High Facial Diastereoselectivity in the Photocycloaddition of a Chiral Aromatic Aldehyde and an Enamide Induced by Intermolecular Hydrogen Bonding

Thorsten Bach,* Hermann Bergmann, and Klaus Harms†

Fachbereich Chemie
Philipps-Universität Marburg
D-35032 Marburg, Germany

Received June 28, 1999
Revised Manuscript Received October 1, 1999

Hydrogen bonding is commonly employed in nature as a tool to attach a substrate to a receptor in a defined rigid orientation.[1] In attempts to gain a better understanding of the natural binding pattern many artifical host molecules have recently been designed and synthesized which bind guest molecules with high enantioselectivity by this means.[2] The study we now describe was initiated to test whether enantioface- and diastereoface-differentiating photocycloaddition reactions are possible in rigid hydrogen-bonded host−guest complexes[3] and to show that the capability of the chiral host for hydrogen bonding is crucial for this selectivity. Although there are some examples in which the facial diastereoselectivity of photocycloaddition reactions in the liquid phase[4,5] was influenced by intra-[6] or intermolecular[7] hydrogen bonding, there have been to the best of our knowledge no studies in which a *chiral* host was designed such that a face differentiation was to occur upon hydrogen bonding and photocycloaddition to an achiral guest.

The chiral host **2a** we employed was prepared in racemic form from the known ester **1a**[8] by saponification and esterification as shown in the scheme. For comparison purposes (vide infra) we also prepared the *N*-methyl analogue **2b** in a similar fashion.

It was expected that compound **2a** can form two hydrogen bonds via its secondary amide functionality and that the self-association of **2a** was low due to steric hindrance of the bulky phenyl ester. Consequently, another amide should readily bind to compound **2a** and if this amide contained an olefinic double bond a Paternò−Büchi reaction could be initiated by irradiation.

Scheme 1

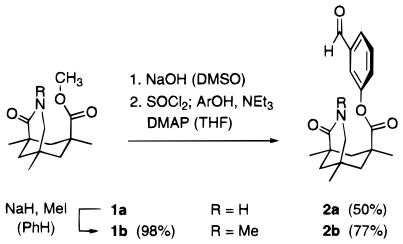
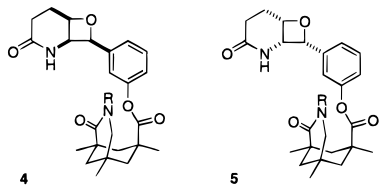


Table 1. Photocycloaddition of the Chiral Amides **2** and the Dihydropyridone **3**

entry	aldehyde	solvent[a]	temp. [°C]	oxetane	yield [%]	dr[b] (**4**/**5**)
1	**2a**	MeCN	65	**4a**/**5a**	56	50/50
2	**2a**	MeCN	30	**4a**/**5a**	*c*	50/50
3	**2a**	benzene	30	**4a**/**5a**	62	83/17
4	**2a**[d]	benzene	30	**4a**/**5a**	50	89/11
5	**2a**	toluene	−10	**4a**/**5a**	56	95/5
6	**2b**	benzene	30	**4b**/**5b**	50	50/50

[a] The reaction was conducted at 65 °C and 30 °C in a merry-go-round apparatus Rayonet RPR-100 ($\lambda = 300$ nm; light source: Rayonet RPR 3000) and at −10 °C in an immerison apparatus (Duran filter; light source: Original Hanau TQ 150). [b] The diastereomeric ratio of oxetanes in the crude product was determined by integration of appropriate ^{1}H NMR signals. [c] The yield of isolated product was not determined in this case. [d] An excess of the chiral aldehyde **2a** was employed (3 equiv).

We selected 3,4-dihydro-1H-pyridin-2-one (**3**)[9] as the olefin component, the enantiotopic faces of which were to be differentiated by the chiral host. The photocycloaddition of this and related enamides proceeds with excellent simple diastereoselectivity.[10] Upon photocycloaddition of **2** and **3** there are consequently only two major products **4** and **5** to be formed, the relative ratio **4**/**5** of which reflects the facial selectivity.



