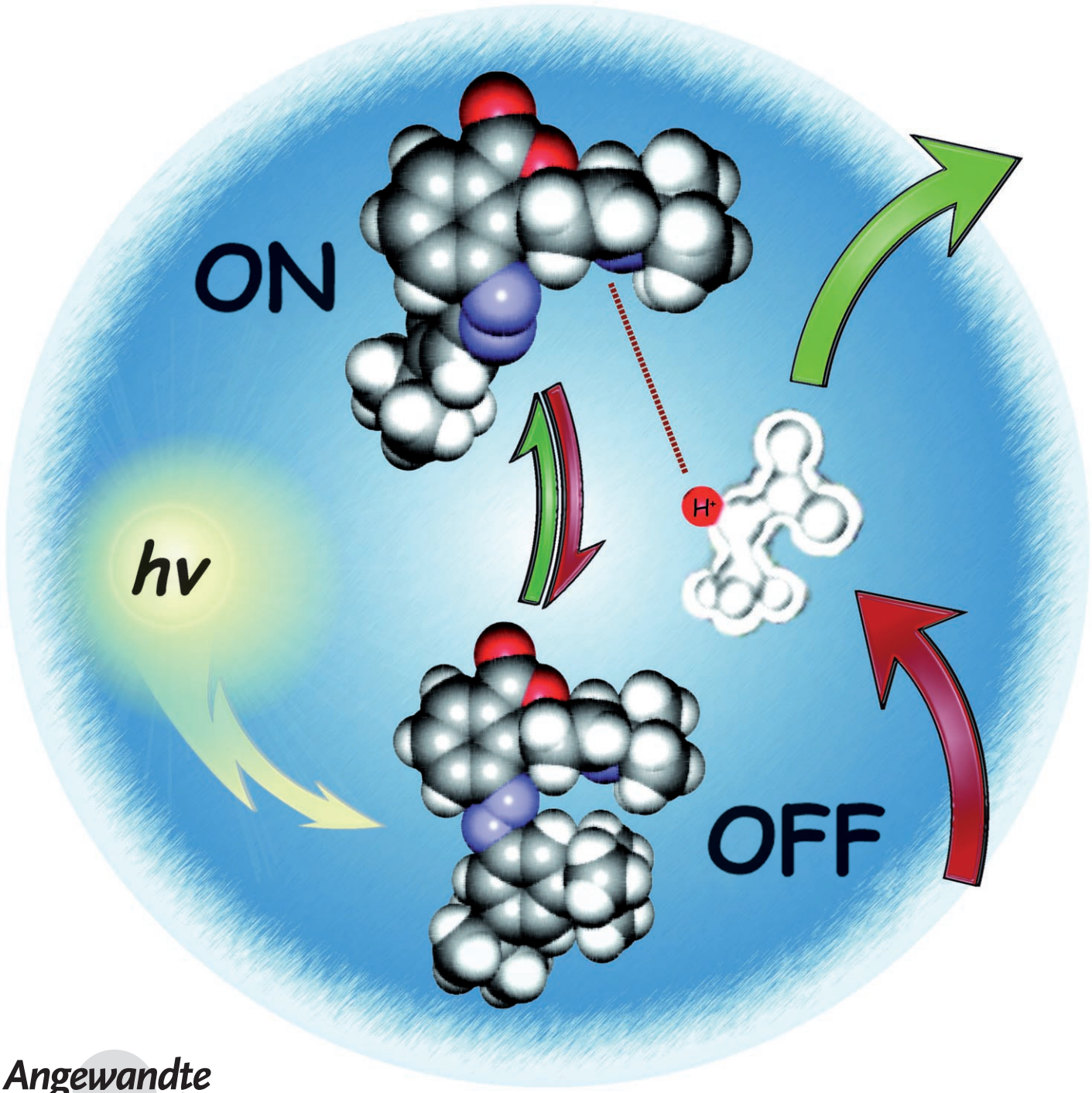
Photochemistry

DOI: 10.1002/anie.200802050

Photoswitching of Basicity**

*Maike V. Peters, Ragnar S. Stoll, Andreas Kühn, and Stefan Hecht**

Dedicated to Professor Manfred T. Reetz on the occasion of his 65th birthday



The ability to control function at the molecular level by means of external stimuli is one of the key requirements for the development of "smart" devices and materials. In particular, the use of light as a trigger offers distinct advantages, as it is a noninvasive stimulus that can be manipulated precisely by modern optics to provide exquisite temporal and spatial resolution. The functional response of the molecular system to light is mediated by photoactive moieties: either photolabile protecting groups, which lead to irreversible activation (caging), or photochromic moieties, which enable reversible activation and deactivation (switching).[1] While a variety of molecular properties have successfully been rendered photoswitchable in recent years,[2] examples in which catalysis—perhaps the most attractive function from a chemist's standpoint—has been reversibly photoregulated are scarce.[3] Such systems are particularly attractive, as they would in principle enable the translation of a light stimulus into a chemical signal, which would be amplified further in the subsequent catalytic cycle. The resulting high efficiency of the overall process, which can be controlled reversibly by light, should lead to various new applications in chemical surface patterning[4,5] and sensing.

