Azobenzenes Hot Paper

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Direct and Versatile Synthesis of Red-Shifted Azobenzenes

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Abstract: *A straightforward synthesis of azobenzenes with bathochromically-shifted absorption bands is presented. It employs an ortho-lithiation of aromatic substrates, followed by a coupling reaction with aryldiazonium salts. The products are obtained with good to excellent yields after simple purification. Moreover, with the presented methodology, a structurally diverse panel of different azobenzenes, including unsymmetric tetra-ortho-substituted ones, can be readily obtained, which paves the way for future development of red-light-addressable azobenzene derivatives for in vivo application.*

Selective, non-invasive, external control of function is a long-standing challenge in both biological and material sciences.[1–4] Light offers exciting solutions for such control, because of the high spatiotemporal resolution of its delivery and ease of application.[5] To realize light-responsive systems at the molecular level, photoswitchable compounds are utilized that show a distinctive change in their properties upon irradiation.[1] Interesting applications of molecular switches for chemical biology were showcased in protein/peptide control[6–8] and photopharmacology,[9,10] allowing the control of drug activity in cancer chemotherapy,[11,12] neurology,[13] and antibiotic treatment,[14] amongst others. To achieve effective and reversible control upon irradiation, azobenzene-based molecular photoswitches[1–3,5,7,10,12,15,16] have been extensively used because of their large change in geometry and dipole moment upon photo-isomerization from the *trans* to the *cis* isomer (Figure 1 A). Traditionally, this *trans–cis* isomerization is achieved with UV-light irradiation, whereas the reverse *cis–trans* isomerization can be evoked by either thermal relaxation or visible-light irradiation.

The recent discovery and application of visible and red-light-switchable azobenzene molecules[4,17–19] are expected to initiate major breakthroughs in photoresponsive biosystems, photopharmacology, and material sciences. The advantages of using visible light over UV light for photoswitching include an increased tissue-penetration depth and reduced phototoxicity.[20] Therefore, the development of bathochromically shifted azobenzenes is key to obtain online, highly precise control of biological systems with light. The design of red-shifted azobenzene derivatives is mainly based on tetra-*ortho*-fluoroazobenzenes, introduced by Hecht and co-workers,[17,21] tetra-*ortho*-methoxyazobenzenes, and tetra-*ortho*-chloroazobenzenes, pioneered by Woolley and co-workers.[15,22–25] So far, their widespread use has been limited by the laborious syntheses of these sterically encumbered azobenzenes. Especially, extensive work-up procedures are required, which, together with the low to moderate yields, hamper ready access to a variety of switches and their application.

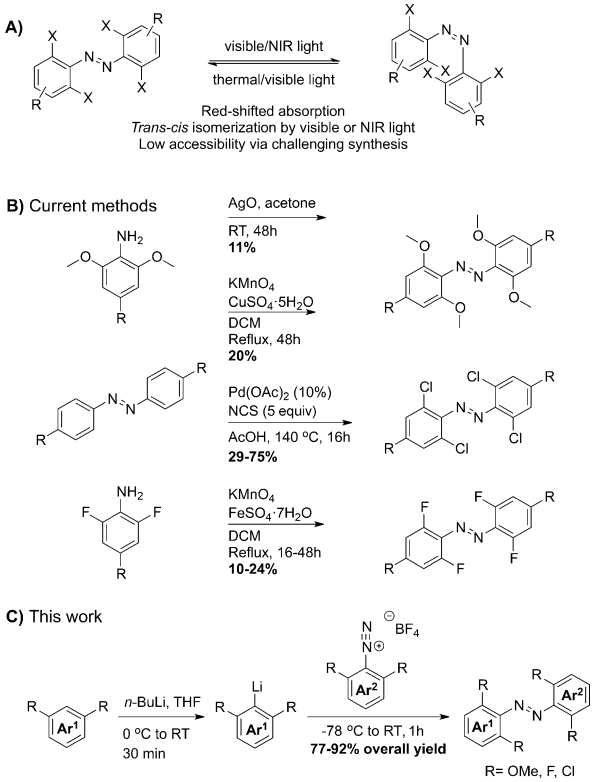

Figure 1. Red-light switchable azobenzenes. A) *trans-cis* isomerization of tetra-*ortho*-substituted azobenzenes. B) Published synthetic methods towards tetra-*ortho*-substituted azobenzenes.[15,21,23,26] C) This work.

