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An Oxidative Approach Enables Efficient Access to Cyclic Azobenzenes

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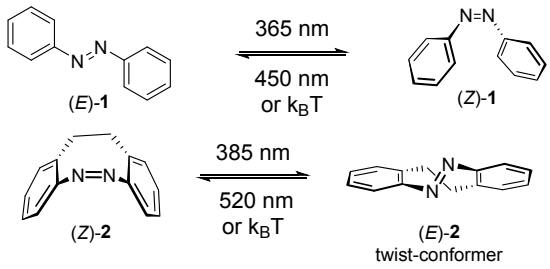
ABSTRACT: Azobenzenes are versatile photoswitches that have found widespread use in a variety of fields, ranging from photopharmacology to the material sciences. In addition to regular azobenzenes the cyclic diazocines have recently emerged. Although diazocines have fascinating conformational and photophysical properties, their use has been limited by their synthetic accessibility. Herein, we present a general, high-yielding protocol that relies on the oxidative cyclization of dianilines. In combination with a modular substrate synthesis, it allows for rapid access to diversely functionalized diazocines on gram scales. Our work systematically explores substituent effects on the photoisomerization and thermal relaxation of diazocines. It will enable their incorporation into a wide variety of functional molecules, unlocking the full potential of these emerging photoswitches. The method can be applied to the synthesis of a new cyclic azobenzene with a nine-membered central ring and distinct properties.

INTRODUCTION

Azobenzene photoswitches contain a diaryl diazene moiety that can exist either in an (*E*) or in a (*Z*) configuration. In general, the elongated (*E*) or *trans* form is thermodynamically preferred and the bent (*Z*) or *cis* form is subject to gradual thermal isomerization (Scheme 1). The half-lives for this thermal relaxation range from picoseconds to days,[1] and photoswitches whose thermal relaxation is comparatively slow are often designated as "bistable". Irradiation of azobenzenes with monochromatic light establishes a photostationary state (PSS) that depends on both the extinction coefficients of the two isomers at a particular wavelength and their respective isomerization quantum yields. Photostationary states as high as $(Z)/(E) \simeq 90/10$ can be achieved, but are generally lower.[2] Due to their photostability, facile synthesis and relatively low molecular weight, azobenzenes have become the photoswitch of choice in many applications. They have been successfully incorporated in photopharmaceuticals, in photoresponsive functional materials, such as polymers and hydrogels, or in catalysts that can be controlled with light.[3]

Despite their long history and popularity, there is still a need to tailor the properties of azobenzenes. One important direction is red shifting the action spectra whilst maintaining thermal bistability.[4] Significant progress towards this goal has been made by developing tetra-*ortho*-substituted azobenzenes, but these are marked by increased steric bulk and changes in dipole moment, which can interfere with their function. Another desirable feature are highly biased PSS, both for wavelengths that favor the (*Z*) isomer and those that give preference to the (*E*) isomer. Although thermal relaxation can revert azobenzenes fully to their (*E*) form, this process can be slow with bistable variants and the faster photochemical conversion to the (*E*) isomer is generally incomplete. Lastly, it can be useful to employ photoswitches that are bent in their default form, i.e. in the absence of light, and become elongated upon irradiation. This is especially true in photopharmacology where tonic "dark-activity" is often undesirable.

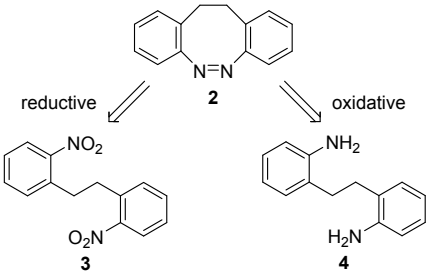
Scheme 1. Photoswitching of azobenzene (1)[1] compared to diazocine (2)[5a]



Cyclic azobenzenes, wherein the diazene unit is embedded in an eight-membered ring, meet many of these challenges. The parent compound of this class is 5,6-dihydrodibenzo[c,g][1,2]diazocine ("diazocine"), which had already been discovered at the beginning of the last century.[6a] It found little attention until recently, when its remarkable photophysical properties were recognized by Herges and Temps.[5] Contrary to regular azobenzenes, the thermodynamically preferred form of diazocines is the (*Z*) isomer due to the increased strain that the ring-system imposes on the (*E*) isomer (Scheme 1). In addition, diazocines can be switched to more than 90% of the (*E*) isomer and quantitatively back to the (*Z*) isomer by irradiation with visible wavelengths around 400 nm and 520 nm, respectively.[21]

Despite these remarkable photophysical properties, diazocines have found relatively few applications to date. The reason for this has been their limited availability due to lack of effective synthetic methods.[5a,6–9] Most reported diazocines have been synthesized by a reductive cyclization of 2,2'-dinitrodibenzyls (Scheme 2).[6,7,9a–c] Apart from low yields, a major limitation of the reductive cyclization is that it does not give straightforward access to unsymmetrical diazocines.[7,9a–c] In addition to the reductive cyclization approach, conditions based on oxidation of 2,2'-ethylenedianilines or hydroxylamine-aniline analogs have been reported, albeit with low to mediocre yields.[8,9d] Very recently, an oxidative strategy has been applied in a synthesis of a photoswitchable glutamate derivative.[8b] However, the potential of the oxidative cyclization of 2,2'-ethylenedianilines has not been investigated systematically and a practical, generally applicable and high-yielding protocol for the synthesis diazocines has been lacking.