Recently, we have become interested in developing photoswitchable catalysts that control catalytic activity on the basis of steric and electronic factors. Initial designs based on metalloporphyrins failed owing to inhibition of the photochromic reactivity through energy transfer to the active site of the catalyst.[6] We therefore turned our attention to photoswitchable bases,[7,8] in which the catalytically active site is optically silent. Herein, we present the first photoswitchable organic bases, the reactivity of which is controlled by reversible steric shielding (Figure 1), and demonstrate the significant structure and reactivity differences associated with the two switching states.

Our photoswitchable base is derived from a conformationally restricted N-alkylated piperidine base. The catalytically active site, that is, the lone pair of electrons on the piperidine N atom, is shielded reversibly by a bulky photochromic azobenzene moiety. The target compounds **4a–c** were readily synthesized from the parent bromospiro compounds **1a**,**b** utilizing Pd-catalyzed N-arylation of the Boc-protected hydrazines **2a**,**b**, followed by oxidative deprotection[9] (Scheme 1).[10] This modular synthetic route enables straightforward structural tuning of the skeleton, most importantly through variation of the substituents R and R′.

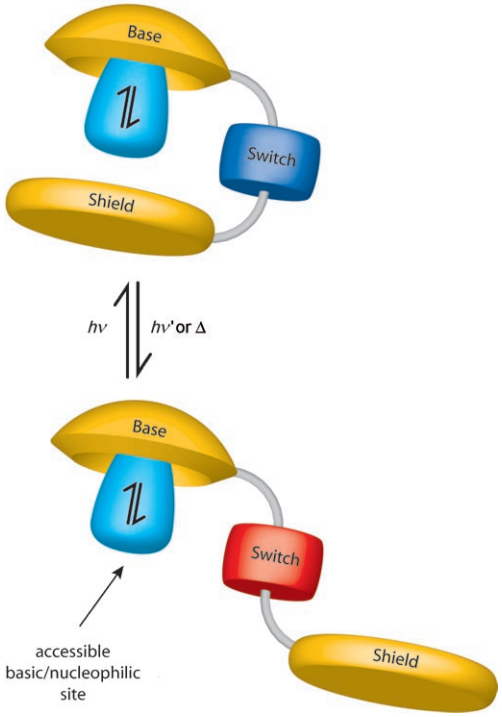
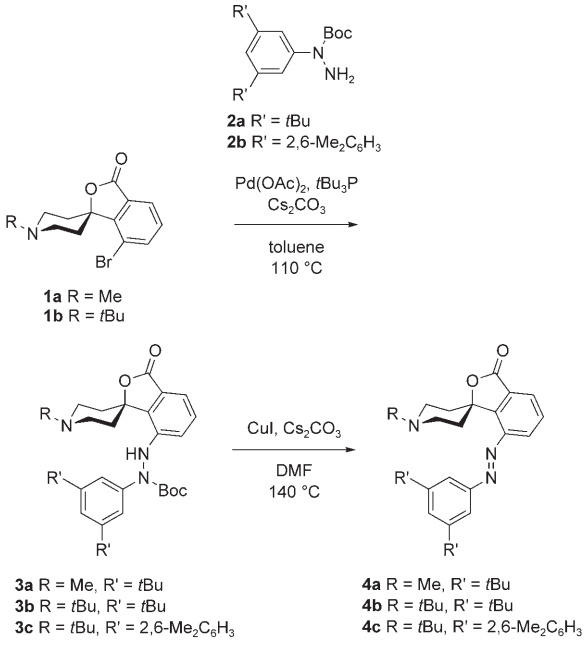


Figure 1. Concept of a photoswitchable base on the basis of reversible steric shielding.