The commonly employed diazonium coupling[16] or Mills reaction[16] often prove unsatisfying for the synthesis of symmetrical tetra-*ortho*-methoxyazobenzenes[23] (Figure 1 B). Tetra-*ortho*-chloroazobenzenes were synthesized via similar coupling reactions. An elegant alternative was recently introduced by the Trauner group, using C–H activation of *ortho* positions, to synthesize tetra-*ortho*-chloro-azobenzenes (see Figure 1 B).[26] For the synthesis of symmetrical tetra-*ortho*-fluoro-azobenzenes (Figure 1 B), an optimized Mills reaction or oxidative coupling has been used in the past,

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which gives the desired products, albeit in low to moderate yields.[21,27] Therefore, major improvements are urgently required to stimulate simple, future application of red-shifted, azobenzene derivatives in chemical biology and medicine. Moreover, the synthesis of red-shifted unsymmetric azobenzenes ($Ar^1 \neq Ar^2$, Figure 1C) is needed to enable selective functionalization and fine-tuning of optical properties.

Herein, we report a versatile, direct synthesis of a multitude of structurally diverse, visible- and red-light-switchable azobenzenes using directed *ortho*-lithiation of aromatic precursors, followed by their reaction with aryldiazonium salts. The azobenzenes are obtained in short time (< 3 h) with good to excellent yields, following straightforward purification methods.

We focused our attention on a simple and efficient method for the preparation of sterically encumbered, tetra-*ortho*-substituted azobenzenes, taking advantage of coupling reactions with organolithium reagents. These coupling reactions have seen increased interest in the past years,[28,29] and were recently shown to be particularly suited for congested systems.[28] 1,3-Disubstituted aromatic compounds, bearing methoxy, fluoro or chloro substituents were identified as potential substrates, since they can undergo facile *ortho*-lithiation.[30–32] We anticipated that the resulting 2,6-disubstituted lithium species could be used as nucleophiles in the direct reaction with 2,6-disubstituted aryldiazonium salts, yielding highly substituted azobenzenes. Early literature on the reaction of Grignard and organozinc reagents[33–35] with aryldiazoniums salts, despite receiving little attention, indicated that the use of organolithium reagents might be a feasible approach towards the synthesis of hindered, red-shifted azobenzenes. This notion was further supported by two known examples of related procedures, in which lithiated species react with diazonium salts to provide heterocyclic azobenzene derivatives, as shown by Herges and co-workers,[36] and in the preparation of two azobenzene intermediates as part of a procedure for the synthesis of 1-iodo-2,6-bispropylthiobenzenes, as reported by Kaszynski and co-workers.[37] Since the *ortho*-lithiation procedure is known to have a broad substrate tolerance,[30] and the preparation of aryldiazonium tetrafluoroborate salts is well established,[38] we expected that our methodology might yield interesting novel azobenzene structures with potentially bathochromically shifted absorption spectra.

In the initial investigations, we focused on the synthesis of tetra-*ortho*-methoxyazobenzene (Figure 1C, R = OMe). The synthesis of this compound requires the *ortho*-lithiation of 1,3-dimethoxybenzene (Figure 2, **1a**), followed by reaction of the formed metallo-organic species with 2,6-dimethoxybenzenediazonium tetrafluoroborate **2a**. We used a slight excess of aryldiazonium salt, inspired by the well-known reaction of aryldiazoniums with phenolates.[16] Treating compound **2a** (1.2 equiv) with 1 equiv of the metallated 1,3-dimethoxybenzene, produced the desired product **3a** in 71% isolated yield after 90 minutes total reaction time, requiring only simple purification (extraction followed by precipitation). Further optimization of the procedure was performed using, among others, additional equivalents of aryldiazonium salt (**2a**) for the coupling reaction, showing that an excess of the salt was tolerated but did not improve the yield, mainly due to increasing amounts of side-products (see Table S2 in the Supporting Information). Excess of *n*-butyllithium was tolerated in the *ortho*-lithiation, however, in the subsequent reaction with the aryldiazonium salt, the liberation of N_2 was observed leading to a significant drop in isolated yield (see Table S2). Therefore, equimolar amounts of the lithiation precursor, *n*-butyllithium and aryldiazonium salt are used throughout, yielding tetra-*ortho*-methoxyazobenzene **3a** in 86% isolated yield.