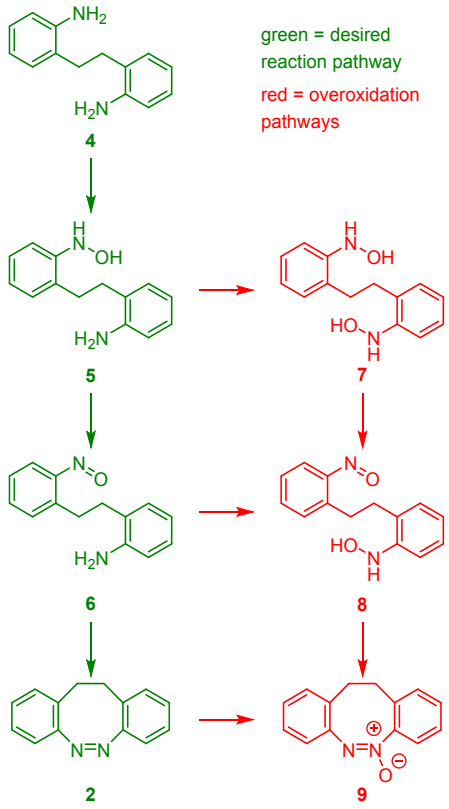
Scheme 2. Synthetic approaches towards the diazocine core



RESULTS AND DISCUSSION

1. Mechanistic considerations. Our investigation commenced with the optimization of reaction conditions for the oxidative cyclization of the commercially available 2,2'-ethylenedianiline **4** to the corresponding diazocine **2**. We considered four key requirements which needed to be fulfilled to make this an effective process (Scheme 3). First, it would be necessary to selectively oxidize 2,2'-ethylenedianiline **4** to 2-amino-2'-nitrosodibenzyl **6**, without formation of the dihydroxylamine **7** from intermediate **5**. Second, the cyclization of the nitroso-aniline **6** to diazocine **2** via a Baeyer-Mills reaction has to be faster than the oxidation to nitroso-hydroxylamine **8**. Third, the product diazocine **2** must not be oxidized further to form the azoxy compound **9**. Fourth, intermolecular reactions leading to oligomeric or polymeric structures need to be suppressed. While temperature, concentration and rate of addition of the oxidant are important considerations for optimization with respect to the second and fourth conditions, the other two conditions are more dependent on the inherent reactivity of the substrates. Based on our mechanistic scheme, we expected slow addition of the oxidant to be the most important parameter.

Scheme 3. Mechanistic considerations for an oxidative cyclization approach towards diazocines



2. Development of reaction conditions. Most commonly, the oxidation of anilines to nitrosobenzenes is performed in a biphasic system of DCM/water using Oxone® as an oxidant. The ensuing Baeyer-Mills reaction is typically performed in acetic acid and mixtures of acetic acid with DCM or toluene. As these two sets of conditions are not compatible, we decided to use typical solvent-systems of the Baeyer-Mills reaction, such as pure acetic acid or acetic acid/DCM, as the solvent and peroxycarboxylic acids as the oxidant. To simplify the workup, we initially focused on peracetic acid.

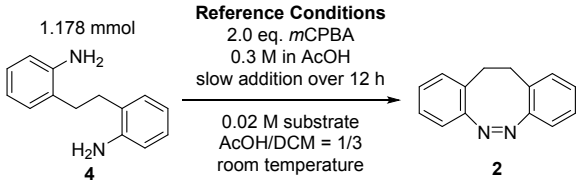
After optimization of oxidant addition rate, stoichiometry and substrate concentrations, we were able to obtain diazocine **2** by the slow addition of two equivalents of peracetic acid in acetic acid to a dilute solution of 2,2'-ethylenedianiline **4** within a twelve hour period in a yield of more than 70%, which was already substantially superior to any previously reported value.[5a,6–9] However, we noticed several inconsistencies during the course of this initial optimization. The most important observations were a noticeably fluctuating yield, a highly detrimental effect of copper salts as well as an unexpected relation between the obtained yields and the equivalents of peracetic acid that were employed.

We suspected the underlying issue to be the presence of considerable amounts of hydrogen peroxide in the commercial peracetic acid solutions. This "dormant oxidant" may either directly participate in the oxidation or slowly be transformed to peracetic acid, thus resulting in an incorrect stoichiometry. The effect can be expected to be more prominent under conditions that should activate

the hydrogen peroxide (e.g. the presence of transition metal ions), which agrees with the observed results. Additionally, we confirmed the reactivity of hydrogen peroxide in acetic acid by treatment of 2,2'-ethylenedianiline with urea hydrogen peroxide as a source of "dry" hydrogen peroxide. This led to the slow formation of diazocine, but could unfortunately not be developed into a synthetically practical procedure.

Building on the knowledge gained from our initial optimization with peracetic acid, we continued our search for optimal reaction conditions (Table 1). We did not perform an additional screening on the rate of addition as well as equivalents of oxidant and continued with the theoretically ideal stoichiometry of two equivalents of oxidant and the addition of oxidant within twelve hours. To identify a more reliable oxidant we compared the most commonly employed commercially available percarboxylic acids. Among peracetic acid, *m*CPBA and MMPP, we found that *m*CPBA performed best. The use of mCPBA to prepare nitrosobenzenes from anilines is well precedented.[10] A screen of solvent mixtures revealed that diluting acetic acid with DCM or toluene resulted in a further increased yield, although a sizeable fraction of acetic acid was necessary for optimal results. Increasing the temperature proved to be slightly detrimental to the reaction outcome, while higher concentrations of the *m*CPBA solution (0.6 M) and substrate (0.04 M) were tolerated without a negative effect on the yield.

