Enantioselective [4+2]-Cycloaddition Reaction of a Photochemically Generated *o*-Quinodimethane: Mechanistic Details, Association Studies, and Pressure Effects

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Abstract: 1,2,3,4-Tetrahydro-2-oxoquinoline-5-aldehyde (**2**) was prepared from *m*-aminobenzoic acid and 3-ethoxyacryloyl chloride (**4**) in 19% overall yield. Compound **2** underwent a photochemically induced [4+2]-cycloaddition reaction with various dienophiles upon irradiation in toluene solution. The *exo* product **10a** was obtained with acrylonitrile (**9a**) as the dienophile, whereas methyl acrylate (**9b**) and dimethyl fumarate (**9c**) furnished the *endo* products **11b** and **11c** (69–77% yield). The reactions proceeded at −60 °C in the presence of the chiral complexing agent **1** (1.2 equiv) with excellent enantioselectivity (91–94% *ee*). The enantiomeric excess increases in the course of the photocycloaddition as a result of the lower product association to **1**. The intermediate (*E*)-dienol **8** was spectroscopically detected at −196 °C in an EPA (diethyl ether/isopentane/ethanol) glass matrix. The association of the substrate **2** to the complexing agent **1** was studied by circular dichroism (CD) titration. The measured association constant (K_A) was $589\,M^{-1}$ at room temperature (25 °C) and normal pressure (0.1 MPa). An increase in pressure led to an increased association. At 400 MPa the measured value of K_A was $703\,M^{-1}$. Despite the stronger association the enantioselectivity of the reaction decreased with increasing pressure. At 25 °C the enantiomeric excess for the enantioselective reaction **2** + **9a** → **10a** decreased from 68% *ee* at 0.1 MPa to 58% *ee* at 350 MPa. This surprising behavior is explained by different activation volumes for the diastereomeric transition states leading to **10a** and *ent*-**10a**.

Keywords: Diels–Alder reactions · enantioselectivity · high-pressure chemistry · hydrogen bonds · photochemistry

Introduction

A chemical reaction during which a prochiral substrate is converted into a chiral product proceeds enantioselectively if enantiotopic groups or enantiotopic faces of the substrate are sufficiently differentiated by a chiral entity. The degree of enantioselectivity is measured by the enantiomeric excess (*ee*) of the corresponding product. In conventional thermal reactions, the entity which delivers the chiral information has very often been the reagent or the catalyst. In photochemical reactions, the "reagent" light has—despite many attempts—never been successfully employed in a similar fashion. Results obtained with circularly polarized light (CPL) as a source of the chiral information have not reached significant *ee* values in preparatively useful reactions.[1] There are two alternative approaches towards enantioselective photochemical reactions. One approach is based on a chiral solid-state environment as the source of chirality.[2] Homochiral crystals,[3] ionic chiral auxiliary approach,[4] inclusion complexes,[5] and reactions in zeolites[6] are a few key concepts to describe this subject in brief. The limitation

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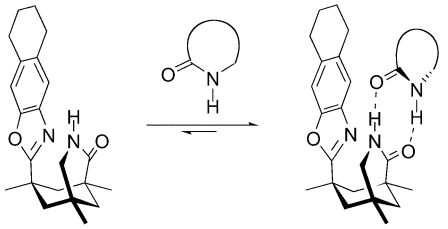
to intramolecular reactions is a major disadvantage associated with this approach. A major advantage is the fact that the choice of substrates is not restricted provided that chiral crystalline material can be obtained. The other approach is based on the use of chiral complexing agents (templates) in solution-phase photochemistry.[1a,7] By definition, chiral complexing agents interact with prochiral substrates by noncovalent interactions in a fast, reversible equilibrium. If the reaction in the template–substrate complex is enantioselective, a high equilibrium constant in favor of complex formation guarantees high enantioselectivity. Enantioselective catalysis is possible if the reaction proceeds faster in the complex than in the unbound substrate. The binding motif most commonly encountered in nature for noncovalent association is hydrogen bonding.[8] Following this precedence we have devised complexing agents which exhibit hydrogen-bond donor and hydrogen-bond acceptor sites.[9–11] The approach appeared particularly promising for enantiocontrol in photochemical reactions, since light does normally not interfere with hydrogen bonds. Our most successful complexing agent is lactam **1** (Scheme 1) and its enantiomer. The compounds are available in multigram quantities[12] and have been employed for several enantioselective photochemical reactions.[13]

Abstract in German: *1,2,3,4-Tetrahydro-2-oxochinolin-5-aldehyd (**2**) wurde ausgehend von* m-*Aminobenzoesäure und 3-Ethoxyacryloylchlorid (**4**) in fünf Schritten und einer Gesamtausbeute von 19 % hergestellt. Die Verbindung ließ sich in Toluol als Lösungsmittel mit verschiedenen Dienophilen in einer photochemisch induzierten [4+2]-Cycloaddition umsetzen (69–77 % Ausbeute), wobei als Hauptprodukt mit Acrylnitril (**9a**) das* exo-*Produkt **10a** entstand. Methylacrylat (**9b**) und Dimethylfumarat (**9c**) lieferten die* endo-*Produkte **11b** and **11c**. In Gegenwart des chiralen Komplexierungsreagenz' **1** (1.2 Äquiv.) verliefen die Reaktionen mit exzellenter Enantioselektivität (91–94 %* ee*). Der Enantiomerenüberschuß nahm im Verlauf der photochemischen Umsetzung zu, was man auf die relativ zum Substrat **2** niedrigere Assoziation des Produkts zurückführen kann. Das intermediär gebildete (*E*)-Dienol **8** wurde spektroskopisch in einer EPA (Ether/i-Pentan/Ethanol) Glasmatrix bei −196 °C nachgewiesen. Die Assoziation des Substrats **2** an das Komplexierungsreagenz **1** wurde durch CD-Titration genauer untersucht. Die Assoziationskonstante (K_A) wurde bei Zimmertemperatur (25 °C) und Normaldruck (0.1 MPa) zu 589 M^{-1} bestimmt. Bei höherem Druck beobachtete man eine verstärkte Assoziation und bei 400 MPa wurde eine Assoziationskonstante von $K_A = 703\ M^{-1}$ bestimmt. Trotz der stärkeren Assoziaion nahm die Enantioselektivität mit wachsendem Druck ab. Bei 25 °C sank der Enantiomerenüberschuß der enantioselektiven Reaktion **2** + **9a** → **10a** von 68 %* ee *bei 0.1 MPa auf 58 %* ee *bei 350 MPa. Dieses überraschende Verhalten läßt sich möglicherweise durch die unterschiedlichen Aktivierungsvolumina für die Übergangszustände erklären, die zu **10a** und* ent-**10a** *führen.*



Scheme 1. Association behavior of a lactam substrate in the presence of complexing agent **1**.

Despite the simple binding motif, the equilibrium constant (K_A) in favor of the complex (**1**·substrate) is sufficiently high to facilitate reactions which proceed in up to 95 % *ee* at −60 °C.[13c] Since the face differentiation is independent from the mode of attack, the complexing agent can be applied to inter- and intramolecular reactions. The study we describe in this account is concerned with a thermal [4+2]-cycloaddition reaction which is photochemically initiated. The results of the cycloaddition studies have been reported in preliminary form.[14] We now provide details on the preparation of the starting material, the structural elucidation of the products, on some mechanistic work, and on the pressure dependence of the reaction. The last of these aspects turned out to be particularly intriguing. We observed an enhanced association and a *decrease* of the enantioselectivity with *increasing* pressure.

Results and Discussion

Upon photochemical excitation, *o*-alkylated aromatic aldehydes of type **A** (Figure 1) undergo a hydrogen abstraction which leads to two diastereomeric dienols. The correspond-

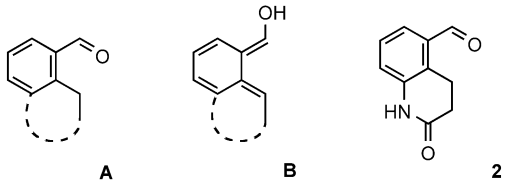
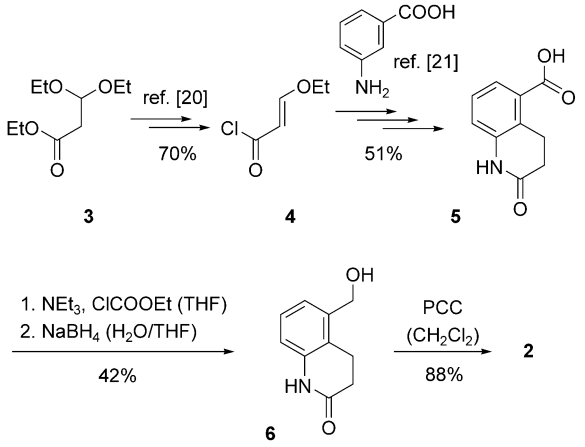


Figure 1. Structures of an *o*-substituted benzaldehyde **A**, the (*E*)-dienol **B** derived from **A**, and the aldehyde **2** used in this study.

