **1a–1e** under elevated pressure at 343 K.[a]

Entry	Compound/solvent	10 MPa		20 MPa	
		k_{rac} [s^{-1}]	$\tau_{1/2}$ [h]	k_{rac} [s^{-1}]	$\tau_{1/2}$ [h]
1	**1a**/EtOH[b]	2.4×10^{-5}	8.0	5.6×10^{-6}[c]	34[c]
2	**1b**/MeCN	6.8×10^{-5}[d]	2.9[d]	–	–
3	**1c**/MCH	2.1×10^{-5}	9.0	7.3×10^{-6}	27
4	**1d**/MCH	2.5×10^{-5}	7.9	5.1×10^{-6}[c]	38[c]
5	**1e**/MCH	6.5×10^{-5}	2.9	4.2×10^{-5}	4.6

[a] Analysis of the racemization kinetics was performed inside a custom-built high-pressure cell with diamond window and monitored by CD spectroscopy. All of these values carry an error of 10%. CD spectra monitored at 260 nm for compound **1a**, 310 nm for compound **1b**, and 250 nm for compounds **1c**–**1e**. $\Delta G^{\ddagger}_{rac}$ values are provided in the Supporting Information. [b] For compound **1a** in EtOH at 5 MPa, k_{rac} = 2.2×10^{-5} s^{-1} and $\tau_{1/2}$ = 8.8 h. [c] Pressure was maintained at 25 MPa. [d] Pressure was maintained at 12 MPa.

ample, in the case of optically pure **1c** at 343 K, a decrease in the ellipticity (θ) was observed in the CD spectra at a pressure of 0.1 MPa, whilst the decrease in θ was minimal at an elevated pressure of 20 MPa. The most-striking contrast in the rate of racemization was displayed by compound **1b**.

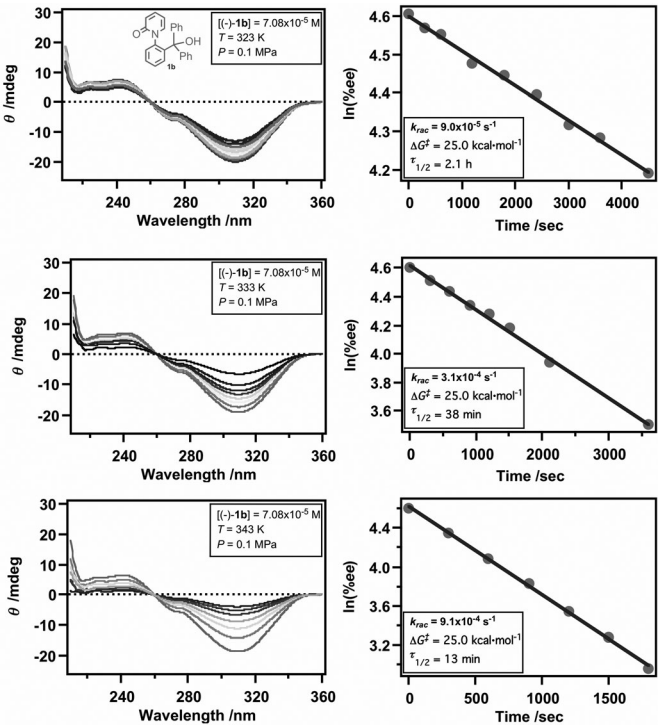

Figure 2. Racemization of optically pure compound (−)-**1b**, as monitored by CD spectroscopy at 0.1 MPa in MeCN.