After establishing the optimized conditions, we studied the scope of the reaction by diversifying both the substrate for lithiation and the aryldiazonium salt. As shown in Figure 2, a multitude of diazonium salts could be efficiently coupled to 1,3-dimethoxybenzene **1a** in good to excellent yields. Moreover, both cyano-substituted (**2d**) and nitro-substituted (**2e**) aryldiazonium salts were well tolerated, which are potential precursors for *para*-aminomethylene- and *para*-amino-azobenzene derivatives. Both *tert*-butoxy-carbonyl- (**2f**) and chloro-substituted (**2g**) aryldiazoniums were converted with satisfying yields, with the potential for subsequent functionalization of the products using amide formation and cross-coupling reactions. Successful preparation of compounds **3d**–**3g** highlights the functional group tolerance, which is of particular importance for the application of our method to the synthesis of photoresponsive materials and drugs. The azobenzene derivatives were purified using either extraction/washing or short flash chromatography allowing the rapid syntheses (2–3 h total time) of these functionalized photoswitches.

Inspired by earlier reports by Woolley and co-workers,[4,24] we aimed next at installing additional methoxy substituents to obtain more bathochromically shifted absorption bands of the azobenzenes. Therefore, the scope of the lithiation and subsequent coupling was tested with different methoxy-substituted benzene derivatives. 1,3,5-Trimethoxybenzene **1b** could be readily lithiated and reacted with aryldiazonium salts to give moderate to excellent yields (41–86%). Moreover, lithiation of 1,3,4-trimethoxybenzene **1c** selectively at the 2-position led, after quenching with the different aryldiazonium salts, to novel azobenzenes (**3k**–**m**) in good yields (58–76%).

Subsequently, we attempted the synthesis of *ortho*-fluoroazobenzenes, because of their promising photochemical properties, as reported by Hecht and co-workers.[21] In line with earlier reports,[39] difluorobenzene **1d** underwent a regioselective lithiation at the 2-position, due to the coordinating potential of the two fluoro-substituents to lithium. Using our method, **3n** was synthesized in high yield (82%) and short reaction times (< 2 h). Moreover, tetra-*ortho*-fluoroazobenzene **3o** was synthesized starting from difluorobenzene **1d** and difluoro-substituted aryldiazonium salt **2h** yielding the product in excellent yield (77% after 2 h) without the need for laborious purification. However, it has to be noted that lower temperatures (up to −50 °C) were required for the lithiation of **1d** to prevent the formation of benzyne.[39]

Due to the recent application of red-shifted tetra-*ortho*-chloro-derivatives,[23,25,26] we applied our method to synthesize these azobenzenes. Lithiation of dichlorobenzene **1e** at

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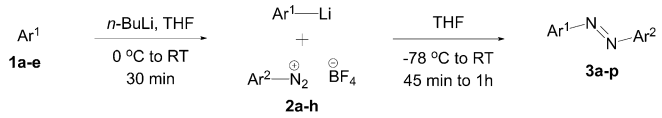

Entry	Ar¹	Ar²—N₂ BF₄	Ar¹—N=N—Ar²	Isolated yield
1	1a	2a	3a	86%
2	1a	2b	3b	59%
3	1a	2c	3c	91%
4	1a	2d	3d	81%
5	1a	2e	3e	67%
6	1a	2f	3f	45%
7	1a	2g	3g	77%
8	1b	2a	3h	81%
9	1b	2b	3i	41%
10	1b	2c	3j	86%
11	1c	2a	3k	76%
12	1c	2b	3l	58%
13	1c	2c	3m	64%
14	1d	2a	3n	82%
15	1d	2h	3o	77%
16	1e	2a	3p	91%
17	1e	2i	3q	92%
18	1e	2h	3r	89%

Figure 2. Scope of the presented one-pot reaction sequence, showing a diversity of tolerated aryl (**1**) and aryldiazonium (**2**) substrates for the synthesis of sterically demanding azobenzenes (**3**).