For efficient shielding of the active center in (*E*)-**4a–c**, we took advantage of several conformationally restricting fea-



Scheme 1. Modular synthesis spirofused piperidines **4a–c** with variable steric demand by a two-step sequence of Pd-catalyzed cross-coupling followed by oxidation. Boc = *tert*-butoxycarbonyl, DMF = *N*,*N*-dimethylformamide.

[*] M. V. Peters, R. S. Stoll, A. Kühn, Prof. Dr. S. Hecht
Department of Chemistry
Humboldt-Universität zu Berlin
Brook-Taylor-Strasse 2, 12489 Berlin (Germany)
Fax: (+49) 302-093-6940
E-mail: sh@chemie.hu-berlin.de
Homepage: http://www.hechtlab.de

[**] M.V.P. and R.S.S. contributed equally to this work. We thank Petra Neubauer and Dr. Burkhard Ziemer (HU Berlin) for carrying out the single-crystal X-ray structure analyses. Generous support by the German Research Foundation (DFG, SPP 1179) and the Fonds der Chemischen Industrie, and initial funding by the Max Planck Society is gratefully acknowledged. We thank Wacker Chemie AG, BASF AG, Bayer Industry Services, and Sasol Germany for generous donations of chemicals.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802050.

tures: 1) the pronounced preference of the piperidine ring to adopt a chair conformation with the *N*-alkyl substituent in an equatorial position,[11] 2) the spiro junction, which enables the rigid and orthogonal positioning of the photochromic azobenzene moiety, and 3) the steric bulk of the symmetrical 3,5-disubstituted phenylazo substituent and its position *ortho* to the spiro center. We envisioned that irradiation of the shielded, inactive *E* isomer, corresponding to the "resting state", would trigger photochemical $E \rightarrow Z$ isomerization, accompanied by a large structural change and thereby revealing the active *Z* isomer, in which the lone pair of electrons on the N atom becomes sterically accessible (shown for **4b** in Figure 2).

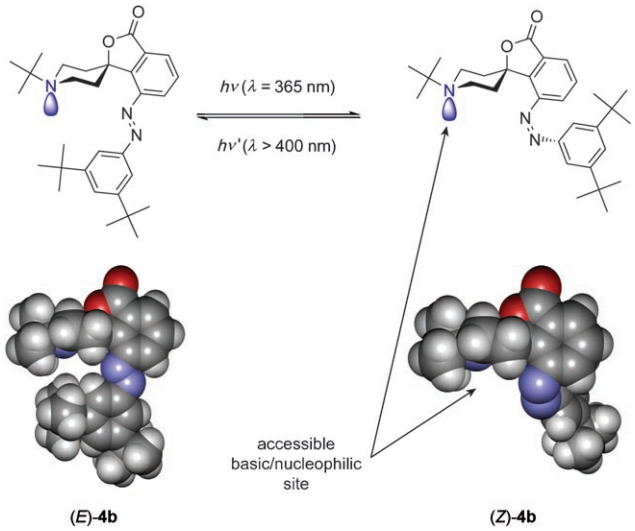


Figure 2. Light-induced reversible conversion of the less-reactive *E* isomer (*E*)-**4b**, with a sterically shielded basic/nucleophilic lone pair of electrons on the piperidine N atom (left), into the accessible and hence more reactive *Z* isomer by $E \rightarrow Z$ isomerization of the spiro-linked azobenzene substituent. Space-filling structures (C dark gray, H light gray, O red, N blue) are derived from single-crystal X-ray structure analysis of (*E*)-**4b** (bottom left, CCDC 686676) and (*Z*)-**4b** (bottom right, CCDC 686677).[12]