Compound **4** is expected as the predominant product if hydrogen bonding can occur via the amide moiety. Irradiation experiments were carried out in different solvents at various temperatures, the results of which are summarized in Table 1. In the polar solvent acetonitrile there was no detectable facial selectivity (entries 1 and 2), and both diastereoisomers **4a** and **5a** were isolated.[11] In contrast, the face discrimination in the photocycloaddition of **2a** and **3** was distinct in the nonpolar solvent benzene (entry 3), and it improved even further by running the reaction with an excess of the host **2a** (entry 4). The best result was obtained at low temperature in toluene as the solvent (entry 5). Under these conditions the diastereoisomeric oxetane **5a** was hardly detected in the crude product by ^{1}H NMR (dr **4a**/**5a** = 95/5), and the oxetane **4a** was the sole product which could be isolated (56% yield). The attack of the photoexcited aldehyde

† To whom inquiries about the X-ray analysis should be addressed at the University of Marburg.

(1) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer: New York, 1991.

(2) For some selected examples, see: (a) Famulok, M.; Jeong, K.-S.; Deslongchamps, G.; Rebek, J., Jr. *Angew. Chem.* **1991**, *103*, 880; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 858. (b) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554. (c) Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823. (d) Cristofaro, M. F.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1994**, *116*, 5089. (e) Kuroda, Y.; Kato, Y.; Higashioji, T.; Hasegawa, J.-y.; Kawanami, S.; Takahashi, M.; Shiraishi, N.; Tanabe, K.; Ogoshi, H. *J. Am. Chem. Soc.* **1995**, *117*, 10950. (f) Schrader, T. *J. Am. Chem. Soc.* **1998**, *120*, 11816.

(3) (a) For studies in which hydrogen bonding was used for selectivity control in thermal reactions, see: Booth, C. A.; Philp, D. *Tetrahedron Lett.* **1998**, *39*, 6987 and references therein. (b) For supramolecular catalysis, see: Saunders: J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378 and references therein.

(4) For a recent review, see: Fleming, S. A.; Bradford, C. L.; Gao, J. J. *Molecular and Supramolecular Photochemistry: Organic Photochemistry;* Ramamurthy, V., Schanze, K. S., Eds.; Dekker: New York, 1997; Vol. 1, p 187.

(5) Reviews on stereoselective photochemical reactions in the solid state: (a) Ito, Y. *Synthesis* **1998**, 1. (b) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (c) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480.

(6) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 10237.

(7) Sieburth, S. McN.; McGee, K. F., Jr.; Al-Tel, T. H. *J. Am. Chem. Soc.* **1998**, *120*, 587. (b) Sieburth, S. McN.; Joshi, P. V. *J. Org. Chem.* **1993**, *58*, 1661.

(8) Jeong, K.-S.; Parris, K.; Ballester, P.; Rebek, J., Jr. *Angew. Chem.* **1990**, *102*, 550; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 555.

(9) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(10) Bach, T. *Angew. Chem.* **1996**, *108*, 976. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 884. (b) Bach, T.; Schröder, J. *J. Org. Chem.* **1999**, *64*, 1265.

(11) It was shown by NOE experiments that **4a** and **5a** do indeed have the same relative configuration within the oxetane ring, i.e., that the *simple* diastereoselectivity of the reaction is high.

10.1021/ja992209m CCC: $18.00
Published on Web 11/03/1999

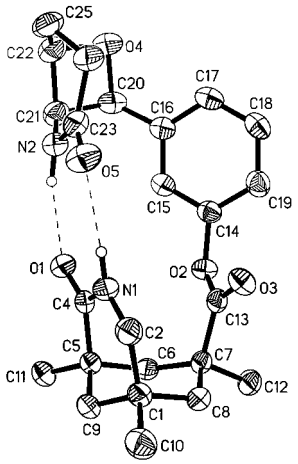


Figure 1. The structure of compound **4a** in the crystal.

2a had occurred exclusively on one of the enantiotopic faces of the alkene **3**. In a control experiment the amide **2b**, which does not have the ability to bind to a secondary amide via two hydrogen bonds, gave no significant diastereomeric excess (entry 6).