−78 °C and subsequent addition of a suspension of diazonium salt (**2a, 2h, 2i**) in THF, to this organo-lithium intermediate, gave the desired tetra-*ortho*-chloroazobenzes **3p–r** in excellent yields (89–92%). We could apply short reaction times (< 2 h), using milder conditions then those reported earlier (Figure 1B).

To allow the straightforward functionalization of these bathochromically-shifted azobenzene derivatives, we aimed at diversifying the functional group scope beyond chloro, nitro, ester and cyano substituents. For the direct Suzuki–Miyaura coupling, we decided to use boronic ester-substituted aryldiazonium salt **2j** (Figure 3), which gave the boronic ester substituted azobenzene with moderate yield. However, purification of the product proved challenging. Thus we performed a direct Suzuki–Miyaura cross-coupling, using standard conditions (see Figure 3), without the need for intermediate purification. With this three-step, one-pot method, involving three distinctly substituted arenes, we obtained compound **3s** in 41% yield. This showcases the versatility of our approach towards functionalized *ortho*-substituted azobenzene derivatives.

Importantly, most of the azobenzene derivatives reported here are novel members of a class of privileged *ortho*-substituted photochromic compounds (for full photochemical characterization and comparison of compounds **3a**,**h**,**k**,**o**, and **q**, see Supporting Information). The overlay of their spectra (Figure 4B and S1) highlights the potential of using our method to fine-tune the photochemical properties of this

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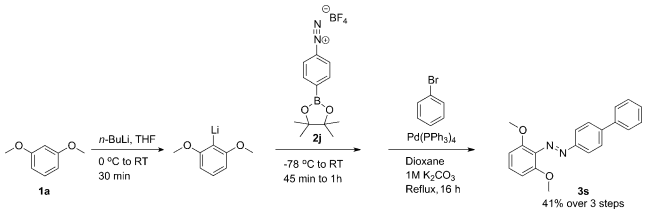

Figure 3. Sequential three-step one-pot procedure highlighting the versatility of the azobenzene formation with well-established cross-coupling methodology.

important class of photochromes. Interestingly, upon changing the substitution pattern from **2a** to **2b**, a hypsochromic shift was observed for the π-π* transition of **3b** whereas the n-π* transition was bathochromically shifted (extended absorption up to 600 nm, see Figure 4A). Upon changing the substitution pattern as shown in **3c**, an opposite shift was observed for both transitions. This trend, bathochromic versus hypsochromic shift, was observed irrespective of the substitution pattern on Ar[1] (**3h**–**m**, see Figures S17, S18).

Encouraged by recent reports of Woolley and co-workers, which showed the ability of *para*-amino-substituted tetra-*ortho*-methoxyazobenzene derivatives to form azonium ions at low pH,[22,24] with absorption bands shifted into the near-IR region of the spectrum,[24] we performed titration experiments on selected new azobenzenes. In these experiments, the effect of substituents on the pH dependence of the formation of azonium ions and their distinctive photochemical properties (Figure 4C) were studied. Azobenzene **3a** showed the formation of the corresponding azonium ion at pH 2. Compound **3h** (with an additional *para*-methoxy substituent) showed the formation of an azonium ion at pH 4, indicating a higher basicity due to the introduction of an electron-donating group at the *para*-position. However, the position of the emerging absorption band was similar as in **3a** (Figure 4C). Subsequently, compound **3i** was tested, which showed a similar basicity but increased bathochromic shift of the azonium ion absorption band, consistent with earlier observations by Woolley and co-workers.[24] Finally, azobenzene derivative **3j** showed the formation of an azonium ion at pH 3, and a bathochromic shift of the emerging band which was again similar to those of the azonium ions derived from **3a** and **3h**.

