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Syntheses of Novel Azobenzene and Stilbene Heterobifunctional Cores Modifiable by CuAAC, Cross-coupling and Alkylation Approaches

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Abstract

Azobenzenes are versatile molecules that have firstly been discovered as dyes and since found its way to various areas of modern life, ranging from food and textiles industry to the cutting-edge research in chemistry and medicine. Stilbenes, sharing the similar structure and isomerization behavior, are important moieties in medicinal and material chemistry. Since molecules of both classes are usually designed *ad hoc* for a specific purpose, studies related to syntheses of ready-to-go azobenzene and stilbene building blocks are scarce. In this article, we present a series of novel heterobifunctional cores possessing pairs of functional groups enabling stepwise or one-pot construction of molecules of interest using thoroughly studied methodologies of the CuAAC click chemistry, cross-coupling and alkylation. Developed synthetic strategies, being simple and tolerable to a wide range of functionalities, can be applied

to azobenzenes and stilbenes having auxiliary substituents and different substitution patterns.

Keywords

azobenzenes; stilbenes; click-chemistry; cross-coupling; alkylation

Introduction

Today, azobenzenes and stilbenes both sharing a similar structure of two phenolic moieties linked by a double bond fragment and ability to isomerize upon irradiation are ubiquitous molecules which have found applications in many fields of fundamental and applied chemistry [1,2].

Azobenzenes, apart from their traditional central role in dye industry, are widely used as a light-controllable moiety to tune properties of various materials ranging from biomacromolecules [3] to metal-organic frameworks [4] and real-time information transmitting substances [5]. In supramolecular chemistry, the ability of azobenzenes to change their spatial arrangement enabled their use as components of molecular switches [6]. Recently, azobenzenes have been applied as a trigger in biomedicine owing to their ability to be cleaved in cells and tissues under hypoxic conditions [7]. Examples of biomedical applications include hypoxia-disintegrable nanocarriers in tumor treatment [8] and FRET-based bioimaging systems [9], while recent development of visible and near-infrared absorbing azobenzenes facilitate and stimulate further research in this field [10]. In turn, stilbenes are used in various materials and devices utilizing their photochemical properties [2], for instance, lasers [11] and organic optical materials [12]. Another important field where stilbene-based compounds are applied is medicinal chemistry. Such molecules are abundant in nature

and thus have long since become an object of interest to medicinal research and industry leading to a wide range of biological activities found for them, including anti-inflammatory, anti-cancer, antiviral, antioxidant and neuroprotective effects [13,14].

Over the years, a plethora of methods for the synthesis of both azobenzenes [15,16] and stilbenes [17] have been developed. Still, many of them feature reaction conditions incompatible with certain functional groups, so a unique synthetic strategy is commonly developed for each targeted compound, often necessitating a number of steps post the synthesis of the core to obtain the desired structure. Apart from the need to elaborate an appropriate synthetic pathway, such approach inevitably leads to its increased complexity and reduced overall yield. The development of azobenzene and stilbene building blocks, possessing auxiliary functional groups which can be easily and, ideally, orthogonally modified to achieve the desired structure and attach required fragments to the photo-sensitive core, seems a reasonable alternative to help overcome the aforementioned difficulties.

Thinking of the reactions enabling a facile modification of the molecular structure and a straightforward linking of different moieties, the click reactions are the ones which first come to mind because their concept is literally about a fast and effective joining of chemical building blocks [18]. Of these reactions, copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), due to its robustness, insensitiveness, a great variety of available Cu(I)-source/ligand pairs and almost quantitative yields, is arguably the most popular and thus have found numerous applications to date [19,20]. Another rapidly expanding field, metal-catalyzed cross-coupling reactions, also became prominent as a tool for joining two different fragments [21]. More importantly, the required functional groups and catalysts used for most cross-couplings are different from those applied in CuAAC, so the construction of a core, orthogonally modifiable in these reactions is achievable in principle. Therefore, both these methods were taken in consideration in

the design of the structures. Lastly, the alkylation with alkyl halides via the nucleophilic substitution was chosen on a rationale of the following facts: this reaction, as most cross-couplings, needs a base allowing for a one-pot setup and also, under the appropriate conditions, should not compete with the other processes or harm functional groups required for them.