Irradiation of (*E*)-**4a–c** with light of wavelength 365 nm led to rapid photoisomerization to yield almost quantitatively the corresponding isomers (*Z*)-**4a–c** with remarkably long thermal half-lives at room temperature (Table 1). Reversion to (*E*)-**4a–c** could be induced thermally or by irradiation with light ($\lambda \geq 400$ nm). Using preparative irradiation, (*Z*)-**4a–c** containing only minor amounts of residual *E* isomer were isolated and characterized. In the case of **4b**, both switching states of the system could be characterized by single-crystal X-ray structure analysis (Figure 2).[12] Owing to the presence of the spiro junction, the isobenzofuran-1-one moiety is oriented perpendicular to the plane of the piperidine ring, which adopts a chair conformation with the *N*-*tert*-butyl group occupying an equatorial position. Taking the van der Waals radii into account, inspection of the structure of (*E*)-**4b** shows that the piperidine lone pair is well shielded by one of the equivalent *tert*-butyl groups of the 3,5-di-*tert*-butylphenylazo fragment (Figure 2, bottom left). On the contrary, in the corresponding isomer (*Z*)-**4b** flipping of the 3,5-di-*tert*-butylphenylazo fragment due to $E \rightarrow Z$ isomerization renders the piperidine lone pair much more accessible (Figure 2, bottom right).[13]

Table 1: Photochemical, kinetic, and thermodynamic data for the piperidine bases **4a–c**.

	PSS[a] (*Z*/*E*)	$t_{1/2}$[b] [h]	k_{off}[c] [10^{-6} s^{-1}]	k_{on}[d] [10^{-6} s^{-1}]	k_{rel} (k_{on}/k_{off})	ΔpK_a[e]
4a	90:10	268	4.96	21.5	4.3	–
4b	90:10	286	0.963	12.7	13.2	0.8
4c	>90:10	466	0.391	13.9	35.5	0.7

[a] Photostationary state (PSS) obtained by irradiation at 365 nm. [b] Half-life of the *Z* isomer, measured at 20 °C. [c] Rate constant of Henry reaction using pure *E* isomer (Figure 3). [d] Rate constant of Henry reaction extrapolated to 100% *Z* isomer (Figure 3). [e] Difference of pK_a values, i.e. $pK_a(PSS) - pK_a(E)$, obtained from titration with trifluoromethanesulfonic acid using Neutral Red as reference base.

These structural differences between the interconvertible isomers are reflected in differences in chemical reactivity. The basicity of the deshielded *Z* isomers is increased by almost one order of magnitude as compared to the shielded *E* isomers as shown by titration experiments with trifluoromethanesulfonic acid in acetonitrile solution using Neutral Red as the reference base (Table 1). The higher basicity of the *Z* isomer can be attributed to the increased thermodynamic stability of $[(Z)\text{-}\mathbf{4}\text{–H}]^+$ relative to $[(E)\text{-}\mathbf{4}\text{–H}]^+$, but also to kinetic factors associated with the enhanced accessibility of the basic site. These kinetic factors will be particularly important for larger electrophiles. Importantly, as protonation was found to have a negligible influence on the photochemical and thermal isomerization behavior of **4**,[10] the basicity function can be decoupled from the switching function.

In a first proof of concept, we exploited the different basicities of the two switching states to photocontrol conversion in the general-base-catalyzed nitroaldol reaction (Henry reaction).[14] The low background rate of the non-catalysed Henry reaction facilitates kinetic analysis. In a $[D_8]$THF solution, 4-nitrobenzaldehyde (**5**) was treated with excess nitroethane (**6**) in the presence of 10 mol% catalyst **4a–c** and the evolution of the mixture of *syn* and *anti* nitroaldol products **7** was monitored in situ using ^{1}H NMR spectroscopy (Table 1, Figure 3).[10,15] In all cases, the use of the *Z* isomer led to faster product formation than that observed with the *E* isomer. Although the on/off ratio, defined as the quotient of the rate constants with the *Z* and *E* isomers is moderate for the sterically least hindered catalyst **4a**, this ratio can be improved to significant values by appropriate molecular design based on the introduction of sterically more demanding substituents R and R′. The involvement of the much less basic N=N group can be excluded on the basis of experiments with azobenzene itself as the catalyst: No product formation was observed.[10] Under the reaction conditions employed, the Henry reaction is known to proceed by general base catalysis, whereby the rate-limiting step is the deprotonation of the CH-acidic nitroalkane by the tertiary amine.[14b] Therefore, the barrier for proton abstraction by the general base catalyst locked in its