In conclusion, we have developed a highly versatile methodology to prepare bathochromically-shifted azobenzenes via regioselective *ortho*-lithiation followed by reaction with aryldiazonium salts. This method allows the fast synthesis (< 3 h) of a wide variety of novel azobenzene derivatives, including symmetric and unsymmetric ones, with good to excellent isolated yields (up to 92%). The generality of this method has been demonstrated through the coupling of a wide variety of lithiation substrates and aryldiazonium partners. Rapid access to a variety of red-shifted azobenzenes paves the way for future in vivo application of these photoresponsive molecules and for a deeper understanding of the relationship between their substitution pattern and photochemical properties (Figure 4).

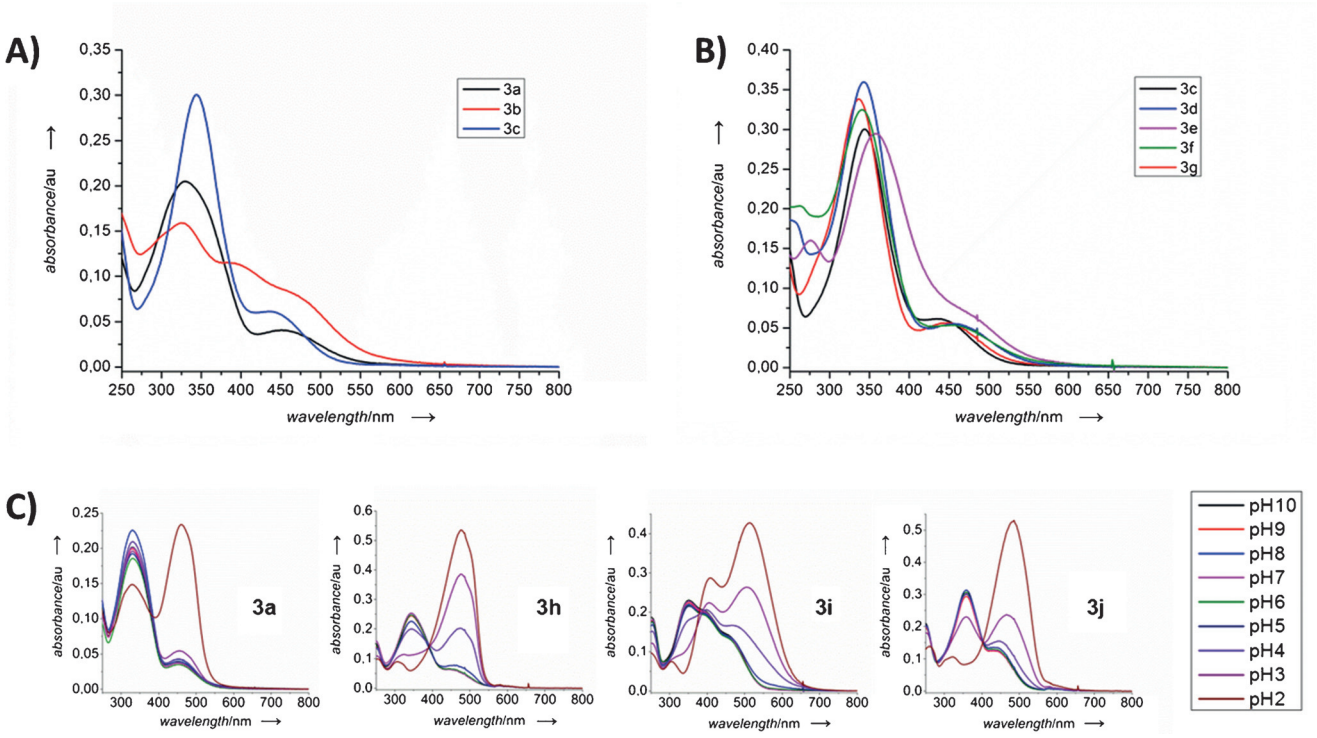

Figure 4. Absorption spectra of a variety of novel azobenzene derivatives. A,B) Spectra showing a structural survey of substitution on one side of the azobenzene ring. C) Titration curves showing the pH dependence for the formation of azonium ions and their respective red-shift.

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