In this manuscript, we present a series of stilbenes and azobenzenes bearing pairs of different functional groups in 4,4'-positions, namely, azidomethyl/chloromethyl, iodo/ethynyl, iodo/bromomethyl and iodo/azidomethyl (Figure 1). Of these functionalities, halomethyl groups can be modified in the nucleophilic substitution and serve as a synthetic predecessor for azides, azidomethyl and ethynyl groups are modifiable in CuAAC, iodo and ethynyl groups can be used in cross-couplings. To demonstrate the possibilities of the novel heterofunctional cores, a series of model one-pot reactions have been successfully conducted, which have shown that such functionalities can be orthogonally modified enabling a facile synthetic pathway for new differently substituted azobenzenes and stilbenes or a linking of various valuable synthons with a photo-sensitive bridge using aforementioned robust methods.

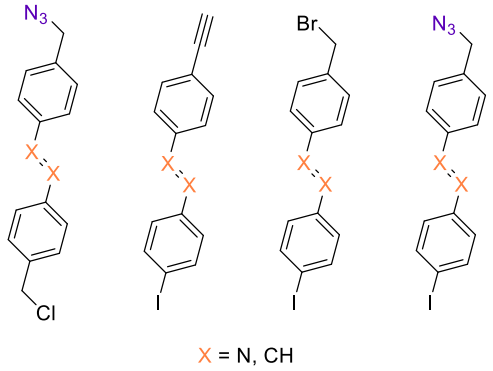
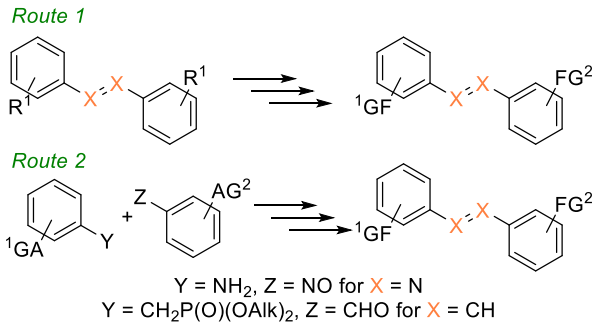


Figure 1: Targeted heterobifunctional azobenzenes and stilbenes.

Results and Discussion

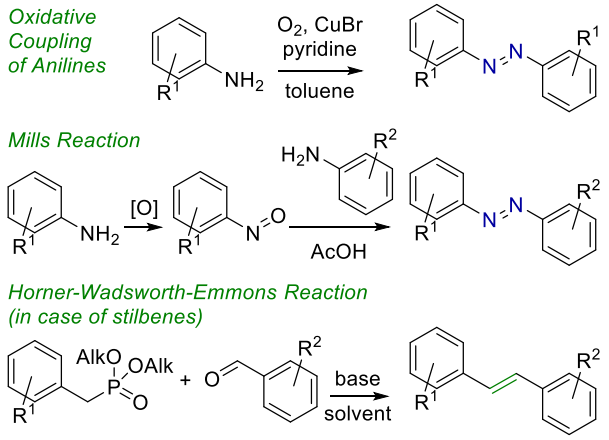
Introduction of two different functional groups on the opposing ends of the azobenzene/stilbene core can possibly be achieved by either of two approaches (Scheme 1): a selective modification of the symmetrical bifunctional molecule (**Route 1**) or a direct synthesis of the core from precursors, possessing required or readily modifiable to required functional groups (**Route 2**). When choosing between these two methods, one should take into consideration such factors as the availability of precursors, the reactivity of the required functional groups and expected synthetic difficulties, for instance, a low solubility and a close polarity of reactants and products. So, a short explanation of the choice of the strategy is presented for each of the discussed below cases.



Scheme 1: Possible routes for the synthesis of heterobifunctional azobenzenes and stilbenes. FG = required functional groups, AG = auxiliary groups, which are either required functional groups or the ones readily modifiable to them.

For the synthesis of stilbene cores, we have chosen the Horner-Wadsworth-Emmons (HWE) reaction, one of the classic methods of the alkene synthesis. This method has a thoroughly studied methodology and is particularly convenient because it offers a high stereoselectivity for (*E*)-alkene formation [22] while the precursors, i.e., aromatic phosphonates and aldehydes in case of stilbenes are readily available. In case of azobenzenes, when Route 1 was chosen, a catalytic oxidative coupling of anilines [23]

was used since it allowed us to achieve a starting symmetric core from one precursor in one step. For the synthesis of asymmetric starting azobenzenes via Route 2, we have selected the Mills reaction because it, unlike some other methods of the azobenzene synthesis, is not dependent on a substitution pattern of the precursors which are available from commercial sources or easily synthesized (Scheme 2).