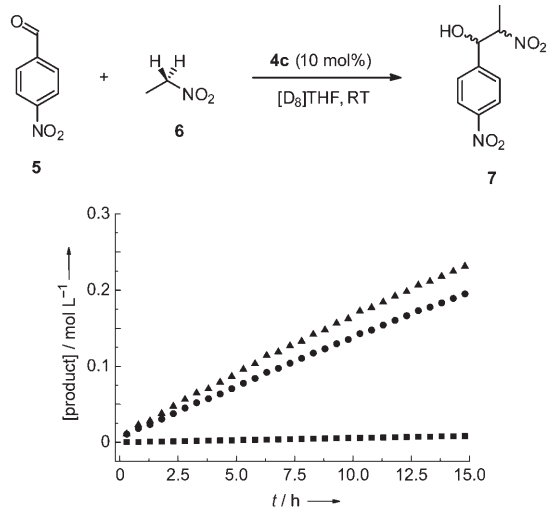


Figure 3. Performance of the photoswitchable piperidine **4c** in its two switching states as general base catalyst for the Henry reaction of **5** with **6** to give **7**: ■ (*E*)-**4c**, ● (*Z*)-**4c** in the photostationary state with residual (*E*)-**4c**, ▲ extrapolation to 100% (*Z*)-**4c** with a correction for the thermal (*Z*)-**4c**→(*E*)-**4c** back reaction. Reaction conditions: catalyst (10 mol%), 4-nitrobenzaldehyde (0.40 M, 1 equiv), nitroethane (12 equiv), [D$_8$]THF, 25 °C.

global-minimum conformation can be modulated externally by light as a result of the significantly different steric demands of the photochromic unit in the two switching states.

We took advantage of the modular synthetic route (Scheme 1) to optimize the system by introducing bulky substituents R and R′. The piperidine ring was locked more efficiently in its chair conformation by increasing the steric demand of the *N*-alkyl substituent (**4a**→**4b**). The steric-shielding capability of the 3,5-disubstituted phenylazo fragment was enhanced by introducing twisted 2,6-dimethylphenyl groups (**4b**→**4c**), which provide significant steric shielding even upon rotation about the C–N single bonds.[13] Both structural modifications resulted in more efficient shielding to decrease the "off" reactivity of the *E* isomer, whereas the reactivity of the *Z* isomer was only slightly diminished and reflected the intrinsic activity of the *N*-*tert*-butylpiperidine skeleton, as shown by the comparable basicities (Table 1). Overall, these changes result in an improved on/off ratio. The photochemical properties of the system also improved with increasing steric bulk of the substituents, in particular for compound **4c**, as exemplified by both the high *Z* content of the photostationary state and the unusually long thermal half-lives (Table 1).[2e]

In summary, we have developed a conceptually new approach to the design of photoswitchable bases on the basis of reversible steric shielding of the reactive site and demonstrated the application of the concept through the photocontrol of a reaction that proceeds under general base catalysis. Detailed mechanistic studies relating to the reactivities of the two switching states are currently in progress in our laboraotories, along with efforts to control polymerization processes. Future studies will focus both on the extension of our steric-blocking approach to intrinsically more reactive bases and catalysts with the aim of maximizing amplification and the on/off ratio, and on the control of chemical selectivity with light to yield new "smart" catalysts.[16]

Received: April 30, 2008
Published online: July 15, 2008

Keywords: azo compounds · basicity · chemical amplification · homogeneous catalysis · photochromism

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[2] a) *Photochromism: Molecules and Systems* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **2003**; b) *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**; c) Special Issue: "Photochromism" (Ed.: M. Irie), *Chem. Rev.* **2000**, *100*, 1683; d) *Organic Photochromic and Thermochromic Compounds* (Eds.: J. C. Crano, R. J. Guglielmetti), Plenum, New York, **1999**; e) *Organic Photochromes* (Ed.: A. V. El'tsov), Consultants Bureau, New York, **1990**; f) S. Hecht, *Small* **2005**, *1*, 26–28.

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[12] CCDC 686676 ((*E*)-**4b**), and 686677 ((*Z*)-**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] To obtain accurate kinetic data, we used catalysts **4a**–**c** in their isolated form, that is, either as the pure *E* isomer or as a mixture of *Z* and *E* isomers in the photostationary state.

[16] Note added in proof: After submission of this manuscript photomodulation of the Lewis acidity of dithienylethene-based boronates has been reported in: V. Lemieux, M. D. Spantulescu, K. M. Baldrigde, N. R. Branda, *Angew. Chem.* **2008**, *120*, 5112–5115; *Angew. Chem. Int. Ed.* **2008**, *47*, 5034–5047.