At 343 K and 0.1 MPa in MeCN, $k_{rac}=9.1\times10^{-4}\,s^{-1}$ and $\tau_{1/2}=0.21$ h, that is, 13 min (Table 2, entry 12). On increasing the pressure to a moderate 12 MPa at 343 K, $k_{rac}=6.8\times10^{-5}\,s^{-1}$ and $\tau_{1/2}=2.9$ h (Table 3, entry 2). Thus, the half-life increased 14 times with a small increase in the pressure from 0.1 MPa to 12 MPa. In the case of compound **1b**, there was a noticeable change in the $\tau_{1/2}$ value upon changing the solvent from MeCN to EtOH ($\tau_{1/2}=0.13$ h, that is, 7.7 min in EtOH; $\tau_{1/2}=0.21$ h, that is, 13 min in MeCN; Table 2, entries 9 and 12, respectively). We had previously postulated that the presence of hydrogen bonds and the polarity of the solvent affected the racemization rates in axially chiral 2-pyridones.[26–31]

The activation enthalpy ($\Delta H^{\ddagger}_{rac}$) and activation entropy ($\Delta S^{\ddagger}_{rac}$) were obtained from the Eyring plots for compounds **1a**–**1e** (Equation (5), Table 4, and Figure 4,). All of the investigated compounds showed negative $\Delta S^{\ddagger}_{rac}$ values and positive $\Delta H^{\ddagger}_{rac}$ values. Negative $\Delta S^{\ddagger}_{rac}$ values are consistent with the fact that the racemization of non-biaryl atropisomers is entropically unfavorable, owing to the restricted bond rotation that most often involves steric hindrance. A point to note is the magnitude of $\Delta S^{\ddagger}_{rac}$ values: The contribution of the $\Delta S^{\ddagger}_{rac}$ value in the case of compound **1b** was lower than that in compounds **1a**, **1c**–**1e**; presumably, this result is due to steric hindrance, which leads to restricted rotation around the N–C_{aryl} bond. In compounds **1a**, **1c**–**1e**, the rotation of the N–C_{aryl} bond has to overcome the steric impediments owing to an alkyl substituent (Figure 5, top). On the other

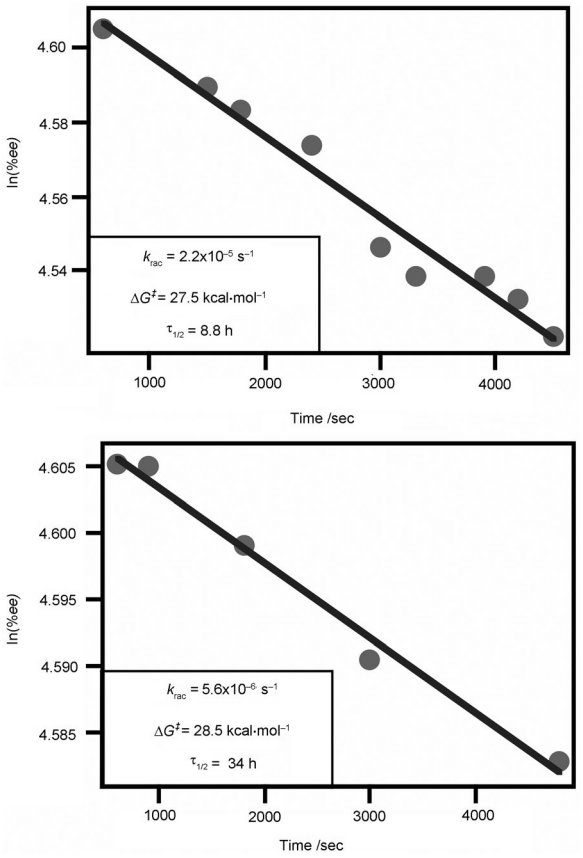

Figure 3. Racemization of optically pure compound **1a**, as monitored by CD spectroscopy at 5 and 25 MPa in EtOH. CD signals were monitored as time-course/scan experiment at 260 nm.