ing *Z* dienol undergoes rapid tautomerization to the starting material, whereas (*E*)-dienol **B** lives long enough to be trapped by an alkene in a Diels–Alder reaction.[15,16] The reaction has proven to be useful for the construction of chiral tetralins and has been frequently applied in synthesis.[17,18]

Substrate **2** contains an *o*-alkylbenzaldehyde moiety required for the photochemically induced Diels–Alder reaction and a lactam binding site required for enantioselective differentiation by complexing agent **1**. It was therefore considered as a useful probe to assess the chances for an enantioselective [4+2] cycloaddition in solution.[19]

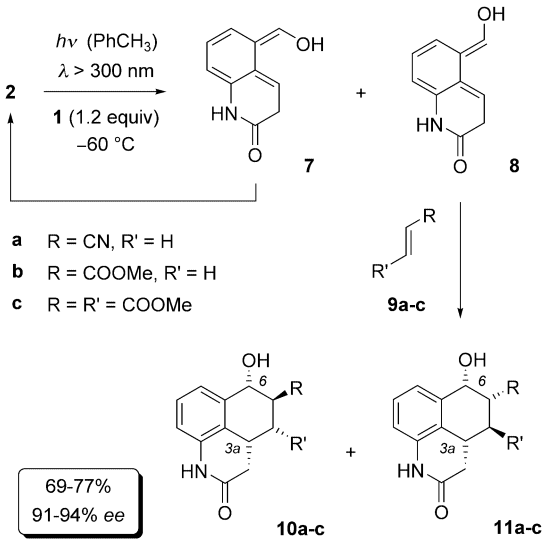
Preparation of the substrate: Commercially available ethyl 3,3-diethoxypropionate (**3**) was converted into 3-ethoxyacryloyl chloride (**4**) by a known two-step procedure (Scheme 2).[20] Acylation of *m*-aminobenzoic acid with chloride **4** led to an anilide (75% yield) which was cyclized under acidic conditions to an unsaturated quinolone (89% yield).[21] The previously reported hydrogenation of the quinolone[21] to dihydroquinolone **5** was conducted at 60°C under 2 MPa (20 bar) H_2 pressure with Pd/C as the catalyst (10 mol%). Under these conditions the hydrogenation proceeded in 75% yield. The activation of acid **5** towards a chemoselective reduction was achieved with ethoxy chloroformate and triethylamine in tetrahydrofuran (THF). After filtration the resulting solution was directly reduced with sodium borohydride. Although the yields achieved in the activation/reduction sequence were only moderate, we did not optimize the reaction any further. The alcohol was eventually oxidized to the desired aldehyde **2** with pyridinium chlorochromate (PCC). The overall yield of substrate **2** was reproducibly 13% in seven steps starting from ester **3**.



Scheme 2. Synthesis of substrate **2**.

Stereoselectivity: Irradiation experiments were conducted with a toluene solution of substrate **2** (ca. 1 mM) in the presence of an excess of the corresponding dienophile (50 equiv). Under these conditions, a complete conversion was achieved at room temperature within 5–10 min or at −60°C within 30 min. For acrylonitrile (**9a**, Scheme 3) as the dienophile, the ratio of product diastereoisomers was roughly 70:30 in favor of the *exo* product *rac*-**10a**, whereas methyl acrylate (**9b**) and dimethyl fumarate (**9c**) gave predominantly the *endo* products *rac*-**11b** and *rac*-**11c**. The yields were 60–80% in all reactions we conducted. The *exo*/*endo* selectivity was not significantly affected by the reaction temperature. A solvent change, however, led to a selectivity reversal in one example. Thus, irradiation of substrate **2** with acrylonitrile (**9a**) in acetonitrile gave preferentially the racemic *endo* product *rac*-**11a** [diastereoisomeric ratio (d.r.) = 92:8, 62% yield].

Cycloaddition reactions in the presence of the complexing agent were performed at 30°C, −35°C, or −60°C with 0.5,



Scheme 3. Enantioselective photoinduced [4+2] cycloaddition of (*E*)-dienol **8** with the dienophiles **9**.

1.2, or 2.5 equivalents of compound **1**. The other reaction conditions remained unchanged. Most of the results have been tabulated elsewhere[14] and will not be repeated in detail. The key issues are that excellent enantiofacial differentiation was achieved at −60°C with only 1.2 equivalents of the complexing agent **1** (91–94% *ee*), and that the selectivity increased further upon increasing the concentration of the complexing agent (up to 97% *ee*) and decreased upon raising the temperature.

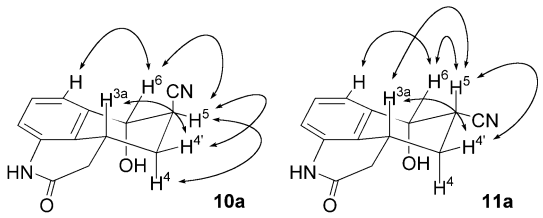
Typical figures which illustrate the correlation between enantiomeric excess and complexing agent concentration were obtained at −35°C: 35% *ee* in favor of **10a** with 0.5 equivalents of **1**, 76% *ee* with 1.2 equivalents, and 92% *ee* with 2.5 equivalents. Table 1 gives some insight into the complexation behavior by looking at the enantiomeric excess of product **10a** in the same reaction after different conversions. The enantiomeric excess increased with increasing conversion.

Table 1. Conversion and enantiomeric excess (*ee*) in the Diels–Alder reaction of compound **2** with dienophile **9a** at −35°C in toluene mediated by complexing agent **1** (1.2 equiv, cf. Scheme 3).

Conversion[a] [%]	8	27	80	100
ee (**10a**)[b] [%]	57	64	74	76

[a] The conversion was determined by GC analysis. [b] The *ee* values were determined by chiral GC analysis (after derivatisation with TMSCl/hexamethyldisilazane).

Proof of configuration and discussion: The relative configuration of the products could be determined by ^{1}H NMR spectroscopy and NOE measurements. The general procedure is exemplified for the two major products obtained from the reaction of substrate **2** with acrylonitrile (**9a**). Figure 2 gives the most prominent NMR data for the two diastereoisomers **10a** and **11a** obtained as [4+2]-cycloaddition products.



^3J(H-5, H-6)	= 2.5 Hz	^3J(H-5, H-6)	= 3.0 Hz
^3J(H-4, H-5)	= 3.4 Hz	^3J(H-4, H-5)	= 12.8 Hz
^3J(H-4', H-5)	= 3.4 Hz	^3J(H-4', H-5)	= 3.0 Hz
^3J(H-3a, H-4)	= 13.6 Hz	^3J(H-3a, H-4)	= 12.6 Hz

Figure 2. Prominent NOE data and relevant $^3J_{H,H}$ coupling constants observed for the *exo* and *endo* diastereoisomers **10a** and **11a**.

The ^3J coupling constants between the hydrogen atoms at C-4, C-5, and C-6 in compound **10a** provide evidence for the fact that these hydrogen atoms are axial/equatorial or equatorial/equatorial to each other. Hydrogen atom H-5 must consequently reside in an equatorial position. Hydrogen atom H-3a is positioned axially, as it has a typically large axial/axial coupling constant to one hydrogen atom at C-4. In product **11a**, the large coupling constant between H-4 and H-5 supports a conformation in which H-5 resides in an axial position. Based on the small ^3J value between H-5 and H-6, H-6 must be equatorial. The major difference in the NOE spectra of **10a** and **11a** concerns the proximity of hydrogen atoms H-3a and H-5. There is no NOE contact in the former case but a strong contact in the latter case. In addition, both hydrogen atoms at C-4 exhibit NOE contacts to hydrogen atom H-5 in compound **10a**, but only one hydrogen atom H-4′ interacts with H-5 in **11a**. Indeed, the crystal structure[22] of compound *rac*-**11a** (Figure 3) confirmed the assignment of the relative configuration and the conformational analysis derived from the NMR data. Hydrogen atoms H-5 and H-3a are in an axial position, whereas H-6 and the cyano group are equatorial.

The ^{1}H NMR and NOE data obtained for the major diastereoisomers of the photocycloaddition products derived from methyl acrylate (**9b**) and dimethyl fumarate (**9c**) were similar to the data of compound **11a**. Most significantly, the NOE contacts between the hydrogen atoms H-3a and H-5 were strong, and the ^{1}H NMR ^3J coupling constants for H-5/H-6 were low (3.4 Hz). The data support a conformation in which the hydrogen atom H-5 is axially positioned, and a configuration in which H-5 and H-6 are *cis* to each other. Further evidence for the relative configuration was again obtained by single-crystal X-ray crystallography (Figure 4).[23] In this case, *endo* diastereoisomer *rac*-**11c** could be crystallized.