Table 1. Optimization of the oxidative cyclization of 2,2'-ethylenedianiline – selected examples



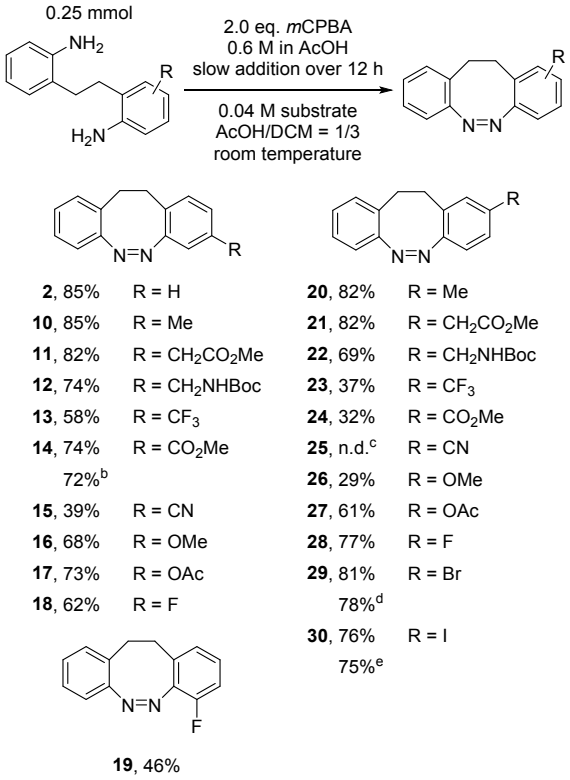
Entry	Variation from Reference Conditions	Yield[a]
1	none	86%
2	Solvent AcOH	75%
3	Solvent AcOH/DCM = 1/1	86%
4	Solvent AcOH/PhMe = 1/1	84%
5	Solvent AcOH/DCM = 1/9	81%
6	Entry 4 + 40 °C	82%
7	Entry 4 + 60 °C	76%
8	0.01 M substrate	85%
9	0.04 M substrate	85%
10	Entry 9 + 0.6 M *m*CPBA	86%
11	Entry 10 + 0.06 M substrate	79%
12	Entry 10 + catalytic Cu(II)	59%

[a]Determined by ^{1}H-NMR spectroscopy with dimethyl terephthalate as internal standard.

Copper salts were reported to be beneficial to the formation of azobenzenes by oxidative dimerization of anilines with peroxy acids.[11] However, we observed that addition of copper acetate reduced the yield and an increased amount of unreacted starting material remained. This supports that our reaction does not depend on trace amounts of metal salts. Finally, we confirmed that the undesired overoxidation of diazocine **2** to azoxy compound **9** does not occur in the presence of unreacted dianiline **4** (see Supporting Information). This finding supports our initial reasoning about the importance of slow addition. Azoxy compound **9** does not primarily result from oxidation of desired product **2**, but forms through nitroso-hydroxylamine **8** (see Scheme 3).

3. Investigation of reaction scope. After optimizing reaction conditions for the parent system, we applied our best protocol to various monosubstituted 2,2' ethylenedianilines (compounds **10**–**30**, Table 2). For a majority of these compounds, we obtained the cyclization products in yields similar to or only slightly lower than observed for the parent system. Substituents that only weakly affect the electronic nature of the arenes, such as most halogens and alkyl groups, had virtually no effect on the yield of the cyclization. The yields observed for the fluorinated compounds followed a trend, decreasing from *para*- to *meta*- to *ortho*-fluoro substitution.

Table 2. Oxidative cyclization yields[a] of monosubstituted 2,2'-ethylenedianilines



2, 85% R = H
10, 85% R = Me
11, 82% R = CH_2CO_2Me
12, 74% R = CH_2NHBoc
13, 58% R = CF_3
14, 74% R = CO_2Me
72%[b]
15, 39% R = CN
16, 68% R = OMe
17, 73% R = OAc
18, 62% R = F

20, 82% R = Me
21, 82% R = CH_2CO_2Me
22, 69% R = CH_2NHBoc
23, 37% R = CF_3
24, 32% R = CO_2Me
25, n.d.[c] R = CN
26, 29% R = OMe
27, 61% R = OAc
28, 77% R = F
29, 81% R = Br
78%[d]
30, 76% R = I
75%[e]

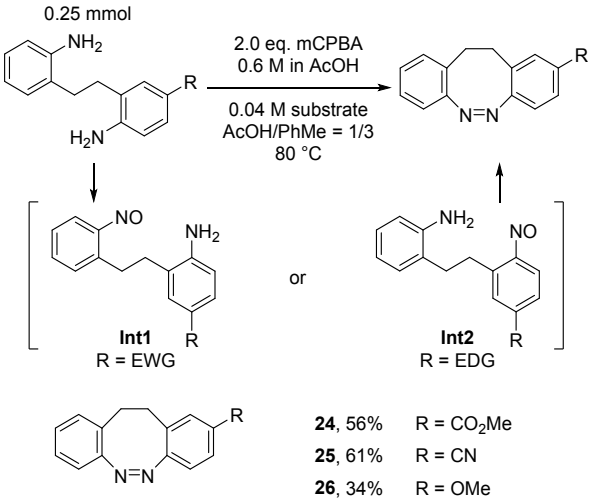
[a]Isolated yields are reported. [b]4.28 mmol scale. [c]Not determined. [d]7.90 mmol scale. [e]7.69 mmol scale.