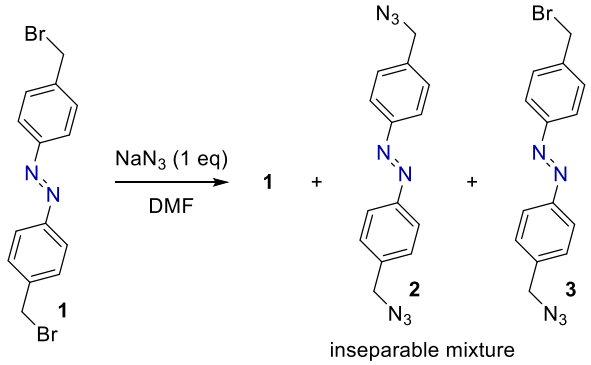
Scheme 2: Synthetic strategies used in this work for the synthesis of azobenzene and stilbene cores.

Syntheses of azobenzene and stilbene bearing a pair of azidomethyl and halomethyl groups

Since the targeted molecules have rather labile benzylic azido and halo groups, we decided not to use Route 2 because in case of stilbenes the conditions of the HWE reaction can prove to be too harsh and in case of azobenzenes both possible pairs of aniline and nitroso precursors are not easily available. Instead, Route 1 has been chosen and firstly we probed the most obvious way: a selective nucleophilic substitution of the bromo groups of the corresponding bis(bromides) with azide.

To this end, we firstly synthesized azobenzene bis(bromide) **1** according to published procedures from the *p*-toluidine upon its Cu-catalyzed oxidative coupling [23] followed by bromination of the methyl groups of the resulting azobenzene with *N*-

bromosuccinimide (NBS) [24]. Bis(bromide) **1** was then subjected to the nucleophilic substitution with an equimolar amount of the sodium azide (Scheme 3). To ensure a complete solubility of the starting bis(bromide), the reaction was carried out in DMF at 80 °C (the concentration of both reactants was $3.76 \cdot 10^{-2}$ M). The reaction was followed by ^{1}H NMR until no further changes in the spectra of the samples obtained after the separation of inorganics and the evaporation of the solvent were seen.



Scheme 3. Attempted synthesis of heterobifunctional azobenzene **3** via nucleophilic substitution of bis(bromide) **1** with azide.

The ^{1}H NMR spectrum of the reaction mixture (Figure 2a) as well as TLC analysis revealed that the reaction proceeded as expected affording starting azobenzene **1**, azobenzene bis(azide) **2** (obtained previously in our lab [25]) and targeted asymmetric azobenzene **3** in close to equal amounts (spectra of pure compounds **1** (Figure 2b) and **2** (Figure 2c) are shown for comparison). Unfortunately, all three compounds proved to be too close in polarity and had rather low solubility in common organic solvents, so we could not find the appropriate conditions for their separation by either column chromatography or crystallization.

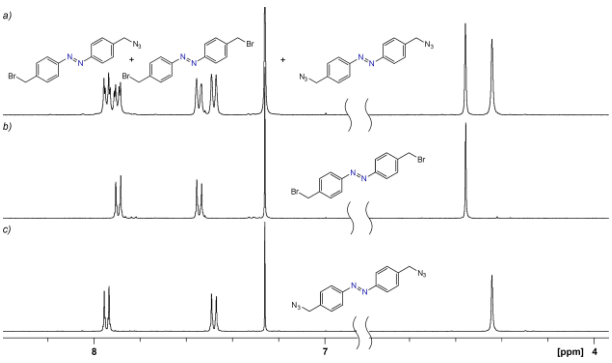
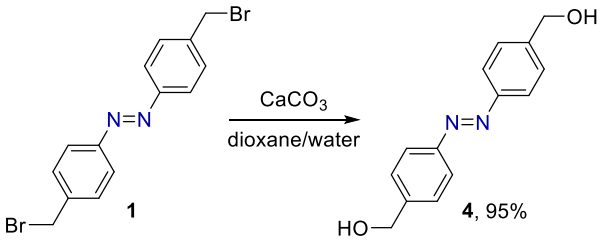


Figure 2: Fragments of ^{1}H NMR spectra of the sample obtained from the reaction of compound **1** with an equimolar amount of NaN_3 (a), bis(bromide) **1** (b) and bis(azide) **2** (c); 400 MHz, $CDCl_3$.

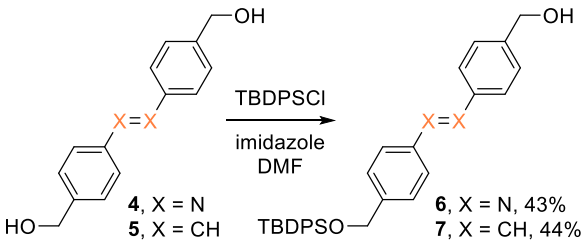
To avoid the aforementioned problems of close polarities and low solubilities, we decided to use the corresponding diols as the starting compounds and selectively functionalize them with the *tert*-butyldiphenylsilyl (TBDPS) protecting groups. Being bulky and non-polar, the TBDPS group could provide means to counteract both difficulties as it should have significantly increased the difference in polarity between all reaction participants while improving solubility of the products. For the implementation of this idea, the azobenzene diol **4** was obtained upon refluxing bis(bromide) **1** with $CaCO_3$ in a dioxane/water solvent mixture (Scheme 4). Stilbene diol **5** was prepared according to published procedure [26].