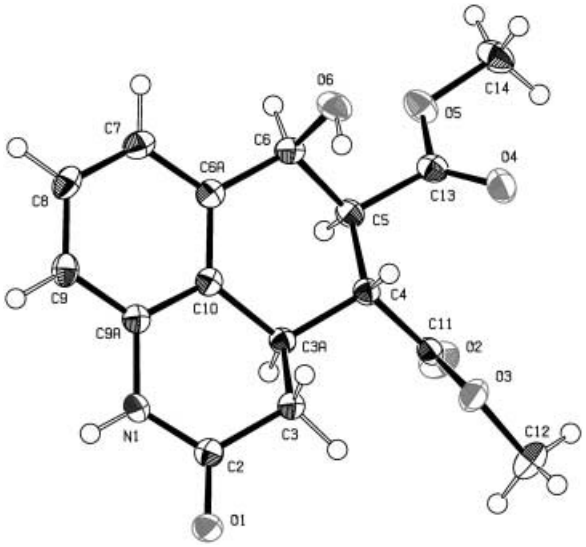


Figure 4. A molecule of compound *rac*-**11c** in the crystal structure.[23]

The elucidation of the absolute configuration has already been discussed in our preliminary paper.[14] It rests on an enantiomerically pure product whose configuration could be determined by anomalous X-ray diffraction, and on the comparison of measured and calculated circular dichroism (CD) spectra. The data are in line with a *Re*-face attack relative to the enol carbon atom which ends up as carbon atom C-6 in the product. As depicted in Figure 5, the absolute configuration at C-6 and C-3a can be nicely explained by an

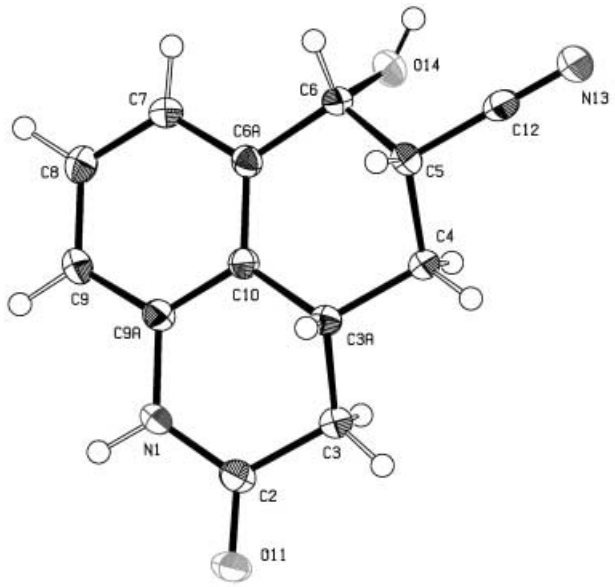


Figure 3. A molecule of compound *rac*-**11a** in the crystal structure.[22]

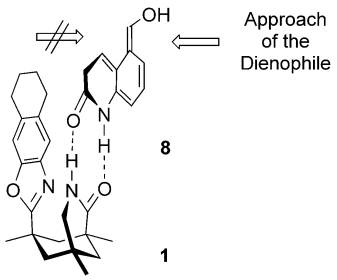


Figure 5. Model to explain the face differentiation in the binary complex **1·8** of template **1** and (*E*)-dienol **8**.

approach of the dienophile to the intermediate (*E*)-dienol **8** bound to complexing agent **1** from the less shielded face. There is evidence that the face differentiation provided by the tetrahydronaphthalene shield is close to perfect,[7,13c] and the enantiomeric ratio therefore corresponds to the ratio of bound to unbound substrate. In earlier work we have shown that an association constant of $500\,M^{-1}$ at room temperature can account for an almost complete complexation at −60 °C and consequently for almost complete selectivity in favor of one enantiomer.[13]

An additional benefit of the cycloaddition we have now studied is the result of the apparently lower association constant of the products **10** and **11** relative to **2** and **8**. Unfortunately, we could not access K_A for **10** or **11** by CD titration (vide infra) because the induced CD absorption was covered by the absorption band of the complexing agent. However, at low template concentration (*c*) the titration data for **10a** gave a semiquantitative picture. The flat binding isotherm *c*(**1**)/*c*(**10a**) was indicative of a weak complexation which in turn can be nicely explained by the steric bulk of the tetralin generated in the [4+2]-cycloaddition reaction. This observation is in agreement with the increase of the product *ee* with increasing conversion (Table 1). The lower association of the product **10a** liberates complexing agent **1**. The concentration of **1** relative to **2** increases leading to an increased association **1**·**2** and to a higher enantioselectivity.

The regioselectivity of the *o*-quinodimethane [4+2]-cycloaddition reactions is in line with previous results.[16,17] There is also precedence for the *endo* selectivity in the reaction of methyl acrylate and dimethyl fumarate with *o*-quinodimethanes.[17c,24] The unexpected *exo* selectivity observed with acrylonitrile in the nonpolar solvent toluene is in agreement with recent computational results by Freccero et al. which suggest an *exo* preference in the gas phase and in nonpolar solvents.[25,26] In polar solvents like acetonitrile, the *endo* product should prevail which it indeed did (vide supra).

Dienol intermediate: The relative product configuration at carbon atoms C-3a and C-6, as determined for compounds **11a**, **10c**, and **11c** by X-ray crystallography and for the other products by NMR spectroscopy, is in line with a stereospecific attack of the dienophile at the (*E*)-dienol **8** (Scheme 3). However, in mechanistic studies the postulated intermediate was initially not observed. The dienol absorption should occur with a bathochromic shift relative to the aldehyde absorption at 324 nm. The experiments were performed by irradiating a toluene solution of photosubstrate **2** in a temperate cuvette in the absence of the dienophile and by subsequent UV spectroscopic detection (<3 s after the irradiation was stopped). The expected dienol band at longer wavelength was not detected at room temperature, −50 °C, or −80 °C. It was speculated that the proton-catalyzed tautomerization **8**→**2** is accelerated by the Brønsted acidic lactam unit. To confirm this speculation, substrate **2** was irradiated in an EPA glass matrix (diethyl ether/isopentane/ethanol, 5:5:2 v/v, −196 °C) in which the intermolecular proton transfer is suppressed (Figure 6).

Indeed, a strong absorption at 422 nm was observed after 30 s, the intensity of which increased upon prolonged irradiation. The new band reached saturation after 440 s. Simultaneously, the aldehyde absorption at 324 nm lost intensity, and an isosbestic point was observed at 344 nm. The absorption wavelength recorded for the intermediate is in good agreement with the spectroscopic properties of other dienols which have been detected so far.[27]

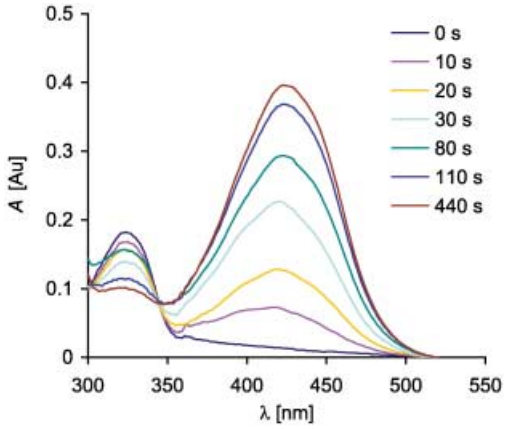


Figure 6. Detection of *E* dienol **8** upon irradiation of aldehyde **2** in an EPA glass matrix at −196 °C. The UV spectra were recorded after irradiating **2** for the indicated period of time.

Pressure dependence: Reactions which proceed via a transition state with a highly negative activation volume can be significantly accelerated by applying high pressure.[28] Many examples of this phenomenon have been reported for Diels–Alder reactions, in which the rate of reaction significantly increased at high pressure.[29] In addition, a shift in the diastereoselectivity[29,30] in favor of the product generated via the more compact transition state, often the *endo* diastereoisomer, has been observed. The enantioselectivity of a Lewis acid catalyzed hetero-Diels–Alder reaction was enhanced at high pressure.[31,32] The *endo*/*exo* diastereoselectivity was also noted to be pressure-dependent in photochemical [2+2]-cycloaddition[33] and photoinduced [4+2]-cycloaddition[34] reactions. In studies of sensitized enantiodifferentiating *E*/*Z* isomerizations, an influence of pressure on the efficiency and direction of the chiral induction has been reported.[35] The pressure dependence of the enantioselectivity is attributed to nonzero differential activation volumes ($\Delta\Delta V^{\neq}_{R-S}$) as described in the relationship (1) between pressure (*P*) and the relative rate of *R* and *S* product formation (k_R/k_S):

$$\ln(k_R/k_S) = \ln[(100 + \%\,ee)/(100 - \%\,ee)] = -(\Delta\Delta V^{\neq}_{R-S}/RT)P + C \quad (1)$$

It appeared interesting to study the pressure effect on the reaction **2**→**10**/**11** (Scheme 3). We had hoped for an increase of selectivity based on a higher association. Indeed, two important parameters of the reaction are altered by pressure. Changing pressure should influence the relative rate of the enantiomer formation as a consequence of different activation volumes as in the sensitized case. Furthermore, the

ground-state equilibrium is also affected by the applied pressure. By NMR titration experiments and microcalorimetric analyses, it was shown that the face differentiation in the complex with template **1** is almost perfect, whereas only at low temperature is the association constant (K_A) high enough to ensure the complexation of most substrate molecules.[13c] The direct relationship between the observed enantioselectivities and K_A renders this parameter the primary lever to increase the efficiency of the chiral induction by complexing agents such as **1**. Since hydrogen-bond-mediated association processes are typically accompanied by a volume decrease, the application of high pressures should lead to better association and concomitantly to higher enantiomeric excesses. We have therefore studied the effect of pressure on the enantioselectivity and diastereoselectivity of the intermolecular [4+2] cycloaddition of the photochemically generated intermediate (*E*)-dienol **8** (Scheme 3).

