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# Enantioselective Photochemical Reactions of 2-Pyridones in Solution

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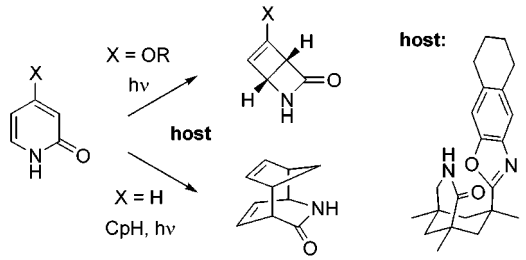
## ABSTRACT




**Two key photochemical reactions of prochiral 2-pyridones were studied in the presence of a chiral host. The [4 + 4]-photocycloaddition with cyclopentadiene (CpH) proceeded smoothly and with high enantioselectivity (84–87% ee). The absolute configuration of the *endo*-diastereoisomer was established by X-ray crystallography. The electrocyclic [4π]-ring closure to 3-oxo-2-azabicyclo[2.2.0]-5-hexenes occurred with lower enantioselectivity (20–23% ee at −20 °C). The velocity of the latter reaction slowed significantly with decreasing temperature.**

The intramolecular electrocyclic [4π]-ring closure to 3-oxo-2-azabicyclo[2.2.0]-5-hexenes[1,2] and the [4 + 4]-photocycloaddition to dienes[3,4] represent two key photochemical reactions of 2-pyridones (pyridin-2(1*H*)-ones).[5] In both reactions complex structures with at least two new stereogenic centers are formed from the prochiral heterocyclic substrate. We could recently show that [2 + 2]-photocycloaddition reactions of quinolones proceed in the presence of chiral lactams as host compounds with high enantioselectivity.[6] The hosts bind to the substrate via two hydrogen bonds[7,8] and provide the steric bias to shield one of the stereoheterotopic faces efficiently.[9] In a similar fashion 2-pyridones should be capable of hydrogen binding to these hosts.[8] We have consequently studied the photochemical reactions of the substrates **1** in the presence of the chiral host **2** more closely (Figure 1). Our preliminary results, which

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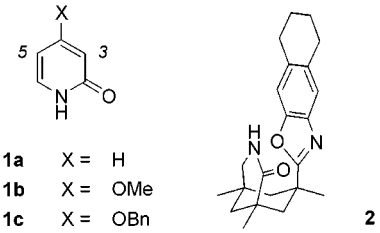
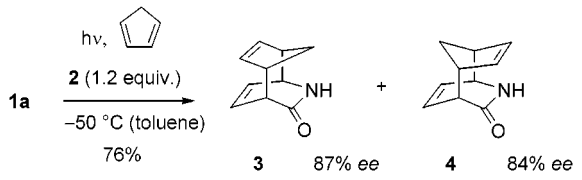



**Figure 1.** The structures of the 2-pyridones **1** employed for the photochemical reactions and the structure of the chiral host **2**.

we report in this communication, include the first enantioselective electrocyclic [4$\pi$]-ring closure reaction in solution[10,11] and the first enantioselective intermolecular [4 + 4]-photocycloaddition. The latter reaction proceeded with excellent face differentiation (84−87% ee).

The [4 + 4]-photocycloaddition of the parent compound **1a** and cyclopentadiene leads to a 3:2 mixture of the *exo*- and *endo*-products.[3] Upon irradiation of 2-pyridone **1a** in the presence of host **2** and cyclopentadiene we obtained the two diastereoisomers **3** and **4**, which could be separated by flash chromatography (Scheme 1).[12] The enantiomeric excess

**Scheme 1**




(ee) of the *endo*-product **3** was obtained from $^1$H NMR shift experiments, and the ee of the *exo*-product **4** was determined by chiral HPLC (column, chiralpak AD; eluent, heptane/2-propanol 95/5).[13] Both ee values were high.

(10) Enantioselective [4$\pi$]-cyclization of 2-pyridones in the solid state: (a) Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 4299−4302. (b) Wu, L.-C.; Cheer, C. J.; Olovsson, G.; Scheffer, J. R.; Trotter, J.; Wang, S.-L.; Liao, F.-L. *Tetrahedron Lett.* **1997**, *38*, 3135−3138.

(11) Auxiliary-induced facial diastereoselectivity in the [4$\pi$]-cyclization of 2-pyridones: Sato, M.; Katagiri, N.; Muto, M.; Haneda, T.; Kaneko, C. *Tetrahedron Lett.* **1986**, *27*, 6091−6094.

(12) **Representative Procedure.** A solution of the substrate **1** (0.53 mmol, 50.0 mg), freshly distilled cyclopentadiene (10.5 mmol, 694 mg), and the chiral host **2** (0.62 mmol, 218 mg) in 40 mL of toluene was irradiated in a liquid-cooled merry-go-round apparatus at −50 °C (irradiation source, Orginal Hanau TQ 150, Duran filter) until the reaction was complete according to TLC (20 h). After evaporation of the solvent the residue was purified by flash chromatography (eluent, pentane/*tert*-butyl methyl ether 50/50 → 15/85). The host **2** was recovered (200 mg, 0.57 mmol, 92%) and the products **3** ($R_f$ = 0.27, EtOAc; 30 mg, 35%) and **4** ($R_f$ = 0.18, EtOAc; 35 mg, 41%) were separated. The enantiomeric excess was subsequently determined by chiral HPLC or by $^1$H NMR shift reagent experiments (see narrative). The [4$\pi$]-photocyclization reactions were conducted in an analogous fashion, but they were run at a lower pyridone concentration (5 mmol/L) to avoid photodimerization. The compounds **3**, **4**, and **6** are known, and their analytical data have been reported (**3**, ref 3; **4**, ref 3; **6a**, ref 1c,d; **6b**, ref 15; **6c**, ref 2b).