Notably, the presence of both strongly electron-withdrawing and electron-donating substituents resulted in a significant reduction in yield. *Para*-substituted substrates gave generally lower yields than the corresponding *meta*-substituted ones, both for electron-

withdrawing and electron-donating substituents. We reasoned that low-yielding substrates would undergo a highly selective oxidation of one of the two amino groups (see Scheme 4). In the corresponding intermediates **Int1** and **Int2** the more nucleophilic aniline moiety is now oxidized, which leaves a deactivated aniline moiety in **Int1** and a deactivated nitrosobenzene moiety in **Int2**. This would make the subsequent Baeyer-Mills cyclization comparatively slow in both cases. Additionally, the tendency for intermolecular, instead of intramolecular, reactions would be increased, as the unreacted substrates (not shown) carry a more reactive amino group than the corresponding intermediates **Int1** and **Int2**. These considerations led us to explore whether, instead of the slow addition protocol, one-batch addition and increased temperatures might be beneficial in these cases.

We tested this alternative protocol for the three compounds that were the most problematic for our slow addition method (Scheme 4). Gratifyingly, we now obtained the known[7a] *para*-cyano diazocine **25** in a respectable yield of 61%. The yield of the *para*-methyl ester diazocine **24** also was improved substantially to 56%. However, the *para*-methoxy product **26** was only obtained with slightly increased yield. A different factor seems to affect the yield in this case. The most probable explanation is the reactivity of *para*-alkoxy-nitrosobenzenes towards nucleophilic aromatic substitution.[12]

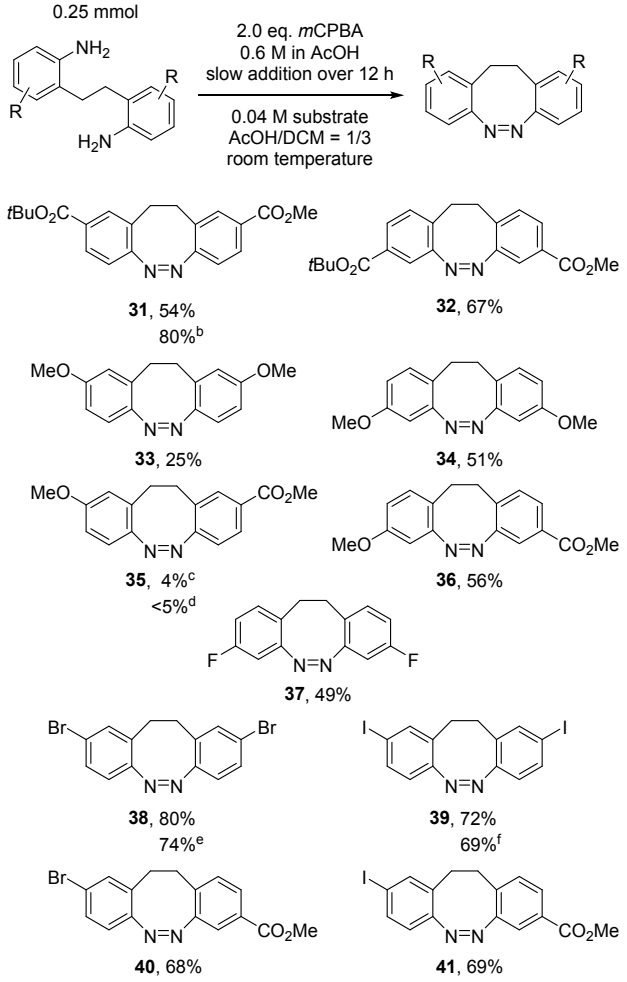
Scheme 4. Synthesis of diazocines using a one-batch addition protocol and presumed intermediates due to oxidation selectivity



Next, we turned our attention towards disubstituted diazocines (compounds **31**–**41**, Table 3). Considering the large amount of combinatorial possibilities, we selected only a small number of examples. Our main goals were to obtain an appropriate set of disubstituted diazocines to investigate the photophysical properties of substituted diazocines, to determine the limitations of our approach and to explore how substituent effects of the monosubstituted substrates extend to disubstituted substrates.

Employing our standard slow addition protocol, we observed that for most compounds the substituent effects were additive. The yields decreased compared to the corresponding monosubstituted analogs but remained in a synthetically useful range. A clear exception was found in the *para*-diester compound **31**, where the yield was significantly increased compared to the *para*-ester **24**. Performing the reaction at higher temperature further increased the yield to 80%, a level similar to the parent compound **5**. An example that shows a limitation of our approach, for both the slow and batch addition protocols, is the push-pull diazocine **35**. Still, we were able to obtain a sufficient quantity for photophysical characterization of this diazocine.

Table 3. Oxidative cyclization yields[a] of disubstituted 2,2'-ethylenedianilines

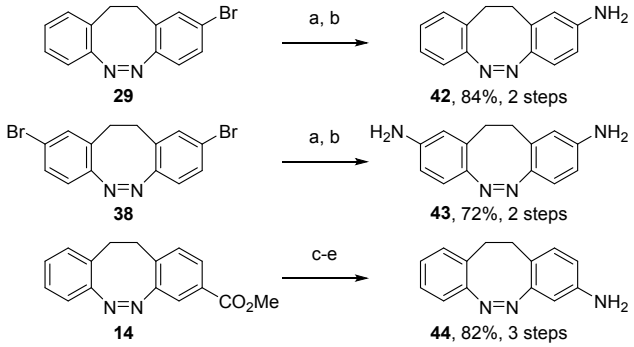


[a]Isolated yields are reported. [b]80 °C. [c]0.832 mmol scale, 0.03 M substrate. [d]0.156 mmol scale, batch addition protocol. [e]7.16 mmol scale. [f]7.87 mmol scale.