To quantify the pressure dependence of K_A, titration experiments were performed at high pressures. Addition of chiral template **1** induced a strong signal at 325 nm in the CD spectrum of a toluene solution of prochiral substrate **2**. The binding isotherm at normal pressure (0.1 MPa) was obtained by CD spectral titration with c(**1**):c(**2**) ratios in the range of 0.33–32 (Figure 7, see Experimental Section). From these data, K_A at 0.1 MPa was determined as 589 M^{-1} by nonlinear curve fitting. This value is in good accordance with the data obtained in NMR titration studies for the binding of 2-quinolone to host **1** ($K_A = 580\ M^{-1}$).

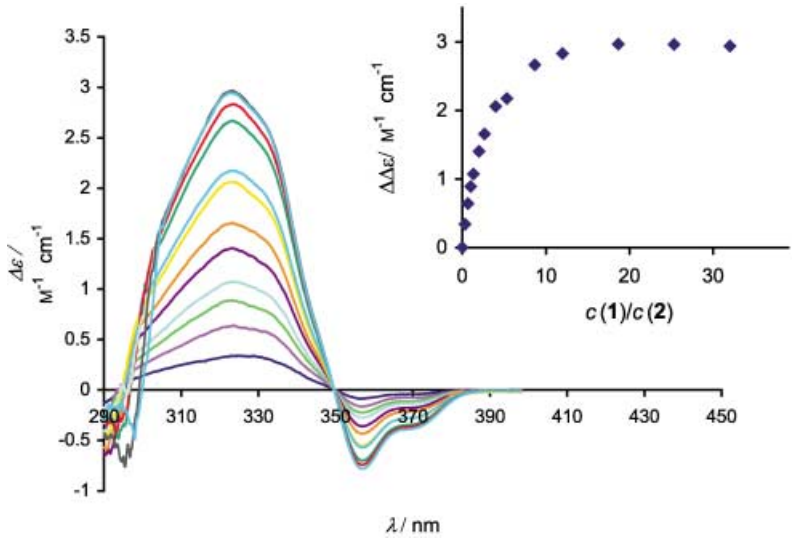


Figure 7. Circular dichroism spectra of substrate **2** induced by titration with template **1** in toluene at 0.1 MPa and 298 K, and the derived binding isotherm.

Analogous CD titrations of substrate **2** with template **1** were conducted at 100, 200, 300, and 400 MPa by using a 0.2-mL cuvette incorporated into a high-pressure vessel fitted with CD-inactive diamond windows. The association constants derived from the binding isotherms[36] by nonlinear curve fitting indeed increased at elevated pressures up to $K_A = 703\ M^{-1}$ at 400 MPa. By plotting $\ln K_A$ against P according to Equation (2), the reaction volume ΔV_A of the association between **1** and **2** was derived to be $-1.24\ cm^3\,mol^{-1}$ (Figure 8).

$$\ln K_A = -(\Delta V_A/RT)P + \ln K_{A,0} \quad (2)$$

Since two hydrogen bonds are involved in the complex formation, this ΔV_A value corresponds to a molar volume decrease of 0.6 $cm^3\,mol^{-1}$ per NH···O hydrogen bond. This is considerably lower than the values of -1.3 to $-4.6\ cm^3\,mol^{-1}$ volume change per NH···O hydrogen bond that have been reported in the literature.[37,38] The low volume decrease can be interpreted as an additional indication of an entropy-driven complex formation between **1** and **2**.[39] Another explanation draws on the close proximity of the two hydrogen bonds which leads to a ΔV_A value similar to that for one hydrogen bond.

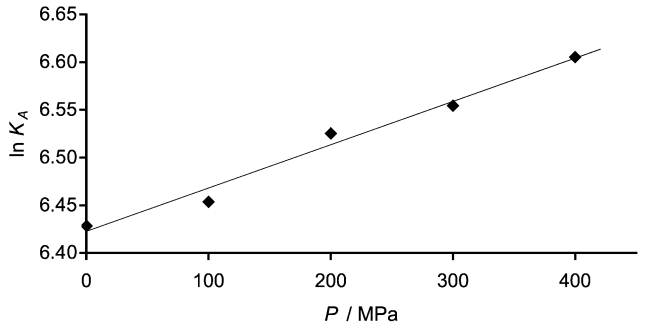


Figure 8. Determination of the volume decrease ΔV_A of the **1**·**2** complex formation from the pressure dependence of K_A.

To elucidate the effect of the enhanced binding on the efficacy of the asymmetric induction, the photoenolization-initiated Diels–Alder reaction of lactam **2** with acrylonitrile (**9a**) was examined at high pressures. In all instances, the products **10a** and **11a** were isolated as a mixture of diastereoisomers in comparable yields (60–65%). The determination of the enantiomeric excess with chiral GC required derivatization with trimethylsilyl chloride (TMSCl)/hexamethyldisilazane. The results are summarized in Table 2.

Unexpectedly, the enantioselectivity *decreased* significantly at higher pressures. With 1.2 equivalents of template **1**, the enantiomeric excess was reduced from 56% *ee* at 0.1 MPa to 50% *ee* at 200 MPa (Table 2, entries 2 and 5). This trend was confirmed by the series with 2.4 equivalents of the chiral complexing agent **1**. The *exo* diastereoisomer **10a** was obtained with 68% *ee* at 0.1 MPa, 62% *ee* at 200 MPa, and only 58% *ee* at 350 MPa (Table 2, entries 3, 6,

Table 2. Enantioselective Diels–Alder reaction of compound **2** with acrylonitrile (**9a**) (cf. Scheme 3) in the presence of the chiral complexing agent **1** at various pressures (see Experimental Section).

Entry	P[a] [MPa]	Equiv[b]	d.r. (**10a**/**11a**)[c]	*ee* (**10a**)[d] [%]	$c(\mathbf{1}\cdot\mathbf{2})/c_0(\mathbf{2})$ [%]
1	0.1	–	64/36	–	–
2	0.1	1.2	71/29	56	43
3	0.1	2.4	76/24	68	64
4	200	–	67/33	–	–
5	200	1.2	65/35	50	51
6	200	2.4	75/25	62	73
7	350	2.4	67/33	58	74

[a] Pressure applied during irradiation at 298 K with a 500-W ultrahigh-pressure Hg lamp (Wacom Co.) fitted with a UV-33 filter. [b] Equivalents of the chiral complexing agent **1**. [c] The diastereomeric ratio (d.r.) was determined by HPLC analysis of the crude product mixture. [d] The *ee*-values of the major diastereoisomer **10a** were determined by chiral GC (after derivatization with TMSCl/hexamethyldisilazane). Margin of error ±0.5%.

and 7). The enhanced complexation is evidently overcompensated by a controversial competing effect of the chiral template **1** on the relative rate of enantiomer formation. This can be illustrated by calculating the relative amount of complexed substrate $c(\mathbf{1}\cdot\mathbf{2})/c_0(\mathbf{2})$ from K_A for the employed pressures (Table 2, column 6). This value represents the enantiomeric excess at the beginning of the reaction in the ideal case of perfect face differentiation.[13c] The observation that the enantiomeric excesses at 0.1 MPa even exceeded this number is attributed to the weaker binding of the sterically demanding product to the chiral template. The amount of unbound host rises in the course of the reaction, and so does the *ee* value. This was experimentally proved by *ee* determination at different levels of conversion (vide infra). The increased K_A values at higher pressure translate to a relative amount of complexed substrate $c(\mathbf{1}\cdot\mathbf{2})/c_0(\mathbf{2})$ that is about 8% (200 MPa) or 10% (350 MPa) higher, giving an estimate for the expected *ee* increase.

In search for an explanation of the unprecedented pressure effect observed, we rely on our model for the face differentiation in this and related reactions (Figure 5). The decisive parameter is the differential activation volume $\Delta\Delta V^{\neq}_{R-S}$ as described by Equation (1). The attack from the shielded face, which leads to the *S* configuration at the carbinol carbon atom, is severely hampered by the tetrahydronaphthalene shield, and gives rise to a sterically congested situation. As a consequence, the activation volume $\Delta V^{\neq}_{S}$ is *lower* (more negative) than $\Delta V^{\neq}_{R}$. The more compact transition state to the minor *S* enantiomer becomes more favorable at higher pressures and the product *ee* decreases. Hence, at higher pressures the enhanced complexation is overridden by the reduced face differentiation of the chiral template, which is in turn caused by a high-pressure acceleration of the attack from the shielded face. This could be a general phenomenon for chiral templates that induce enantiomeric excesses by providing face differentiation in a noncovalent complex.