The enantiomerically pure host (+)-**2a** was subsequently prepared from racemic **2a** by deprotonation (LDA in THF, −78 °C) and *N*-acylation with (−)-menthyl chloroformate (THF, −78 °C → rt) and subsequent chromatographic separation. After acidic cleavage of the carbamate (TFA), compound (+)-**2a** was obtained in enantiomerically pure form, and its reaction with dihydropyridone **3** was studied under optimized conditions (entry 5 in Table 1). No racemization occurred in the course of the photocycloaddition and the reaction product (−)-**4a** was shown to be enantiomerically pure by chiral HPLC (column: Chiracel OD, eluent: hexane/2-propanol = 92/8). The bicyclic oxetano[2,3-*b*]-piperidone fragment could be readily cleaved from the host by transesterification (NaOMe in MeOH).

The relative configuration in oxetane **4a** was determined by single-crystal X-ray crystallography.[12] The result of this analysis is depicted in Figure 1. The structure not only supported our initial consideration concerning the side differentiation, but it additionally revealed the orientation of the corresponding amide groups which are still hydrogen-bonded in the product.

NMR titration studies carried out with **2a** and **3** at −10 °C in toluene-d_8 as the solvent enabled us to observe the system under scrutiny more closely.[13] As originally postulated the self-association constant K_a for **2a** is low (24 ± 1 M^{-1})[14] but not neglible. In addition, compound **3** also shows self-association with an association constant $K_a = 85 \pm 7$ M^{-1}. Compounds **2a** and **3** form a 1:1 complex as could be demonstrated by the Job plot shown in Figure 2. The association constant for the hydrogen-bonded complex **2a**/**3** was determined to be 227 ± 34 M^{-1}. Consequently, the high facial diastereoselectivity observed in toluene at −10 °C is a consequence not only of the fact that the rate constant of the intramolecular reaction is higher than the one of the intermolecular reaction but also of the fact that dihydropyridone **3** is more strongly bound by the host **2a** than by itself. The latter result should make host systems such as **2a** good candidates for enantioselective reactions in which the host does not participate in the reaction but serves merely as a chiral template. Studies along these lines are currently underway in our laboratory.

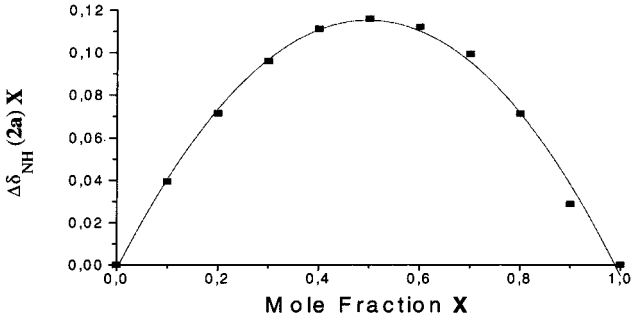


Figure 2. Job plot analysis of δ_{NH} (**2a**) in toluene at −10 °C for the system **2a**/**3**.

Acknowledgment. This work was generously supported by the Deutsche Forschungsgemeinschaft (Ba 1372/4-1), and by the Fonds der Chemischen Industrie. We cordially thank Professor Craig S. Wilcox (University of Pittsburgh) for making his HOSTEST program available to us. The help and assistance of Priv.-Doz. Dr. Thomas Schrader and Professor Dr. Burkhard König are also gratefully acknowledged.

Supporting Information Available: Detailed synthetic schemes for the preparation of **1b**, **2a**, (+)-**2a**, **2b**, **4a,** and **4b**, NMR data (^{1}H, ^{13}C) of **1b**, **2a**, **2b**, **4a**, **5a**, and **4b**/**5b** (mixture of diastereoisomers), HPLC analysis of (−)-**4a**, and curve fits (HOSTEST) for the NMR titration of **2a**, **3,** and **2a/3** (PDF). An X-ray crystallograhic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992209M

(12) **4a**: colorless crystals; triclinic, $P\bar{1}$, $a = 814.5(1)$ pm, $b = 1117.0(1)$ pm, $c = 1324.1(1)$ pm; $\alpha = 105.191(1)°$, $\beta = 106.46°$, $\gamma = 101.38°$; $Z = 2$; $R = 4.9\%$; GOF = 1.046.

(13) The HOSTEST program was used for determining the association constants: Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991; pp 123.

(14) The given error limits represent the standard deviation obtained from applying a curve fit program (HOSTEST) to the measured data points.