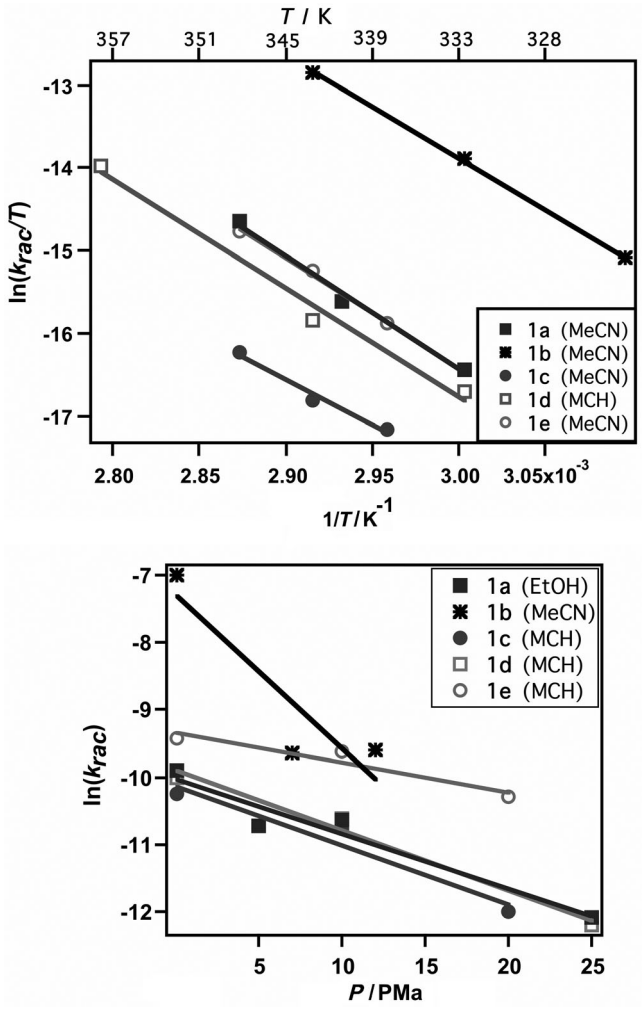

Figure 4. Top: Eyring plots for the racemization of substrates **1a**–**1e** at 0.1 MPa. Bottom: Plot of the pressure dependence of racemization to determine the activation volumes for compounds **1a**–**1e** at 343 K; the solvent that was used for a given compound is noted in the inset.

hand, in the case of compound **1b**, the rotation has to overcome the steric hindrance of an OH substituent. This lesser steric bulk in the case of compound **1b** is reflected in the magnitude of $\Delta S^{\ddagger}_{rac}$, which is, in turn, reflected in the racemization rate ($\tau_{1/2}$). Whilst an increase in the temperature enhances the racemization rates of non-biaryl atropisomers, an increase in the pressure has the opposite effect. A comparison of Table 2 and Table 3 shows that, at a given temperature, the racemization rate is faster at normal pressure (0.1 MPa) and slower at elevated pressure (5–20 MPa); this influence of pressure on the racemization rate was reflected by an increase in the $\Delta G^{\ddagger}_{rac}$ value, as well as in $\tau_{1/2}$ value (Figure 1).[33]

To understand the influence of pressure, it is important to appreciate the influence of activation volume during a chemical transformation (in this case, racemization). Analysis of Equations (1) and (2) indicates that, at a constant temperature, the processes that occur through a transition state with negative differential activation volume will be accelerated under elevated pressure, whereas transition state(s) with a positive differential activation volume will be decelerated. For example, in the case of cycloaddition and condensation reactions that have shown rate acceleration under elevated pressure, a decrease in the partial molar volume in the transition state along the reaction coordinate was postulated to be responsible for the enhanced chemical reactivity.[34–36] In our system (Table 4), the activation volume was positive for the racemization process; that is, the partial molar volume in the transition state increased considerably when compared to the partial molar volume of the optically pure atropisomeric reactant(s).