Conclusion

In summary, the enantioselective photochemically induced [4+2]-cycloaddition reaction of compound **2** and the dienophiles **9** in the presence of complexing agent **1** has provided us not only with a new method for the construction of chiral tetralins but it has also allowed us to gain new insight into important phenomena involved in template-based photochemistry. The temperature dependence of the enantiomeric excess is in line with previous work[13] and can be explained by an increased association at low temperature. The *ee* values obtained under optimized conditions (toluene, −60°C, 2.5 equiv of the complexing agent) are excellent (96–97% *ee*). Even with 1.2 equivalents of complexing agent **1**, an enantiomeric excess above 90% *ee* is possible at −60°C or alternatively with 2.5 equivalents of **1** at −35°C. These numbers surpass all previous *ee* values we have been able to obtain. The reason for the superiority of this photochemical reaction compared to previous systems is most likely not the higher association of **1·2**, but rather the fact that the products **10** or **11** of the reaction exhibit a much lower association to the template. The intermediate (*E*)-dienol **8** of the reaction could be spectroscopically detected in an EPA glass matrix. A study of the enantiomeric excess in the reaction **2** + **9a**→**10a** relative to external pressure revealed a surprising *ee* decrease with increasing pressure. Although the association constant increased—as expected—the determined *ee* decreased from 68% *ee* (25°C, 0.1 MPa) to 58% *ee* (25°C, 350 MPa). A possible reason for this behavior could be the lower (more negative) activation volume $\Delta V^{\neq}_{S}$ for the transition state leading to the minor enantiomer *ent*-**10a** compared to a higher $\Delta V^{\neq}_{R}$ for the major product.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Irradiation experiments were performed in Merck p. a. solvents (Uvasol). Common solvents (pentane (P), methanol (MeOH), ethanol (EtOH), ethyl acetate (EtOAc), tetrahydrofuran (THF), diethyl ether (Et_2O), CH_2Cl_2) were distilled prior to use. All other reagents and solvents were used as received. ^1H and ^{13}C NMR spectra were recorded at 303 K. Chemical sifts are reported relative to tetramethylsilane as an internal reference. Apparent multiplets which occur as a result of accidental equality of coupling constants to those of magnetically nonequivalent protons are marked as virtual (virt.). NOESY contacts are reported as weak (′), medium (″), or strong (‴). Thin-layer chromatography (TLC) was performed on aluminum sheets (0.2-mm silica gel $60F_{254}$) with detection by UV (254 nm) or by coloration with ceric ammonium molybdate (CAM). Flash chromatography[40] was performed on silica gel 60 (230–400 mesh; ca. 50 g for 1 g of material to be separated) with the indicated eluent.

1,2,3,4-Tetrahydro-2-oxoquinoline-5-carboxylic acid (5): 1,2-Dihydro-2-oxoquinoline-5-carboxylic acid (6.00 g, 31.7 mmol) was dissolved in aqueous NaOH (0.3 M, 150 mL). Pd on charcoal (10 mol% Pd, 3.38 g, 3.10 mmol Pd) was added. The mixture was stirred in a high-pressure vessel for 10 d at 60°C in an atmosphere of hydrogen (20 bar). After filtration, aqueous HCl (conc.) was added to the filtrate until no further precipitate was formed. The white precipitate was filtered, dried under reduced pressure, and recrystallized from MeOH (250 mL) to give tetrahydroquinoline **5** (4.54 g, 75%) as a colorless solid. M.p. 307°C (lit.[21]: 309–311°C); ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta = 2.40$ (t, $^3J = 7.7$ Hz,

2H; C^3H_2), 3.20 (t, ^3J=7.7 Hz, 2H; C^4H_2), 7.03 (d, ^3J=8.0 Hz, 1H; CH_{ar}), 7.21 (dd, ^3J=8.0 Hz, ^3J=7.2 Hz, 1H; C^7H), 7.41 (d, ^3J=7.2 Hz, 1H; CH_{ar}), 10.13 (s, 1H; NH), 12.54 ppm (s, 1H; OH); ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ=22.6 (CH_2), 29.9 (CH_2), 118.6 (CH_{ar}), 123.7 (CH_{ar}), 124.8 ($C_{q,ar}$), 126.9 (CH_{ar}), 130.5 ($C_{q,ar}$), 139.5 ($C_{q,ar}$), 168.5 (CO), 170.2 ppm (CO); IR (KBr): $\tilde{\nu}$=3420 (m, OH), 3200 (m, NH), 3070 (m, CH_{ar}), 2924 (s, CH_{al}), 1720 (vs, C=O), 1682 (vs, NHC=O), 1469 (s, CH_{al}), 1388 (vs), 1290 (s, C–N), 755 cm^{-1} (w, CH_{ar}); MS (70 eV, EI): *m*/*z* (%): 191 (100) [M^+], 163 (42) [M^+–CO], 146 (8) [M^+–COOH], 118 (10). The spectroscopic data were in accordance with reported data.[21]

(1,2,3,4-Tetrahydro-2-oxo-quinolin-5-yl)methanol (6): NEt_3 (1.50 mL, 1.09 g, 10.8 mmol) was added slowly to a suspension of acid **5** (1.91 g, 10.0 mmol) in THF (200 mL) under an atmosphere of argon. The mixture was cooled to 0 °C. Ethyl chloroformate (1.03 mL, 1.17 g, 10.8 mmol) was added dropwise, and the resulting mixture was stirred for 1 h at 0 °C. The mixture was then allowed to warm to room temperature and was stirred for 1 h. The precipitate was filtered, and the filtrate was slowly added to a solution of $NaBH_4$ (0.76 g, 0.20 mmol) in water (200 mL). The solution was stirred for 4 h, after which the THF was removed in vacuo. The residual aqueous solution was acidified to pH 2 with aqueous HCl (1 M) and extracted with CH_2Cl_2 (5×200 mL). The combined organic layers were dried over Na_2SO_4. After filtration the solvent was removed in vacuo to give alcohol **6** (0.80 g, 42%) as a colorless solid. R_f=0.29 (EtOAc/MeOH, 95:5); m.p. 164–165 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=2.60 (t, ^3J=7.6 Hz, 2H; C^3H_2), 3.04 (t, ^3J=7.6 Hz, 2H; C^4H_2), 4.66 (s, 2H; CH_2OH), 6.86 (d, ^3J=7.9 Hz, 1H; CH_{ar}), 7.10 (d, ^3J=7.4 Hz, 1H; CH_{ar}), 7.18 (dd, ^3J=7.9 Hz, ^3J=7.4 Hz, 1H; C^7H), 12.54 ppm (s, 1H; OH); ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ=22.5 (C^3H_2), 31.4 (C^4H_2), 63.4 (CH_2OH), 116.6 (CH_{ar}), 123.8 ($C_{q,ar}$), 124.5 (CH_{ar}), 128.5 (CH_{ar}), 139.4 ($C_{q,ar}$), 140.3 ($C_{q,ar}$), 173.1 ppm (CO); IR (KBr): $\tilde{\nu}$=3200 (m, NH), 2930 (w, CH_{al}), 1698 (vs, C=O), 1593 (s, C=C_{ar}), 1471 (s, CH_{ar}), 1221 (m, C–N), 1075 (m), 1030 cm^{-1} (m, C–O); MS (70 eV, EI): *m*/*z* (%): 177 (72) [M^+], 159 (80) [M^+–H_2O], 128 (60), 110 (100); HRMS: *m*/*z* calcd for $C_{10}H_{11}NO_2$: 177.07898; found: 177.07887.

1,2,3,4-Tetrahydro-2-oxo-quinoline-5-aldehyde (2): Alcohol **6** (0.30 g, 1.69 mmol) was dissolved in CH_2Cl_2 (300 mL) and treated with pyridinium chlorochromate (1.10 g, 5.08 mmol). The solution was stirred at room temperature for 8 h, and the solvent was removed in vacuo. The residue was directly subjected to flash chromatography (EtOAc/P, 9:1) to afford aldehyde **2** (0.26 mg, 88%) as a slightly yellow solid. R_f=0.40 (EtOAc); m.p. 200–201 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=2.60 (t, ^3J=7.6 Hz, 2H; C^3H_2), 3.04 (t, ^3J=7.6 Hz; 2H, C^4H_2), 4.66 (s, 2H; CH_2OH), 6.86 (d, ^3J=7.9 Hz, 1H; CH_{ar}), 7.10 (d, ^3J=7.4 Hz, 1H; CH_{ar}), 7.18 (dd, ^3J=7.9 Hz, ^3J=7.4 Hz, 1H; C^7H), 12.54 ppm (s, 1H; OH); ^{13}C NMR (90.6 MHz, [D$_6$]DMSO): δ=22.5 (C^3H_2), 31.4 (C^4H_2), 63.4 (CH_2OH), 116.6 (CH_{ar}), 123.8 ($c_{q,ar}$), 124.5 (CH_{ar}), 128.5 (CH_{ar}), 139.4 ($c_{q,ar}$), 140.3 ($c_{q,ar}$), 173.1 ppm (CO); IR (KBr): $\tilde{\nu}$=3145 (m, NH), 2746 (m, CHO), 1734 (s, C=O), 1681 (vs, NHC=O), 1468 (s, CH_{al}), 1388 (vs), 1378 (s), 1061 (m), 801 cm^{-1} (s, CH_{ar}); UV/Vis (MeOH): λ_{max} (ε)=326.6 nm (1764); MS (70 eV, EI): *m*/*z* (%): 175 (100) [M^+], 146 (28) [M^+–CHO], 119 (27), 118 (28), 110 (22); HRMS: *m*/*z* calcd for $C_{10}H_9NO_2$: 175.06332; found: 175.06336.