Scheme 4: Synthesis of azobenzene diol **4**.

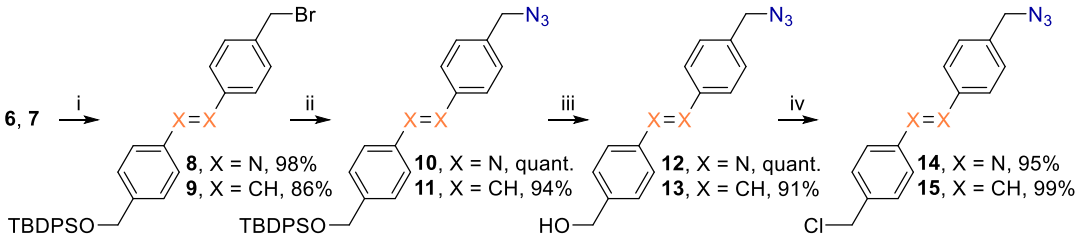
Next, diols **4**/**5** were treated with TBDPSCl under conditions that was previously used for the selective monosilylation of 4-hydroxymethylbenzyl alcohol (0.7 eq of TBDPSCl, 2.5 eq of imidazole as a base, DMF) [27]. The introduction of the TBDPS group indeed simplified the purification and upon chromatographic work-up (hexane/EtOAc) in both

cases we were able to isolate targeted monoprotected diols **6**/**7** in excellent yields (Scheme 5).



Scheme 5: Syntheses of monoprotected diols **6**/**7**. Yields are reported in relation to the respective diols.

The hydroxy groups of monosilylated esters **6**/**7** were then substituted for the bromo groups upon treatment with NBS in the presence of PPh_3 affording bromides **8**/**9**. Nucleophilic substitution of bromides **8**/**9** with sodium azide led to respective azides **10**/**11**, which were subjected to deprotection with TBAF yielding azobenzene **12** and stilbene **13**, both having one hydroxymethyl and one azidomethyl group. Lastly, targeted heterofunctional cores **14**/**15** were obtained, according to the method previously used for the preparation of benzyl chlorides [28], upon reacting alcohols **12**/**13** with thionyl chloride in the presence of catalytic amounts of DMF (Scheme 6).



Scheme 6: Syntheses of protected azides **14** and **15**: (i) NBS, PPh_3, THF, rt; (ii) NaN_3, acetone/H_2O, rt; (iii) TBAF, THF/H_2O, rt; (iv) $SOCl_2$, DMF, CH_2Cl_2, rt.

Syntheses of azobenzene and stilbene bearing a pair of iodo and ethynyl groups

In this case, the final functional groups, namely iodo and alkynyl, are stable enough, so that the precursors bearing them can be directly used in the Mills reaction as well as in the HWE reaction if the conditions are properly selected. At the same time, Route 1 in this case implies the selective Sonogashira coupling of the starting symmetric iodo-compounds with trimethylsilylacetylene (TMSA). This can be hampered by the same previously encountered difficulties of low solubility and close polarity of the resulting iodo/2-trimethylsilylethynyl and bis(2-trimethylsilylethynyl) products and starting diiodo compounds. Keeping these factors in mind, we decided to use Route 2 instead.

To obtain the targeted azobenzene, we started from *p*-iodoaniline, the Sonogashira coupling of which with TMSA afforded aniline **16** (Scheme 7). We then attempted the synthesis of *p*-iodonitrosobenzene **17** by oxidation of *p*-iodoaniline with Oxone according to the published procedure [29] but, unfortunately, in several test runs, complex mixtures of products were obtained with nitrosobenzene **17** not being the major component as was shown by the ^{1}H NMR spectra. So instead, the oxidation was conducted according to the procedure reported for the synthesis of 2-iodo-4-*tert*-butylnitrosobenzene [30] with H_2O_2 as the oxidant and Ph_2Se_2 as the catalyst. To ensure the optimal route was selected, we compared the product mixtures obtained after subjecting both *p*-iodoaniline and TMS-protected aniline **16** to oxidation by this system. In the ^{1}H NMR spectrum of the *p*-iodoaniline sample, there were two sets of signals corresponding to the targeted nitrosobenzene and 4,4'-diiodoazobenzene, with the former being the major component (Figure 3a). The formation of the azobenzene

but not the azoxybenzene admixture is worth noting because the oxidation of anilines to nitrosoarenes usually results in the latter as the minor by-products [31].