4. Late-stage derivatization. Despite the large number of mono- and disubstituted diazocines accessible with our oxidative method, it could not readily deliver amino substituted diazocines. Therefore, we developed a practical late-stage derivatization (Scheme 5). The known *para*-amino-diazocine **42**[7c] was synthesized in 84% yield from the *para*-bromo diazocine **29**[7a] by Buchwald-Hartwig coupling with *tert*-butyl carbamate, followed by deprotection of the Boc group by treatment with TBAF.[13] Although the TFA protocol could be used, TBAF afforded a

cleaner product and avoided side reactions resulting from the presence of *tert*-butyl cations. The known *para*-diamino diazocine **43**[6e] was prepared in 72% yield in an identical fashion to the monoamino compound **42**. To access the *meta*-amino diazocine **44**, we started from *meta*-ester **14**. Ester hydrolysis followed by Curtius rearrangement in the presence of allyl alcohol, followed by removal of the Alloc group gave the desired product **44** in 82% yield.

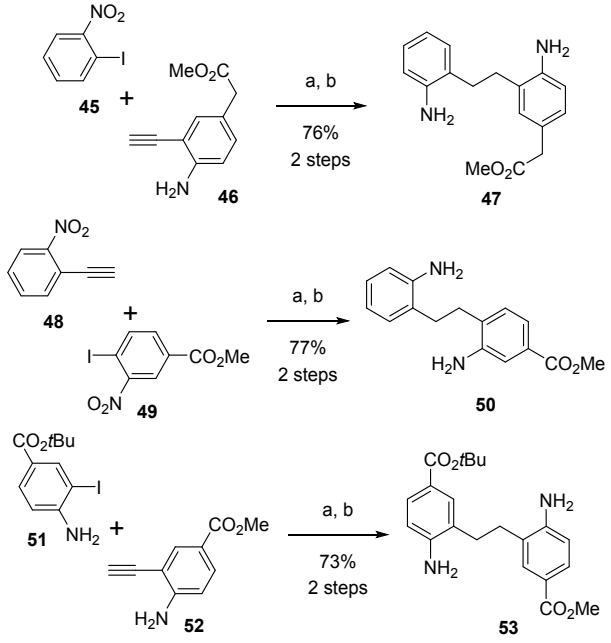
Scheme 5. Late-stage diversification



a) $BocNH_2$, Cs_2CO_3, XanthPhos Pd G3, 1,4-dioxane, 100 °C; b) TBAF·$3H_2O$, Me-THF, 70 °C; c) LiOH, THF/MeOH/H_2O; d) Allyl alcohol, DPPA, Et_3N, PhMe, RT to 80 °C; e) pyrrolidine, $Pd(PPh_3)_4$, DCM.

5. Cyclization substrate synthesis. A major advantage of the oxidative cyclization approach is the relative ease with which the requisite 2,2'-ethylenedianilines can be accessed. To this end, we developed a Sonogashira coupling strategy, which is exemplified in Scheme 6. Several combinations of alkynes and aryl halides are possible, pending on the nature of the coupling partners and their oxidation states.

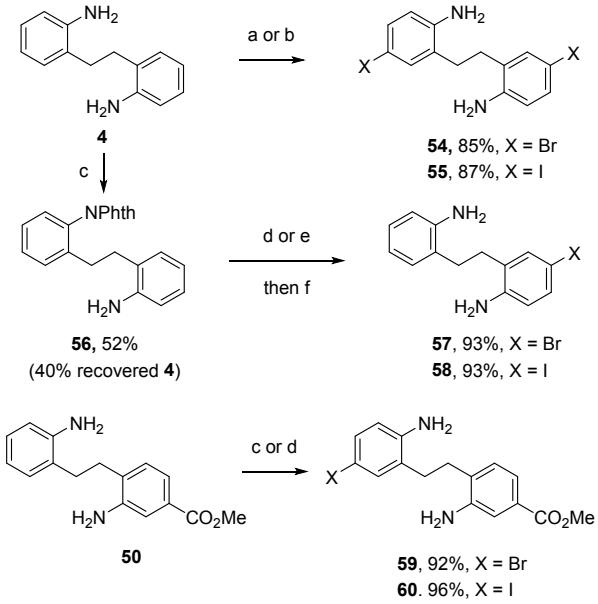
Scheme 6. Example 2,2'-ethylenedianiline syntheses by Sonogashira coupling/hydrogenation



a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, RT; then TMS-acetylene; b) H_2, Pd/C, MeOH/DCM.

The first and most useful variant is based on the coupling of a 2-aminophenylacetylene with 2-iodonitrobenzene, as depicted for dianiline **47**. The second route proceeds through the coupling of a 2-nitrophenylacetylene with a 2-iodonitrobenzene, which is exemplified for compound **50**. In some cases, however, considerable decomposition of the 2-nitrophenylacetylenes was observed under the conditions of the Sonogashira coupling.[14] The third route involved the coupling of a 2-amino-phenylacetylene with a 2-iodoaniline as shown for dianiline **53**. This route is less general, as 2,2'-diamino-diphenylacetylenes tend to undergo cyclization to indoles.[15] Regarding the hydrogenation of the diarylacetylenes, we found that substrates must not contain any contaminants remaining from the Sonogashira reaction. Otherwise, we observed significant catalyst poisoning resulting in unreasonably high catalyst loading. Since our cross-coupling approach involves a hydrogenation step that is not compatible with aryl halides, we prepared several halo-substituted dianilines via electrophilic aromatic substitution (Scheme 7).

Scheme 7. Halogenation of 2,2'-ethylenedianilines



a) NBS (2 eq.), DMSO; b) NIS (2 eq.), DMSO; c) phthalic anhydride, BSA, PhMe, reflux; d) NBS (1 eq.), DMSO; e) NIS (1 eq.), DMSO; f) N_2H_4·H_2O, THF, reflux.