General irradiation procedure at normal pressure: A solution of aldehyde **2** and the chiral template **1**/*ent*-**1**[12] in toluene (Merck Uvasol, 150 mL) was added to a 200-mL irradiation vessel with a cooled lamp insert (duran glass) and then degassed by purging with argon for 20 min. In the case of a low-temperature irradiation the solution was cooled by an acetone/dry ice bath to the desired temperature. To maintain a temperature of −60 °C during the irradiation, the lamp insert was thermostated to −60 °C by an external cryostat. After the solution had equilibrated to the desired temperature, the dienophile was added whilst carefully maintaining the argon atmosphere. After stirring for 10 min the solution was irradiated (light source: Original Hanau TQ150, duran filter) to complete conversion (10 min at 30 °C, 20 min at −15 °C/−35 °C, 30 min at −60 °C; GLC control). The solution was allowed to warm to room temperature, and the solvent was removed in vacuo. The product mixture was separated by flash chromatography (EtOAc/MeOH, 97:3→95:5).

5-Cyano-6-hydroxy-3a,4,5,6-tetrahydro-1*H*,3*H*-1-azaphenalen-2-one (10a, *ent*-10a, 11, *ent*-11a): A solution of aldehyde **2** (50.0 mg, 0.29 mmol), template **1**/*ent*-**1** (2.4 equiv: 0.69 mmol, 241 mg; 1.2 equiv: 0.34 mmol, 121 mg; 0.5 equiv: 0.14 mmol, 50 mg), and freshly distilled acrylonitrile (**9a**, 14.3 mmol, 0.76 g, 0.94 mL) was irradiated as described in the general procedure. From the crude product mixture the diastereomeric ratio was determined by HPLC (YMC ODS-A, 250×4.6-mm i.d.; CH_3CN/H_2O, 5:95→30:70 in 30 min). After separation by flash chromatography, the *exo* and *endo* diastereoisomers **10a** and **11a**, and the template **1**/*ent*-**1** (>90%, i.e., 2.4 equiv: >217 mg; 1.2 equiv: >109 mg; 0.5 equiv: >45 mg) were isolated. The enantiomeric excess was determined upon TMS derivatization: 0.5 mg of each diastereoisomer was separately dissolved in acetone (1 mL) and treated with hexamethyldisilazane/TMSCl (2:1 v/v, 0.1 mL) and 3 drops of pyridine. After shaking for 10 min, the suspensions were filtered over silica gel and, after concentration to about 0.2 mL, these were analyzed by GC with a chiral stationary phase (2,3-di-*O*-methyl-6-*O*-TBDMS-β-cyclodextrin column, 200 °C→230 °C at 0.5 °C min^{-1}).

***exo* diastereomer 10a**: R_f=0.15 (EtOAc); m.p. 230–236 °C (decomp); $[\alpha]_D^{20}$=+21.9 (*c*=0.10, MeOH) [96% *ee*]; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ=2.00 (ddd, ^2J=12.0 Hz, ^3J=13.6 Hz, ^3J=3.5, 1H; C^4H), 2.13 (virt. dt, ^2J=12.0 Hz, $^3J\approx{}^3J$=4.1 Hz, 1H; C^4H), 2.29 (virt. t, $^2J\approx{}^3J$=15.8 Hz, 1H; C^3H), 2.52 (dd, ^2J=15.8 Hz, ^3J=4.9 Hz, 1H; C^3H), 3.16 (m, 1H; $C^{3a}H$), 3.26 (virt. q, $^3J\approx{}^3J\approx{}^3J$=3.4 Hz, 1H; C^5H), 4.90 (dd, ^3J=5.5 Hz, ^3J=2.5 Hz, 1H; C^6H), 5.07 (d, ^3J=5.5 Hz, 1H; OH), 6.81 (d, ^3J=7.9 Hz, 1H; C^9H), 7.03 (d, ^3J=7.5 Hz, 1H; C^7H), 7.17 (virt. t, ^3J=7.6 Hz, 1H; C^8H), 9.18 ppm (s, 1H; NH); NOESY experiment (500 MHz, [D$_6$]acetone): H (2.00)–H (3.26)′, H (2.13)–H (3.16)′, H (2.13)–H (3.26)″, H (2.29)–H (2.52)‴, H (2.29)–H (3.16)′, H (2.52)–H (3.16)′, H (3.26)–H (5.07)′, H (5.07)–H (7.03)′, H (6.81)–H (7.17)″, H (7.03)–H (7.17)″; ^{13}C NMR (90.6 MHz, [D$_6$]acetone): δ=26.2 (C^4H_2), 30.0 ($C^{3a}H$), 34.1 (C^5H), 37.6 (C^3H_2), 68.7 (CHOH), 116.8 (C^9H), 120.8 ($C_{q,ar}$), 123.8 (CN), 126.5 (C^7H), 129.5 (C^8H), 136.1 ($C_{q,ar}$), 138.8 ($C_{q,ar}$), 173.4 ppm (CO); IR (KBr): $\tilde{\nu}$=3198 (s, NH), 3020 (s, CH_{ar}), 2965 (m, CH_{al}), 2927 (m, CH_{al}), 2242 (m, C≡N), 1654 (vs, NHCO), 1589 (s, C=C_{ar}), 1474 (s, CH_{ar}), 1290 (m, C–N), 1100 (m, C–O), 1054 (m), 791 cm^{-1} (s, CH_{ar}); MS (70 eV, EI): *m*/*z* (%): 228 (70) [M^+], 175 (72) [M^+–CH_2CHCN], 151 (30), 128 (23), 100 (100); HRMS: *m*/*z* calcd for $C_{13}H_{12}N_2O_2$: 228.08987; found: 228.08998.

***endo* diastereomer 11a**: R_f=0.28 (EtOAc); m.p. 220–223 °C (decomp); $[\alpha]_D^{20}$=+39.3 (*c*=0.10, MeOH) [55% *ee*]; ^{1}H NMR (500 MHz, [D$_6$]acetone): δ=1.85 (virt. q, $^3J\approx{}^3J\approx{}^3J$=12.6 Hz, 1H; C^4H), 2.15 (m, 1H; C^4H), 2.26 (virt. t, $^2J\approx{}^3J$=16.1 Hz, 1H; C^3H), 2.52 (dd, ^2J=16.1 Hz, ^3J=5.2 Hz, 1H; C^3H), 2.98 (m, 1H; $C^{3a}H$), 3.18 (virt. dt, ^3J=12.8 Hz, $^3J\approx{}^3J$=3.0 Hz, 1H; C^5H), 4.92 (dd, ^3J=3.0 Hz, ^3J=6.4 Hz, 1H; C^6H), 5.03 (d, ^3J=6.4 Hz, 1H; OH), 6.76 (d, ^3J=7.9 Hz, 1H; C^9H), 6.99 (d, ^3J=7.5 Hz, 1H; C^7H), 7.12 (virt. t, $^3J\approx{}^3J$=7.7 Hz, 1H; C^8H), 9.11 ppm (s, 1H; NH); NOESY experiment (500 MHz, [D$_6$]acetone): H (2.15)–H (2.98)′, H (2.26)–H (2.52)″, H (2.26)–H (2.98)′, H (2.52)–H (2.98)′, H (2.98)–H (3.18)″, H (3.18)–H (5.03)″, H (5.03)–H (6.99)‴, H (6.76)–H (7.12)″, H (6.99)–H (7.12)″; ^{13}C NMR (90.6 MHz, [D$_6$]acetone): δ=28.3 (C^4H_2), 33.1 ($C^{3a}H$), 34.9 (C^5H), 39.0 (C^3H_2), 67.2 (CHOH), 116.8 (C^9H), 122.2 ($C_{q,ar}$), 123.9 (CN), 126.3 (C^7H), 129.6 (C^8H), 137.6 ($C_{q,ar}$), 139.0 ($C_{q,ar}$), 173.5 ppm (CO); IR (KBr): $\tilde{\nu}$=3202 (m, NH), 3101 (w, CH_{ar}), 2924 (m, CH_{al}), 2243 (m, C≡N), 1667 (vs, C=O), 1590 (s, C=C_{ar}), 1474 (s, CH_{al}), 1374 (s), 1099 (m, C–O), 979 (w), 796 (m, CH_{ar}), 745 (w), 696 cm^{-1} (m, CH_{ar}); MS (70 eV, EI): *m*/*z* (%): 228 (85) [M^+], 175 (100) [M^+–CH_2CHCN], 151 (43), 128 (39), 100 (68); HRMS: *m*/*z* calcd for $C_{13}H_{12}N_2O_2$: 228.08987; found: 228.09006.