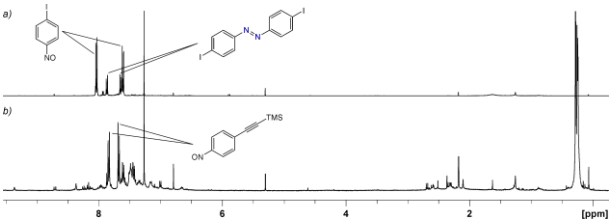
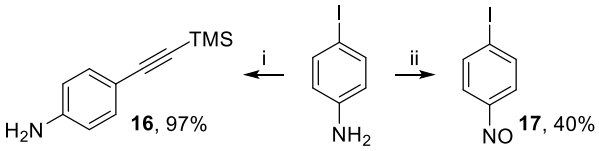


Figure 3: ^{1}H NMR spectra of samples obtained from the reaction mixtures of the H_2O_2/Ph_2Se_2-mediated oxidation of 4-iodoaniline (a) and 4-(2-trimethylsilyl)ethynylaniline **16** (b); 400 MHz, $CDCl_3$.

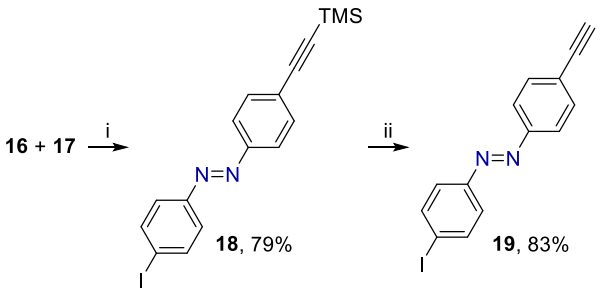
In turn, the ^{1}H NMR spectrum of the sample obtained from the protected aniline contained several sets of signals some of which were broadened (Figure 3b) probably indicating that trimethylsilyl group was also affected by oxidation. Thus, *p*-iodoaniline was selected for the oxidation reaction and in the preparative synthesis nitrosobenzene **17** was obtained in 40% yield after the work-up (Scheme 7).



Scheme 7: Syntheses of protected aniline **16** and nitrosobenzene **17**: (i) TMSA, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, 70 °C; (ii) H_2O_2, Ph_2Se_2, CH_2Cl_2, rt.

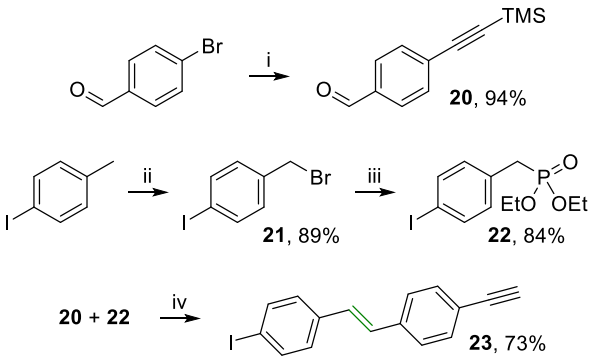
The Mills reaction between aniline **16** and nitrosobenzene **17** according to reported procedure successfully afforded asymmetric azobenzene **18** [32]. A careful separation of the admixtures of 4,4'-diiodoazobenzene and 4,4'-diiodoazoxybenzene (both are known compounds and were identified by NMR) by column chromatography in this case resulted in higher yield than previously reported. The former most likely appeared as the minor impurity of the starting nitrosobenzene. The latter resulted from the coupling of nitrosobenzene and hydroxylamine formed from it by the reduction by the presented arylamine that could happen under the conditions of the Mills reaction [33].

Finally, heterobifunctional iodo/ethynyl azobenzene **19** was obtained via the basic deprotection of **18** (Scheme 8).



Scheme 8: Synthesis of heterobifunctional azobenzene **19**: (i) AcOH, rt; (ii) KOH, THF/MeOH/H_2O, reflux.

For the synthesis of the targeted stilbene via the HWE reaction, aldehyde have been selected as the ethynyl-containing part since the Sonogashira coupling proceeds much easier in the case of haloaromatics having electron-withdrawing groups. Therefore, trimethylsilyl protected aldehyde **20** was readily synthesized from *p*-bromoaldehyde via the Sonogashira coupling with TMSA. Next, *p*-iodotoluene was subjected to radical bromination with NBS followed by the Arbuzov reaction of resulting benzylic bromide **21** with $P(OEt)_3$ affording iodo-aromatic phosphonate **22** (Scheme 9).