These differences in volume change can be understood based on the structures of the compounds that are employed and on the factors that influence the racemization process. In the case of compounds **1a**, **1c**–**1e**, the hindered rotation around the N–C_{aryl} bond is due to the steric bulk of the *ortho-tert*-butyl substituent on the *N*-phenyl group (Figure 5). On the other hand, in the case of compound **1b**, both steric hindrance (from the *ortho*-hydroxydiphenylmethyl substituent) and H-bonding interactions (from the OH group) influence the N–C_{aryl} bond rotation (Figure 5). Thus, to rotate the N–C_{aryl} bond in compounds **1a**, **1c**–**1e**, the molecule has to effectively "expand" to accommodate the bulky *ortho-tert*-butyl substituent. A closer look at the acti-

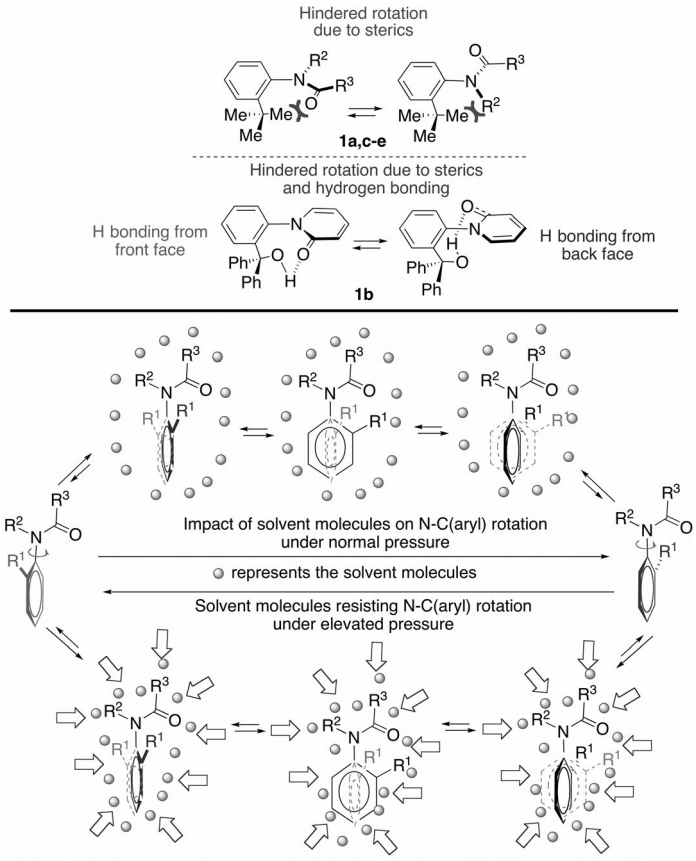

Figure 5. Pressure effects on racemization: Role of the solvents and non-bonding interactions.

Table 4. Activation enthalpy, entropy, and volume for the racemization of optically pure compounds **1a**–**1e** at 343 K.

Entry	Compound/ solvent	$\Delta S^{\ddagger[a]}$ [J mol^{-1} K^{-1}]	$\Delta H^{\ddagger[a]}$ [kJ mol^{-1}]	$\Delta V^{\ddagger[b]}$ [cm^3 mol^{-1}]
1	**1a**/EtOH	−29.0	103	234
2	**1b**/MeCN	−2.55	103	651
3	**1c**/MCH	−38.3	101	251
4	**1d**/MCH	−9.23	109	254
5	**1e**/MCH	−82.2	82.9	126

[a] Obtained from Equation (5) by using the values in Table 2. [b] Obtained from Equation (2) by using the values in Table 3. All of these values carry an error of 10%.

to form H bonds). At elevated pressure, the solvent shell surrounding the atropisomeric compounds will be packed closely, so as to "freeze" the molecular conformation. Because racemization involves rotation around the N–C_{aryl} bond, owing to tight packing of the solvent molecules/solvent cluster around the atropisomeric compounds at elevated pressure, bond rotation is likely hindered, thereby resulting in the observed slow racemization. In addition, the N–C_{aryl} bond rotation has to be accompanied by a change in the arrangement of the "solvent cluster" that surrounds the molecule during the racemization process. This change is reflected in the $\Delta V^{\ddagger}_{rac}$ values (Table 4). Changes in the volume, owing to "molecular confinement", would be pronounced in the case of compound **1b** because H-bonding interactions are expected to contribute to the structure and stability of the solvent shell surrounding the atropisomeric substrate. Because the activation volume was large (125–650 cm^3 mol^{-1}) for the atropisomeric systems that were investigated herein (Table 4), a moderate increase in pressure (5–20 MPa) was able to slow the racemization process very effectively.