(13) We thank Dipl.-Chem. Oliver Simic and Prof. Dr. Carsten Bolm (RWTH Aachen) for their help with the HPLC analyses.

To elucidate the absolute configuration of compound **3**, its *N*-acylation with chiral enantiomerically pure acid chlorides was attempted. The *N*-menthyloxycarbonyl lactam **5**, which was obtained from the reaction of substrate **3** with (−)-menthyl chloroformate (*n*-BuLi, THF, −78 °C, 73%), was crystalline, and an unambiguous proof of the structure was eventually possible with the aid of single-crystal X-ray crystallography (Figure 2).[14]

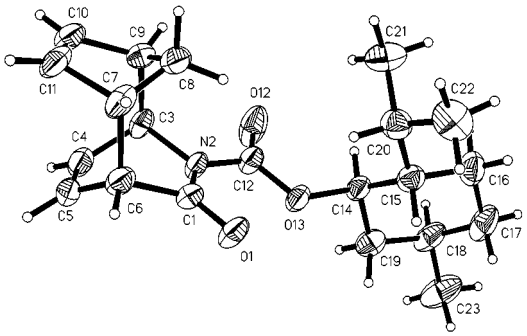
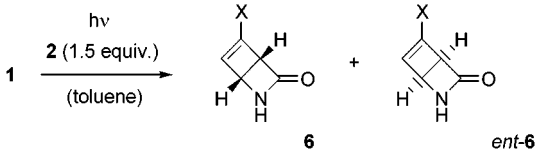



**Figure 2.** The structure of compound **5** in the crystal.

According to Figure 2 the photoexcited 2-pyridone was attacked by cyclopentadiene from the *Si*-face relative to the prostereogenic carbon atom C-3 (Figure 1). Upon association to the host **2** the *Si*-face represents consequently the accessible front of the substrate. The back of the 2-pyridone **1a** is shielded by the tetrahydronaphthalene unit of the host. Indeed, structure **5** is the first direct proof that intermolecular photocycloaddition reactions follow this selection principle. The absolute configuration of compound **4** was assigned in analogy to this result.

The intramolecular [4$\pi$]-cyclization of the unsubstituted 2-pyridone **1a** is known to proceed with low yields (15−21%).[1c,d] We additionally employed for this study the 4-substituted pyridones **1b**[15] and **1c**[16] (Figure 1), which cyclize more readily.[2] Nonetheless, it was found experimentally that the velocity of their reaction significantly decreases with decreasing temperature. The cyclization experiments were conducted with compounds **1** in the presence of host **2** employing toluene as the solvent (Scheme 2).

**Scheme 2**




Since low temperatures are required for a high association of pyridones **1** with compound **2** the potential of the host

(14) Data for **5**: colorless crystals; orthorhombic, $P2_12_12_1$, $a$ = 726.2-(1) pm, $b$ = 854.1(1) pm, $c$ = 3046.8(1) pm; $Z$ = 4; $R$ = 3.4%; GOF = 1.046.

could not be fully exploited. The best enantioselectivity was observed with substrate **1c** at −20 °C (entry 5, Table 1).

**Table 1.** Electrocyclic [4$\pi$]-Ring Closure of Pyridones **1** in the Presence of the Chiral Lactam **2** (cf. Scheme 2)

| entry | pyridone | X | time[a] (h) | temp[b] (°C) | product | yield (%) | ee[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | H | 4 | 30 | **6a** | 18 | 10 |
| 2 | **1b** | OMe | 2.5 | 30 | **6b** | 75 | 17 |
| 3 | **1b** | OMe | 96 | −20 | **6b** | 44 | 20 |
| 4 | **1c** | OBn | 3.5 | 30 | **6c** | 75 | 19 |
| 5 | **1c** | OBn | 96 | −20 | **6c** | 51 | 23 |

[a] Time after which the irradiation was stopped. [b] Irradiation temperature. Irradiation source: Original Hanau TQ 150. [c] The ee values {ee = [(+)-**6** − (−)-*ent*-**6**]/[(+)-**6** + (−)-*ent*-**6**]} were determined by chiral HPLC (column, chiracel OD; eluent, *n*-hexane/2-propanol 92/8).

The absolute configuration of the major product **6b** (entries 2 and 3) obtained from pyridone **1b** was determined from its specific rotation. The sign of the rotation was shown to be opposite to the sign of the known antipode *ent*-**6b**.[2d] In analogy, the major enantiomers obtained from the reaction of pyridones **1a** and **1c** were assigned structures **6a** and **6c**.

As expected, the enantiomeric excess of the products **6** improved with a decrease in temperature (entries 2/3 and 4/5, Table 1). It is also clear from these data, however, that the insufficient association is only to a limited extent responsible for the lower enantioselectivity of the reaction as compared to the [4 + 4]-photocycloaddition. In the course of the ring closure, either the hydrogen atoms at C-3 and C-6 of the pyridone or the substituted carbon atoms C-4 and C-5 move toward the sterically demanding tetrahydronaphthalene unit. Apparently, the approach of the hydrogen atoms is favored, but the free enthalpy difference of the diastereotopic transition states is not very pronounced. Possible explanations are that the transition states are located very early on the reaction coordinate or that the steric differences of the two cyclization modes differ marginally. An increased steric bulk at the carbon atom C-4 should lead to higher selectivities if the latter explanation is correct. Further studies are underway to further clarify this point.

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**Supporting Information Available:** An X-ray crystallographic file (CIF) on the structure determination of compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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