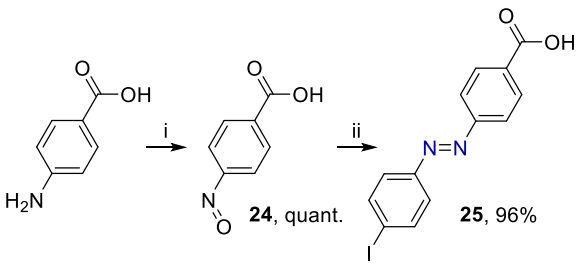
Scheme 9: Synthesis of heterobifunctional stilbene **23**: (i) TMSA, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, rt; (ii) NBS, AIBN, CCl_4, 70 °C; (iii) $P(OEt)_3$, 150 °C; (iv) *t*-BuONa, THF, rt.

As a base/solvent system for the HWE reaction between **20** and **22** *t*-BuONa/THF was used. The use of an alkoxide and THF is common for the HWE reaction [34] and it is beneficial in our case since in this system the base is strong enough to simultaneously

deprotonate the phosphonate and remove the silyl protecting group upon methanolic treatment of the reaction mixture but not as strong as to deprotonate the free alkyne moiety. As expected, the reaction of **20** and **22** proceeded smoothly in the selected conditions and heterobifinctional stilbene **23** was achieved in good yield (Scheme 9).

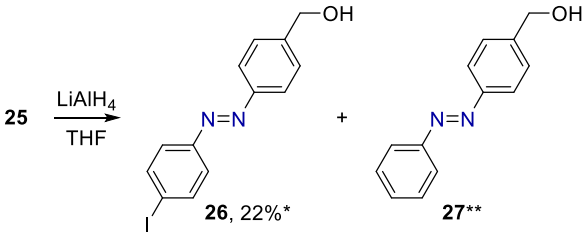
Syntheses of azobenzene and stilbene bearing a pair of iodo and halomethyl/azidomethyl groups

The last two pairs of azobenzene and stilbene cores contain iodo and halomethyl/azidomethyl groups which cannot be installed by Route 1. So, the Route 2 has been chosen. As in the case of the azidomethyl/halomethyl-containing cores we opted to install benzylic functionalities post azobenzene/stilbene synthesis to avoid any possible side reactions. Anilines with carboxyl functionalities showed great reactivity in nitrosoarene synthesis via Oxone-mediated oxidation [31]. At the same time, this functionality could in principle be readily converted to the azidomethyl moiety via successive reduction to the hydroxymethyl group, bromination to the bromomethyl group and substitution to the azidomethyl group. Therefore, we started from the *p*-aminobenzoic acid for the synthesis of the nitroso-containing part. Oxidation of *p*-aminobenzoic acid with Oxone according to the reported procedure [35] afforded *p*-nitrosobenzoic acid **24** which were successfully coupled with *p*-iodoaniline to give azobenzene acid **25** in excellent yield (Scheme 10).



Scheme 10: Synthesis of azobenzene acid **25**: (i) Oxone, CH_2Cl_2/H_2O, rt; (ii) *p*-iodoaniline, AcOH, 40 °C.

The iodoaromatic compounds are known to be reduced by $LiAlH_4$ [36] which is also commonly used for the reduction of acids and esters. However, the relative rates of the reductions of there groups presented in one compound are not obvious, so we attempted to reduce acid **25** to corresponding alcohol **26** with $LiAlH_4$ (Scheme 11). Equimolar amount of $LiAlH_4$, room temperature and THF were applied.



Scheme 11: Reduction of acid **25** with $LiAlH_4$. *Isolated yield. **Not isolated.

The ^1H NMR of the samples obtained after washing the residue, resulting from the basic quenching of the reaction, separation from inorganics and evaporation of the solvent, with Et_2O (Figure 4) showed that both reductions took place. Unfortunately, in the preparative synthesis alcohol **26** was obtained in only 22% yield, so we opted to search for another approach.