Because increasing the pressure in these systems clearly increases the barrier for rotation around the N–C_{aryl} bond, excitation of the chromophores results in increased stereospecificity during the photochemical transformations. Because the *ee* values of the photoproduct are easily ascertained at various pressures, the influence of the relative rate constant on the formation of the individual enantiomers was expressed as a linear function of pressure, as in Equation (6) where $k_S/k_R = (100+\%\,ee)/(100-\%\,ee)$, T is the temperature in Kelvin, P is the pressure in MPa, R is the gas constant (8.314 cm^3 MPa K^{-1} mol^{-1}), and k_S and k_R represent the rate of formation of individual enantiomeric photoproducts. From this function, the differential activation volume ($\Delta\Delta V^{\ddagger}_{S\text{-}R}$) was calculated at a given temperature (Figure 6). From the linear plot of $\ln k$ versus P, it is clear that the hydrostatic pressure causes no alteration of the reaction mechanism or of the activation volumes over the employed pressure range.

$$ln(k_S/k_R) = -(\Delta\Delta V^{\ddagger}_{S-R}/RT)P + C \qquad (6)$$

vation volume ($\Delta V^{\ddagger}_{rac}$) for racemization (Table 4) indicated that $\Delta V^{\ddagger}_{rac}$ value was higher in the case of compound **1b** (about 650 cm^3 mol^{-1}) than in compounds **1a**, **1c**–**1e** (about 120–250 cm^3 mol^{-1}), in stark contrast to the activation entropy values ($\Delta S^{\ddagger}_{rac}$) for compound **1b** compared to compounds **1a**, **1c**–**1e**. To appreciate this dichotomy, a key factor that needs to be considered in the racemization process (especially at elevated pressure) is the solvent clusters that surround atropisomeric molecules. At normal pressure, the solvent shell that surrounds compounds **1a**, **1c**–**1e** is expected to be loose (van der Waals forces), whereas, with compound **1b**, the molecule interacts with the solvent/solvent shell through H bonding (with solvent that has ability

A point that should be emphasized is with regards to the difference between $\Delta V^{\ddagger}_{rac}$ and $\Delta\Delta V^{\ddagger}_{S\text{-}R}$. The activation volume ($\Delta V^{\ddagger}_{rac}$) is the change in volume that is required for racemization of the atropisomers, whereas the differential activation volume ($\Delta\Delta V^{\ddagger}_{S-R}$) is a reflection of the difference in the volume of the diastereomeric transition state during the course of the phototransformation that leads to the photoproduct. Hence, a direct comparison (both magnitude and sign) of the two parameters should not be made.

This study has uncovered a very simple and effective way to suppress racemization in non-biaryl atropisomeric compounds. Because the activation volume during racemization is large, a moderate increase of the pressure in the system

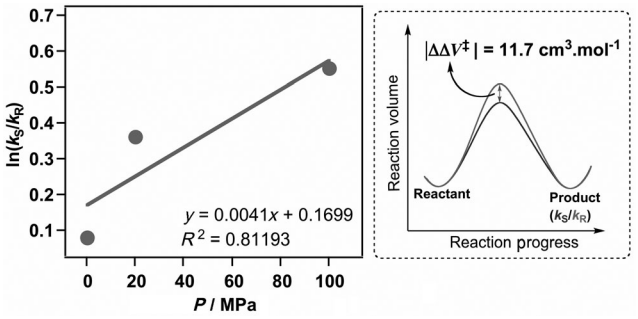

Figure 6. Left: Plot of the pressure dependence of the relative rate constant at 343 K to determine the differential activation volume ($\Delta\Delta V^{\neq}$) during the photo-induced 4π-ring closure of compound **1b** in MeCN. Right: The absolute value of $\Delta\Delta V^{\neq}$ is provided because the sign will depend on which enantiomer in the photoproduct is enhanced during the photochemical transformation. k_S *and* k_R represent the rate of formation of the individual enantiomeric photoproducts.