5-Methoxycarbonyl-6-hydroxy-3a,4,5,6-tetrahydro-1*H*,3*H*-1-azaphenalen-2-one (11b, *ent*-11b): A solution of aldehyde **2** (50.0 mg, 0.29 mmol), template **1**/*ent*-**1** (2.4 equiv: 0.69 mmol, 241 mg; 1.2 equiv: 0.34 mmol, 121 mg), and freshly distilled acrylic acid methyl ester (**9b**, 14.3 mmol, 1.22 g, 1.29 mL) was irradiated as described in the general procedure. From the crude product mixture the diastereomeric ratio was determined by HPLC (YMC ODS-A, 250×4.6-mm i.d.; CH_3CN/H_2O, 5:95→30:70 in 30 min). After separation by flash chromatography, the *endo* diastereoisomer **11b** and the template **1**/*ent*-**1** (>90%, i.e., 2.4 equiv: >217 mg; 1.2 equiv: >109 mg) were isolated. The enantiomeric excess was determined upon TMS derivatization by chiral GC as described in the aforementioned procedure. R_f=0.22 (EtOAc/MeOH, 97:3); m.p. 218–220 °C (decomp); $[\alpha]_D^{20}$=+67.2 (*c*=0.61, MeOH) [97% *ee*]; ^{1}H NMR (360 MHz, CD_3OD): δ=1.65 (dd, ^2J=15.0 Hz, ^3J=13.2 Hz, 1H; C^4H), 1.99 (m, 1H; C^4H), 2.14 (virt. t, $^2J\approx{}^3J$=15.7 Hz, 1H; C^3H), 2.39 (dd, ^2J=15.7 Hz, ^3J=5.0 Hz, 1H; C^3H), 2.65 (virt. dt, ^3J=13.2 Hz, $^3J\approx{}^3J$=3.2 Hz, 1H;

C^5H), 2.79 (m, 1H; $C^{3a}H$), 4.52, (s, 1H; NH), 4.84 (d, $^3J=3.4$ Hz, 1H; C^6H), 6.62 (d, $^3J=7.8$ Hz, 1H; C^9H), 6.87 (d, $^3J=7.0$ Hz, 1H; C^7H), 7.00 ppm (virt.t, $^3J\approx{}^3J=7.4$ Hz, 1H; C^8H); NOESY experiment (500 MHz, [D$_6$]acetone): H (1.65)–H (1.99)‴, H (1.65)–H (2.14)′, H (1.99)–H (2.65)′, H (1.99)–H (2.79)′, H (2.14)–H (2.39)‴, H (2.39)–H (2.79)″, H (2.65)–H (2.79)″, H (2.65)–H (4.84)″, H (4.84)–H (6.87)″, H (6.62)–H (7.00)″, H (6.87)–H (7.00)″; ^{13}C NMR (90.6 MHz, CD_3OD): $\delta=$ 26.0 (C^4H_2), 33.1 ($C^{3a}H$), 33.1 (C^3H_2), 47.2 (C^5H), 52.6 (OCH_3), 68.7 (CHOH), 116.3 (C^9H), 124.8 ($C_{q,ar}$), 126.3 (C^7H), 129.2 (C^8H), 138.6 ($C_{q,ar}$), 138.7 ($C_{q,ar}$), 173.8 (CO), 175.1 ppm (CO); IR (KBr): $\tilde{\nu}=3204$ (w, NH), 3063 (w, CH_{ar}), 3008 (w, CH_{ar}), 2952 (m, CH_{al}), 1711 (vs, C=O), 1674 (vs, NHC=O), 1592 (s, C=C$_{ar}$), 1472 (s, CH_{ar}), 1443 (s), 1072 (m), 943 (w), 767 (m, CH_{ar}), 732 (m), 691 cm^{-1} (w, CH_{ar}); MS (70 eV, EI): *m*/*z* (%): 261 (95) [M^+], 229 (22), 184 (100), 175 (32), 151 (22), 128 (15); HRMS: *m*/*z* calcd for $C_{14}H_{15}NO_4$: 261.10010; found: 261.09998.

4,5-Di(methoxycarbonyl)-6-hydroxy-3a,4,5,6-tetrahydro-1*H*,3*H*-1-aza-phenalen-2-one (10c, *ent*-10c, 11c, *ent*-11c): A solution of aldehyde **2** (50.0 mg, 0.29 mmol), template **1**/*ent*-**1** (2.4 equiv: 0.69 mmol, 241 mg; 1.2 equiv: 0.34 mmol, 121 mg), and dimethyl fumarate (**9c**, 14.5 mmol, 2.09 g) was irradiated as described in the general procedure. From the crude product mixture the diastereomeric ratio was determined by HPLC (YMC ODS-A, 250×4.6-mm i.d.; CH_3CN/H_2O, 5:95→50:50 in 30 min). After separation by flash chromatography, the *exo* and *endo* diastereoisomers **10c** and **11c**, and the template **1**/*ent*-**1** (>90%, i.e., 2.4 equiv: >217 mg; 1.2 equiv: >109 mg) were isolated. The enantiomeric excess was determined by ^{1}H NMR spectroscopy with template **1** as chiral shift reagent: 2–5 mg of each diastereoisomer was dissolved separately with 2 equiv of **1** in [D$_6$]acetone. The NH signal split into two signals ($\delta_{NH,\mathbf{11c}}=9.58$, $\delta_{NH,ent\text{-}\mathbf{11c}}=9.93$, $\delta_{NH,\mathbf{10c}}=9.41$, $\delta_{NH,ent\text{-}\mathbf{10c}}=9.69$ ppm), the integral ratio of which corresponds to the enantiomeric ratio.

***endo* diastereomer 11c**: $R_f=0.17$ (EtOAc/MeOH, 97:3); m.p. 209–215°C (decomp); $[\alpha]_D^{20}=+93.6$ (*c*=0.55, MeOH) [96% *ee*]; ^{1}H NMR (360 MHz, CD_3OD): $\delta=2.46$ (dd, $^2J=16.0$ Hz, $^3J=14.2$ Hz, 1H; C^3H), 2.57 (dd, $^2J=16.0$ Hz, $^3J=5.0$ Hz, 1H; C^3H), 3.03–3.09 (m, 2H; $C^{3a}H$, C^4H), 3.22 (dd, $^3J=11.8$ Hz, $^3J=3.4$ Hz, 1H; C^5H), 3.34 (s, 1H; NH), 3.75 (s, 3H; OCH_3), 3.77 (s, 3H; OCH_3), 5.07 (d, $^3J=3.4$ Hz, 1H; C^6H), 6.86 (d, $^3J=7.9$ Hz, 1H; C^9H), 7.08 (d, $^3J=7.5$ Hz, 1H; C^7H), 7.24 ppm (virt.t, $^3J\approx{}^3J=7.7$ Hz, 1H; C^8H); NOESY experiment (500 MHz, [D$_6$]acetone): H (2.46)–H (2.57)‴, H (2.46)–H (3.03–3.09)″, H (2.57)–H (3.03–3.09)″, H (3.03–3.09)–H (3.22)″, H (3.22)–H (5.07)″, H (5.07)–H (7.08)″, H (6.86)–H (7.24)″, H (7.08)–H (7.24)″; ^{13}C NMR (90.6 MHz, CD_3OD): $\delta=34.6$ (C^3H_2), 34.7 ($C^{3a}H$), 41.8 (C^4H), 48.5 (C^5H), 50.8 (OCH_3), 50.9 (OCH_3), 66.6 (CHOH), 114.7 (C^9H), 120.4 ($C_{q,ar}$), 124.0 (C^7H), 127.7 (C^8H), 135.9 ($C_{q,ar}$), 136.6 ($C_{q,ar}$), 170.7 (CO), 172.0 (CO), 174.5 ppm (CO); IR (KBr): $\tilde{\nu}=3241$ (w, NH), 2961 (m, CH_{al}), 1734 (vs, C=O), 1672 (vs, NHCO), 1595 (m, C=C$_{ar}$), 1470 (m, CH_{ar}), 1440 (w, CH_{ar}), 1361 (s), 1251 (w, C–N), 1210 (m, C–O), 1163 (s), 798 (w, CH_{ar}), 766 cm^{-1} (w); MS (70 eV, EI): *m*/*z* (%): 319 (45) [M^+], 301 (24) [M^+-H_2O], 269 (22) [$M^+-CH_3OH-H_2O$], 241 (100), 228 (20), 210 (38), 183 (28), 163 (21); HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_6$: 319.10559; found: 319.10573.