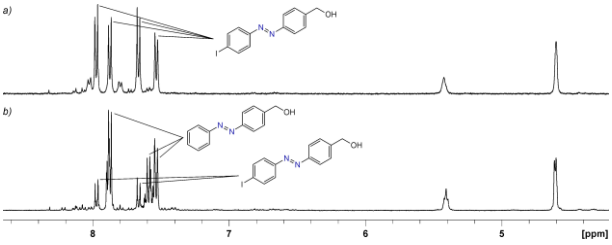
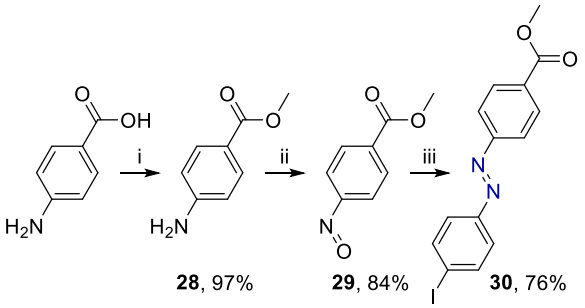


Figure 4: Fragments of ^1H NMR spectra of the precipitate (a) and filtrate (b) fractions obtained after washing with Et_2O the sample of the reaction mixture of the reduction of acid **25** after quenching and separating from inorganics; 400 MHz, DMSO-d_6.

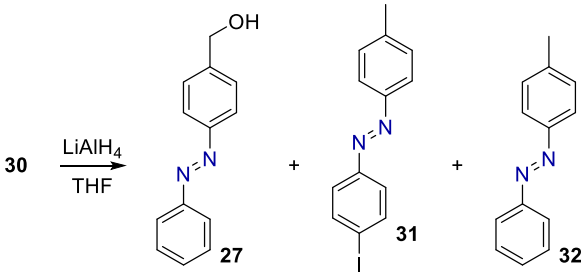
The extremely low solubility of the azobenzene acid **25** and its salt did not allow us to adequately probe different reaction conditions for its reduction, so we decided to try and use the corresponding alkyl ester instead. To this end, we synthesized methyl ester **28** upon $SOCl_2$-mediated esterification of *p*-aminobenzoic acid and then

subjected it to oxidation with Oxone affording nitrosobenzene **29** [31]. The Mills reaction between **29** and *p*-iodoaniline proceeded smoothly and gave azobenzene **30** [37] although an admixture of the corresponding azoxybenzene was detected in this case so the chromatographic purification was needed resulting in lower yield compared to that of the acid **25** (Scheme 12).



Scheme 12: Synthesis of azobenzene ester **30**: (i) $SOCl_2$, MeOH, rt; (ii) Oxone, CH_2Cl_2/H_2O, rt; (iii) *p*-iodoaniline, AcOH, 40 °C.

Next, the attempts to reduce ester **30** were carried out (Scheme 13).



Scheme 13: Reduction of ester **30** by $LiAlH_4$.

Applying the same conditions that was used for the acid **25** resulted in incomplete conversion of the starting material after full conversion of $LiAlH_4$. However, the accurate assignment of components of the product mixture was complicated due to overlapping signals in the aromatic region of the spectrum (Figure 5a). After the two-fold increase of the amount of $LiAlH_4$, the full conversion of ester **30** was achieved but the major product appeared to be alcohol **27** (Figure 5b), with the products of the reduction of alcohol moiety to alkyl one also detected upon chromatographic separation (CH_2Cl_2/EtOH) of the mixture (Figure 5c). Apparently, the rates of reduction

of carboxyl and iodo groups with $LiAlH_4$ in studied azobenzenes are close enough to forbid the selective preparation of alcohol **26**, so we shifted to other reducing agents.

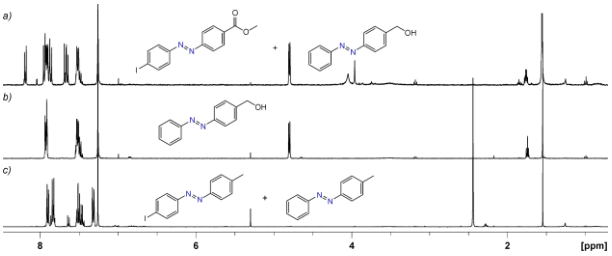
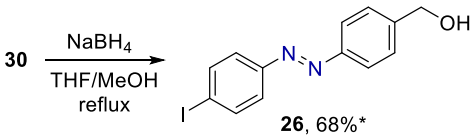


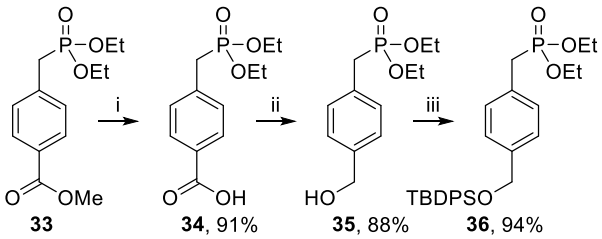
Figure 5: ^1H NMR spectra of the reaction mixtures of the reduction of ester **30** after quenching and separating from inorganics: the initial attempt under the condition used for acid **25** (a), the major fraction obtained after increasing the amount of $LiAlH_4$ (b), the minor fraction obtained after increasing the amount of $LiAlH_4$ (c), 400 MHz, $CDCl_3$.