While the synthesis of the precursors leading to the symmetrical *para*-dihalogenated compounds **54** and **55** was straightforward, access to precursors of monohalo diazocines was more difficult. We initially used an unselective, statistical halogenation followed by purification via chromatography and precipitation. However, to avoid the tedious separation of mono- and dihalogenation products, as well as unreacted substrate, we developed a more scalable and practical sequence. Desymmetrization of the commercially available dianiline **4** by protection of one amino group as the phthalimide, followed by highly selective halogenation of phthalimide

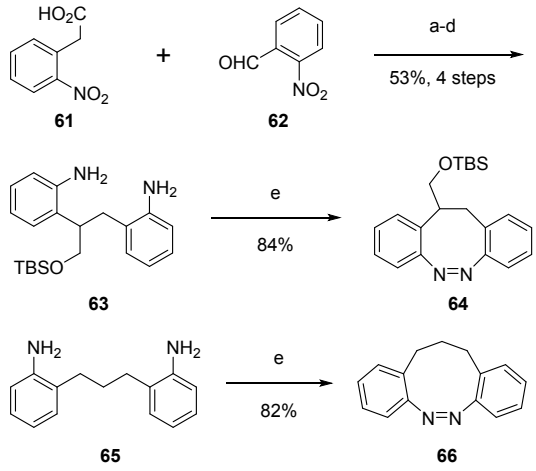
56 and deprotection allowed to access the desired products **57** and **58** without any chromatographic purification. Selective halogenation could also be achieved by exploiting electronic differences in substituted dianilines. We tested this on ester **50**, which afforded the halogenation products **59** and **60** in high yield and without any undesired isomers.

6. New Cyclic Azobenzenes. Cyclic azobenzenes may not only be substituted on their arene moieties but also on their central ring.[7f,8b] Indeed, several hetero-diazocines have recently emerged.[9] Confident in our new methodology, we have begun to explore cyclic azobenzenes with substitutions on the central bridge and with an increased ring size (Scheme 8).

Condensation[16] of aldehyde **62** with acid **61**, followed by carboxylic acid reduction, TBS-protection and hydrogenation afforded cyclization precursor **63** in 53% yield over four steps. The oxidative cyclization of the dianiline **63** to diazocine **64** proceeded in 84% yield, which is virtually the same efficiency as for the unsubstituted parent system. The dianiline **65**[17] could be cyclized equally well to diazonine **66**, affording the first cyclic azobenzene that features a propylene bridge in the central ring.

Both syntheses of dianilines **63** and **65** can in principle be adapted to allow access to symmetric and non-symmetric substitution on the aromatic rings as well as to the halogenation strategy that we described in the previous section. Thus, the syntheses of diazocine **64** and diazonine **66** may be used as blueprints for new types of azobenzenes with interesting photophysical and pharmacological features.

Scheme 8. Synthesis of new cyclic azobenzenes



a) Ac_2O, Et_3N, neat, 50 °C; b) EtOCOCl, Et_3N, THF then $NaHB_4$, H_2O; c) TBSOTf, 2,6-lutidine, DCM; d) H_2, Pd/C, MeOH/DCM; e) *m*CPBA in AcOH (2 eq, slow addition), AcOH/DCM = 1/3.

7. UV-Vis Spectroscopic Characterization. With more than forty cyclic azobenzenes in hand, we turned towards their photophysical characterization in order to gain insight into the effects of substituents and backbone-modifications on UV-Vis spectra and photoswitching behavior. To determine the optimal wavelength (λ_{opt}) for a high (*Z*)/(*E*) ratio, we illuminated a 50 μM DMSO solution of each compound for 10 minutes in 20 nm increments from 540 nm to 360 nm and measured the resulting absorption spectra (Figures S4 to S8).

For all diazocines, the lowest energy absorption was not significantly affected by substitution and typically centered around 400 nm for the (*Z*) isomer and around 490 nm for the (*E*) isomer. Like the parent compound **2**, the majority of the diazocines can be isomerized most efficiently to their thermodynamically less stable (*E*) form with 400 nm light (Tables 4 and S1). A slightly longer wavelength of 420 nm or even 440 nm was required in the case of several electron-rich diazocines. The backbone-substituted compound **64** also did not show special features compared to the parent system **2**.

Finally, we also investigated the spectra and switching of the nine-membered diazonine **66**. Analogously to the eight-membered system, it could be isomerized to the (*E*) isomer with 400 nm irradiation and back to the (*Z*) isomer using 520 nm light. Interestingly, compared to the (*E*) isomer of diazocine **2** the spectrum of the (*E*) isomer of diazonine **66** exhibits a notably higher absorbance for the band corresponding to the ππ*-transition, which also is found at a longer wavelength of 316 nm. Therefore, the spectrum of (*E*) diazonine resembles that of a regular (*E*) azobenzene, while the (*Z*) diazonine spectrum is similar to (*Z*) diazocine (Figure 1 and Table S3).