***exo* diastereomer 10c**: $R_f=0.30$ (EtOAc/MeOH, 97:3); m.p. 215–220°C (decomp); $[\alpha]_D^{20}=+24.8$ (*c*=0.10, MeOH) [84% *ee*]; ^{1}H NMR (360 MHz, CD_3OD): $\delta=2.31$ (dd, $^2J=15.8$ Hz, $^3J=4.8$ Hz, 1H; C^3H), 2.73 (dd, $^2J=15.8$ Hz, $^3J=14.8$ Hz, 1H; C^3H), 3.09 (dd, $^3J=8.2$ Hz, $^3J=7.0$ Hz, 1H; C^5H), 3.43 (ddd, $^3J=14.8$ Hz, $^3J=7.5$ Hz, $^3J=4.8$ Hz, 1H; $C^{3a}H$), 3.49 (dd, $^3J=8.2$ Hz, $^3J=7.5$ Hz, 1H; C^4H), 3.70 (s, 3H; OCH_3), 3.72 (s, 3H; OCH_3), 4.88 (d, $^3J=7.0$ Hz, 1H; C^6H), 5.48 (s, 1H; NH), 6.82 (virt.t, $^3J\approx{}^3J=4.5$ Hz, 1H; C^8H), 7.20–7.22 ppm (m, 2H, C^7H; C^9H); NOESY experiment (500 MHz, [D$_6$]acetone): H (2.31)–H (2.73)‴, H (3.09)–H (3.49)′, H (3.09)–H (4.88)′, H (4.88)–H (7.20–7.22)″, H (6.82)–H (7.20–7.22)″; ^{13}C NMR (90.6 MHz, CD_3OD): $\delta=29.6$ ($C^{3a}H$), 33.0 (C^3H_2), 41.5 (C^4H), 48.0 (C^5H), 50.4 (OCH_3), 50.7 (OCH_3), 68.0 (CHOH), 113.8 (C^7H), 120.1 ($C_{q,ar}$), 121.0 (C^9H), 126.7 (C^8H), 136.3 ($C_{q,ar}$), 137.7 ($C_{q,ar}$), 171.4 (CO), 171.8 (CO), 172.8 ppm (CO); IR (KBr): $\tilde{\nu}=3358$ (m, NH), 2954 (m, CH_{al}), 1732 (vs, C=O), 1708 (vs, C=O), 1673 (vs, NHCO), 1591 (s, C=C$_{ar}$), 1227 (s, C–N), 1213 (s, C–O), 788 (w, CH_{ar}), 743 cm^{-1} (w); MS (70 eV, EI): *m*/*z* (%): 319 (32) [M^+], 301 (28) [M^+-H_2O], 287 (28) [M^+-CH_3OH], 269 (22) [$M^+-CH_3OH-H_2O$], 241 (100), 228 (10), 210 (58), 183 (40); HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_6$: 319.1055; found: 319.10511.

Detection of the intermediate dienol in the EPA glass matrix: A solution of aldehyde **2** (0.1 mM, 50.0 mL, 0.9 mg, 5 μmol) in Et_2O/isopentane/ethanol (5:5:2 v/v) was degassed by purging with argon for 10 min and then transferred to fill a quartz cuvette (1 cm×1 cm×3 cm) fitted with a 25-cm glass tube. The cuvette was slowly immersed into a quartz glass Dewar with a square bottom filled with liquid nitrogen. Inside the Dewar, the cuvette was irradiated for 10, 20, 30, 80, 110, 440 s with a Hg high-pressure lamp (Pyrex filter), and a UV spectrum was directly recorded. After 20 s of irradiation the cuvette contents turned yellow. As expected, the colour disappeared when the matrix was allowed to warm.

General irradiation procedure at high pressure: A solution of aldehyde **2** (2.0 mM, 0.7 mg, 4.0 μmol), acrylonitrile (80 mM, 10.5 μL, 8.5 mg, 0.16 mmol), and complexing agent **1** (2.4 equiv: 4.8 mM, 9.6 μmol, 3.4 mg; 1.2 equiv: 2.4 mM, 4.8 μmol, 1.7 mg) in toluene was degassed by purging with argon for 10 min. A 2-mL portion of the solution was transferred into a 2-mL quartz cuvette incorporated into a high-pressure vessel fitted with a sapphire window for UV irradiation (Teramecs Co., Kyoto) and thermostated at 298 K by water circulating through the reactor body. The vessel was pressurized up to 350 MPa (which is the maximum pressure to be applied when using the 2-mL cuvette), and the solution was irradiated for 60 min through a UV-33 filter with a 500-W ultrahigh-pressure Hg lamp (Wacom Co., Tokyo), which led to complete conversion. The solution was retrieved from the vessel, and the solvent was removed in vacuo. From the crude mixture, the d.r. (**10a**:**11a**) was determined by reversed-phase HPLC. The residue was dissolved in MeOH (0.5 mL) and separated by preparative TLC (CH_2Cl_2/MeOH, 92:8). The product was isolated as a mixture of diastereoisomers **10a** and **11a** with a combined yield of 60–65%. The enantiomeric excess (error $<\pm0.5$% *ee*) was determined after TMS derivatization by gas chromatography on a Supelco β-DEX 325 column (0.2 mm ∅×20 m) using a Shimadzu GC-14AM instrument equipped with a C-R6A integrator.

Pressure dependence of the association constant

CD titration at normal pressure: A solution of template **1** (200 mM, 35.2 mg in 0.5 mL toluene) was added stepwise (5, 5, 5, 5, 10, 10, 20, 20, 50, 50, 100, 100, 100 μL) to 3 mL of a solution of aldehyde **2** (1 mM, 4.4 mg in 25 mL toluene) to prepare solutions with *c*(**1**):*c*(**2**) ratios of 0.333, 0.667, 1.000, 1.333, 2.000, 2.667, 4.000, 5.333, 8.667, 12.000, 18.667, 25.333, 32.000. After each addition the mixture was transferred into a quartz cuvette (light path 1 cm), and a CD spectrum (Jasco J-720W spectropolarimeter, bandwidth 5.0 nm, response time 4 s, 20 nm min^{-1}, 4–8 accumulations) was recorded at 298 K. Each spectrum was corrected for the CD spectrum of pure **2** by subtraction. The difference spectra were transformed from the induced molar ellipticity $\Delta\theta$ into the induced molar circular dichroic absorption $\Delta\Delta\varepsilon$ ($d=1$ cm, $c=0.001$ mol L^{-1}, i.e., the volume change resulting from the addition of the template was neglected). The maximum circular dichroic absorption $\Delta\Delta\varepsilon$ of the band at 326 nm was plotted against the template–substrate ratio *c*(**1**):*c*(**2**). From this curve the association constant (K_A) of 589 M^{-1} was determined by nonlinear curve regression.

Determination of the pressure-induced volume reduction of toluene: A 0.15-mL high-pressure quartz cuvette (light path 0.2 cm) filled with a solution of naphthalene (2.6 mg, 0.02 mmol) in toluene (20 mL) was incorporated into a high-pressure vessel fitted with sapphire windows for UV measurement (Teramecs Co., Kyoto) and thermostated at 298 K by water circulating through the reactor body. The vessel was pressurized to 100 MPa, 200 MPa, 300 MPa, and 400 MPa. At each pressure a UV spectrum was recorded (V-550 spectrometer, 280–340 nm, slit width 1 nm). Analogous measurements were done with pure toluene. These spectra were subtracted from the spectra of the naphthalene/toluene solution at the corresponding pressure. The pressure-induced volume reduction was determined at the absorption maximum of 290–295 nm [$V/V^-{}_{0.1\text{ MPa}}=$ 0.9038 (100 MPa), 0.8597 (200 MPa), 0.8247 (300 MPa), 0.8044 (400 MPa)].

CD titrations at high pressures: Analogous titrations were performed by employing a 0.15-mL high-pressure quartz cuvette (light path 0.2 cm) incorporated into a high-pressure vessel fitted with diamond windows for CD measurements (Teramecs Co., Kyoto) and thermostated at 298 K by water circulating through the reactor body. The vessel was pressurized to 100 MPa, 200 MPa, 300 MPa, and 400 MPa. Each spectrum was corrected for the CD spectrum of pure **2** at the corresponding pressure by subtraction. The difference spectra were transformed from the induced molar ellipticity $\Delta\theta$ into the induced molar circular dichroic absorption $\Delta\Delta\varepsilon$ ($d=$

0.2 cm). The concentration was corrected for the pressure-induced volume reduction (vide supra). The volume change resulting from the addition of the template was neglected. For each pressure the maximum circular dichroic absorption $\Delta\Delta\varepsilon$ of the band at 326 nm was plotted against the template–substrate ratio c(**1**):c(**2**). From this curve the association constants $K_A(P)$ were determined by nonlinear curve regression to be $K_A(100\text{ MPa}) = 604\text{ M}^{-1}$, $K_A(200\text{ MPa}) = 649\text{ M}^{-1}$, $K_A(300\text{ MPa}) = 668\text{ M}^{-1}$, and $K_A(400\text{ MPa}) = 703\text{ M}^{-1}$.

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[23] X-ray data for compound *rac*-**11c**: $C_{16}H_{17}NO_6 \cdot H_2O$, $M_r = 337.32$, crystal size $0.23 \times 0.33 \times 0.43$ mm, monoclinic, space group $P2_1/n$ (No. 14), $a = 6.9796(1)$, $b = 9.8708(1)$, $c = 22.2769(2)$ Å, $\beta =$

91.5307(3)°, $V=1534.20(3)$ Å^3, $Z=4$, $\rho_{calcd}=1.460$ g cm^{-3}, $F_{000}=712$, $\mu=0.115$ mm^{-1}, Nonius κ-CCD diffractometer, rotating anode, $\lambda=0.71073$ Å, $T=173$ K, $\Theta_{max}=25.36°$, 31668 integrated ($h:\pm8$, $k:\pm11$, $l:\pm26$), 2816 independent and 2613 observed reflections [$I_o>2\sigma(I_o)$], 2816 reflections used for refinement, 293 parameters, $R1=0.0301$ (obs. data), $wR2=0.0783$ (all data), residual electron density 0.21/−0.21 e Å^{-3}, direct methods, hydrogen atoms refined. Strong hydrogen bonds build up a three-dimensional network between the interstitial water and the target molecules.[22b]

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