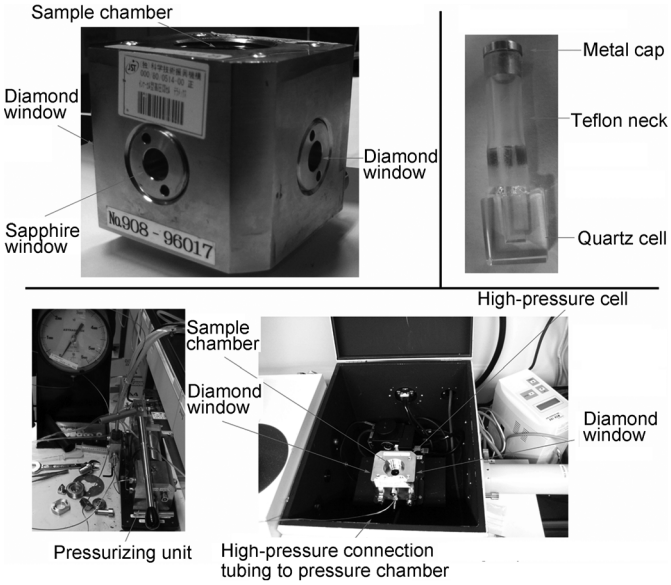

Figure 7. Custom designed high-pressure vessel for spectroscopic measurements and for photochemical reactions.

enables us to slow the racemization process and freeze the axial chirality, even at higher temperatures. This simple strategy of employing moderate pressures has enabled us to manipulate stereospecific photochemical transformations in solution, even at elevated temperatures. Thus, this strategy could be very useful for overcoming the racemization of atropisomeric photochromophores at a given temperature and for employing them in effective stereospecific photochemical transformations.

Conclusion

Our investigation provides a simple route for modulating the rate of racemization in non-biaryl chromophores by moderately increasing the pressure in the system. This strategy may be extended to the asymmetric transformations of other non-biaryl compounds at elevated temperatures with minimal racemization. Owing to the slow rate of racemization, the enantiospecific chiral transfer was effective at elevated pressure during the photoreactions. In addition, because non-biaryl atropisomers are potential ligands for asymmetric synthesis, either the slow racemization or frozen chiral configuration that are obtained at moderate pressures open up avenues to employ them in reactions that require high temperatures.

Experimental Section

High-pressure spectroscopic measurements, apparatus, setup, and data collection: All spectroscopic measurements under high pressure were performed in a custom-built high-pressure vessel (Figure 7, left). This vessel was fitted with three optical windows that were made of sapphire or diamond, with an effective aperture of 9 mm or 3 mm (i.d.), respectively. The apparatus was designed and manufactured by Teramecs Co. (Kyoto, Japan). The materials for the windows were sapphire for UV/Vis and fluorescence spectroscopy and birefringence-free diamond for CD spectroscopy. A quartz inner cell (Figure 7, right) with an inner dimension of 3 mm (W) × 2 mm (D) × 7 mm (H), which was connected to a short flexible Teflon tube for adjusting the volume change under pressure, was filled with a solution of the sample. The top end of the quartz cell was stoppered and the whole cell was placed inside the pressure vessel. The vessel was fixed inside the sample chamber of the spectrometer (Figure 7, bottom). The temperature inside the sample chamber was maintained by a temperature-control unit and the sample was maintained at a set hydrostatic pressure (0.1–100 MPa).

General procedure for the photoreactions of compounds 1a–1e under pressure: Compound **1** was dissolved in dry MeCN (**1a**: 11.5 mM, **1b**: 1.4 mM, **1c**: 11.5 mM, **1d**: 10 mM, **1e**: 5.7 mM) and the solution was transferred into a custom-designed quartz cell (Figure 7, top-right). Then, this cell was placed inside a high-pressure vessel that was equipped with a sapphire window. Irradiation was performed by using an optical fiber that contained a light source from a Xenon lamp with a 300(±10) nm band-pass filter (Asahi spectra, 302 Max power-supply unit).

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