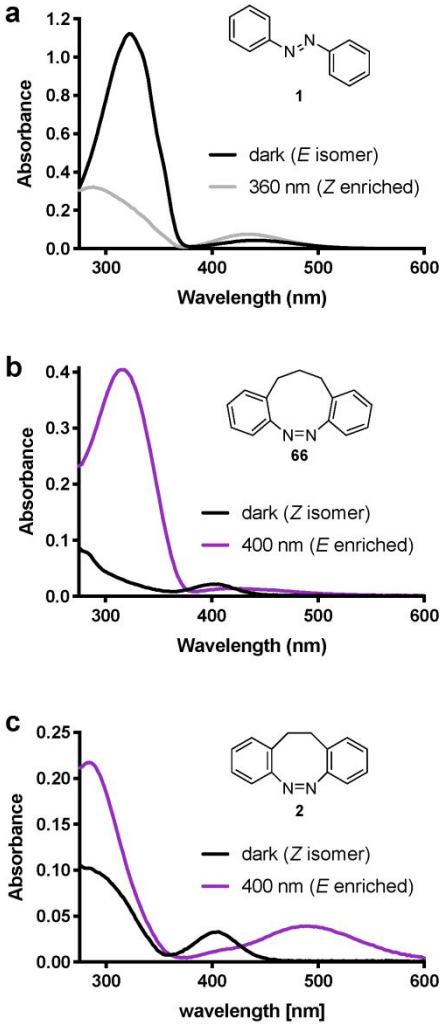
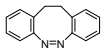
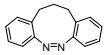
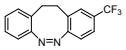
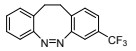
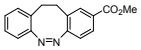
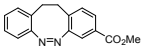
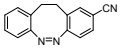
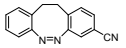
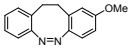
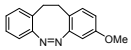
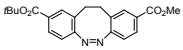
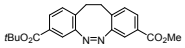
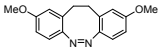
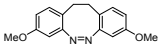
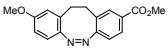
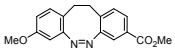
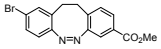
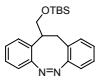


Figure 1. Comparison of UV-Vis spectra of a) azobenzene **1** b) diazonine **66** and c) diazocine **2** in the dark and under illumination. All spectra in DMSO, 50 μM.

Table 4. Photophysical properties of selected cyclic azobenzenes

Compound		λ_{opt}[a]	$T_{1/2}$	PSS (Z/E)[b]	Compound		λ_{opt}[a]	$T_{1/2}$	PSS (Z/E)[b]
	**2**	400 nm	9.4 h	12/88[c]		**66**	400 nm	n.d.[e]	14/86[c]
	**23**	400 nm	51 min	12/88[c]		**13**	400 nm	4.3 h	14/86[c]
	**24**	400 nm	14 min	14/86[c]		**14**	380 nm	6.7 h	14/86[c]
	**25**	400 nm	6 min	15/85[c]		**15**	400 nm	3.3 h	14/86[c]
	**26**	420 nm	3.0 h	33/67[c]		**16**	420 nm	10.4 h	45/55[d]
	**31**	400 nm	24 min	14/86[c]		**32**	400 nm	6.0 h	15/85[c]
	**33**	420 nm	3.5 h	32/68[c]		**34**	420 nm	11.2 h	55/45[d]
	**35**	420 nm	2.2 min	55/45[c]		**36**	420 nm	7.5 h	52/48[d]
	**40**	400 nm	4.7 h	14/86[c]		**64**	400 nm	14.2h	19/81[c]

[a]For (Z) to (E) switching, determined by UV-Vis spectroscopy. [b]For (Z) to (E) switching, determined by ^{1}H-NMR spectroscopy in DMSO-d_6. [c]390 nm. [d]415 nm. [e]Not determined, no measurable isomerization within two weeks.

The comparatively small effect of substituents on the lowest energy absorption band of diazocines are not surprising since it results from a nπ*-excitation.[23] A stronger effect was observed for the next absorption band at shorter wavelengths, which corresponds to a ππ*-transition. This band was notably red-shifted for diazocines carrying electron-donating substituents (e.g. compounds **16** and **26**) or with a push-pull substitution. Increased overlap of the bands corresponding to ππ*-transitions of the (E) forms with the nπ*-transitions of the (Z) forms might be contributing to the poorer switching behavior observed for these diazocines (see PSS investigation by NMR spectroscopy below).

8. Thermal Relaxation. In respect to thermal relaxation, we observed broad variability (Tables 4 and S1) with trends similar to regular azobenzenes. Thermal relaxation was monitored in 50 µM DMSO solution at 25 °C over a period of 24 hours. Reduced half-lives for the (E) isomer were observed with electron-withdrawing groups in *meta*-position as well as both electron-withdrawing and electron donating groups in *para*-position. Strong electron withdrawing groups and push-pull substitution in *para*-position resulted in rapidly relaxing photoswitches. When comparing the effect of a substituent in *meta*-position to the same substituent in *para*-position, we found that *para*-substituted compounds were generally more affected than their *meta*-substituted counterparts. To determine the effect of water on the relaxation rates, we also investigated solutions in PBS/DMSO mixtures for three selected compounds (see Table S2). Surprisingly, we observed up to two or three times longer half-lives upon increasing the fraction of the aqueous component in the solvent mixture.

None of the aromatic substitutions resulted in a major increase in relaxation times compared to the parent system **2**. However, improved bistability could be achieved by changes in the central ring system. An increased thermal stability of the (E) form was observed for the ethylene-bridge substituted diazocine **64**. For diazonine **66** no relaxation could be observed at room temperature after enrichment of the (E) isomer by both UV-Vis (40 hours) as well as NMR measurements (two weeks). Still, diazonine **66** did fully relax to the (Z) isomer upon prolonged storage in the solid state in the dark. The high bistability of diazonine **66** is expected to be connected to the low energy difference between (E) and (Z) isomer, which is a consequence of the longer three carbon bridge ($\Delta G_{Z\rightarrow E}$ = 10.6 kJ/mol in the gas phase and 17.4 kJ/mol in DMSO, see Tables S14 and S15).

9. PSS investigation by NMR spectroscopy. Having determined the best switching wavelengths and relaxation times, we turned towards determination of the PSS compositions (Tables 4 and S1, Figure S3). We chose to determine the PSS as (Z)/(E) ratio observed with one pulse ^{1}H-NMR spectroscopy measurements of 10 mM solutions in DMSO-d_6. The samples were first measured before illumination, then after 30 seconds of illumination with a 390 nm high-power LED and after successive 30 seconds of illumination with a 520 nm high-power LED (Prizmatix). We additionally tested the (Z) to (E) isomerization with a 460 nm high-power LED and a 415 nm Mic-LED (Prizmatix) for the compounds where we had either determined an optimal switching wavelength higher than 400 nm in our UV-Vis experiments or where we observed poor (Z)/(E) ratios (>20/80) after 390 nm illumination.

Despite handling the samples without precautions to avoid exposure to ambient light, most samples contained no detectable (E) isomer and all diazocines showed an initial (Z)/(E) ratio of at least 97/3. For the (Z) to (E) isomerization upon irradiation with violet/blue light, we observed distinct differences between individual groups of diazocines. With the majority of the compounds, we were able to establish a PSS between 12/88 and 19/81. This included compounds with electron-withdrawing

substituents, backbone-substitution, some electron-donating substituents and weakly interacting substituents, such as alkyl or halogen, which all showed excellent PSS. However, methoxy and most amino substituents lowered the (*E*) isomer fraction and more of the (*Z*) isomer remained. Furthermore, the push-pull combination of methoxy and methyl ester led to a drastic PSS deterioration, regardless of their position on the ring.

The photoisomerization from the (*E*) to the (*Z*) form was found to be highly effective for all diazocines. In all cases illumination with 520 nm led to quantitative isomerization to the thermodynamically favored (*Z*) form. This is an important distinction from regular azobenzenes. In summary, all tested diazocines can be reversibly isomerized with visible light.

For diazonine **66** we observed no (*E*) isomer before illumination and a PSS of 14/86 after illumination with 390 nm light. While this result for the (*Z*) to (*E*) isomerization was virtually identical to the unsubstituted diazocine **2**, a non-quantitative conversion was observed for the (*E*) to (*Z*) photoisomerization of diazonine **66** and only a (*Z*)/(*E*) ratio of 89/11 could be achieved with 520 nm light. Still, the value for the photoisomerization to the thermodynamically preferred form is better for diazonine **66** than for azobenzene **1**, which exhibited at best a PSS of 83/17 for (*Z*) to (*E*) isomerization in DMSO (Table S4).

Finally, it is important to mention that we had to reduce the concentration of azobenzene **1** for our NMR experiments from 10 mM to 1 mM, as we had observed a very low (*E*) to (*Z*) conversion at 10 mM. Probably this issue results from incomplete sample penetration during irradiation due to complete absorption of light. This issue is alleviated by the lower extinction coefficients of diazocine and diazonine. Thus, at least at the present concentrations, both diazocines and the diazonine allow for a more rapid and efficient establishment of the PSS than regular azobenzenes.

Conclusion

The broad implementation of diazocines as photoswitches with useful new functional properties has been limited by their poor synthetic accessibility. With this work, we have shown that the oxidative cyclization of dianilines can largely overcome this limitation. In combination with a modular cross coupling approach to furnish the cyclization substrates, as well as late stage functionalization, the oxidative protocol gives access to a wide variety of diazocines that are substituted on one or both aromatic rings. Additionally, we were able to prepare a diazonine with a nine-membered ring and a diazocine substituted on the ethylene bridge, which we consider the vanguard of new types of photoswitches.

Furthermore, we have compared the photophysical properties and thermal relaxation data of diazocines. This allowed us to identify substitution patterns that are tolerated without affecting the useful photoswitch characteristics of the parent system as well as the patterns that should be avoided due to their detrimental effects. Based on our results, it is also possible to tune the thermal relaxation of diazocines over a broad range. This knowledge will facilitate the choice of diazocines in a variety of applications.

ASSOCIATED CONTENT

Supporting Information.
Synthetic procedures and characterization data; Photophysical characterization; Optimization of reaction conditions; Synthetic recommendations; Computational data; X-ray crystallographic data for **38**.
"This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DCM, dichloromethane; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; *m*CPBA, *meta*-chloroperoxybenzoic acid; MMPP, magnesium monoperoxyphthalate; TBAF, tetra-*N*-butylammonium fluoride; NIS, *N*-iodosuccinimide; NBS, *N*-bromosuccinimide; TFA, trifluoroacetic acid; BSA, Bis(trimethylsilyl)acetamide; Boc, *tert*-butyloxycarbonyl; TBS, *tert*-butyldimethylsilyl; Alloc , allyloxycarbonyl; EWG, electron-donating group; EDG, electron-withdrawing group;

PSS, photostationary state; UV, ultraviolet; Vis, visible; NMR, nuclear magnetic resonance; PBS phosphate-buffered saline; LED, light-emitting diode.

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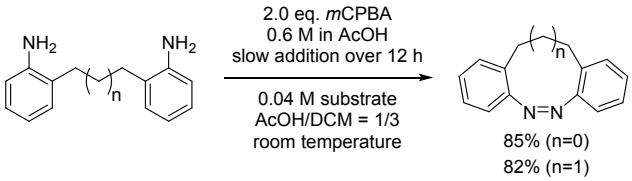
NH2
NH2
n
2.0 eq. mCPBA
0.6 M in AcOH
slow addition over 12 h
0.04 M substrate
AcOH/DCM = 1/3
room temperature
n
N=N

85% (n=0)
82% (n=1)