Another common reducing agent in organic chemistry is $NaBH_4$ and while it is generally accepted that it does not reduce carboxylic acids or esters *per se*, there are a number of systems based on this compound that can be used for this purpose, e.g., a $NaBH_4$/MeOH system which is suitable for the reduction of methyl aromatic esters [38]. Since this system requires only methanol as an additive and implies simple methodology we decided to try and use it to reduce ester **30**. The initial attempt under the reported conditions showed that alcohol **26** indeed formed although the reaction was incomplete. After increasing the amount of $NaBH_4$ to 20 eq the conversion of starting ester **31** was scaled up to approximately 75% according to NMR data but no further alterations of the reaction conditions (increasing the amount of $NaBH_4$, prolonging the reflux or addition of the reducing agent in several portions) could lead to any improvement. Nonetheless, targeted alcohol **26** was isolated in remarkable 68% yield in preparative 5 mmol run while 19% of starting ester **30** was also recovered during chromatographic purification (Scheme 14).



Scheme 14: Synthesis of azobenzene alcohol **26** via reduction of ester **30** with $NaBH_4$. *19% of starting ester **30** was also recovered upon purification.

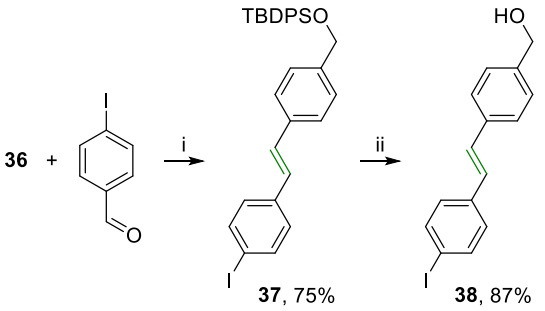
For the synthesis of analogous stilbene alcohol, we decided to avoid carboxyl functionalities due to the difficulties encountered earlier and instead install the hydroxyl group on the phosphonate precursor which is rather straightforward in comparison to aniline and nitroso precursors in the azobenzene synthesis. To this end, carboxyl ester group of phosphonate **33** obtained previously [25] was selectively hydrolyzed with $LiOH{\cdot}H_2O$ affording acid **34** [39] which upon reduction with $BH_3{\cdot}Me_2S$ gave alcohol-phosphonate **35** [40]. To avoid any possible side reactions, the hydroxyl group of **35** was protected with TBDPSCl in the presence of imidazole yielding phosphonate **36** [41] (Scheme 16).



Scheme 16: Synthesis of protected phosphonate **36**: (i) $LiOH{\cdot}H_2O$, $MeOH/H_2O$, rt; (ii) $BH_3{\cdot}Me_2S$, THF, rt; (iii) TBDPSCl, imidazole, DMF, rt.

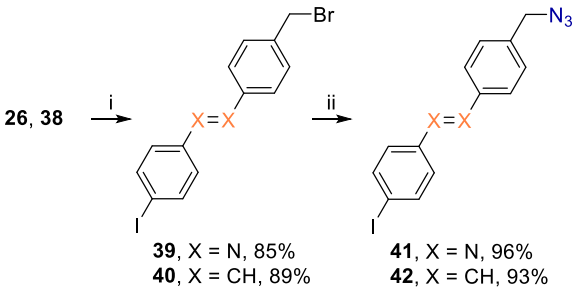
The HWE coupling of **36** with *p*-iodobenzaldehyde under the same conditions that was used in the synthesis of compound **23** afforded stilbene **37** having TBDPS protecting groups intact. These were successfully removed with TBAF yielding targeted stilbene alcohol **38** (Scheme 17). Considering that the yield of the reduction of carboxyl moiety in case of azobenzene **26** was 68% and that yields of the HWE reactions are generally comparable with the one achieved for **37** or lower, should the similar approach via

carboxyl functionalization had been applied, the overall yield of 49% of alcohol **38** from starting phosphonate proved that the selected route was appropriate.



Scheme 17: Synthesis of stilbene alcohol **38**: (i) *t*-BuONa, THF, rt; (ii) TBAF, THF/H_2O, rt.

The following introduction of bromo- and azido groups in place of hydroxyl ones of azobenzene **26** and stilbene **38** proceeded smoothly under the same conditions that was used for **6**/**7** and **8**/**9** pairs. Thus, heterobifunctional bromides **39**/**40** were obtained upon treatment of **26**/**38** with NBS/PPh_3 and nucleophilic substitution of bromine in the presence of NaN_3 gave respective azides **41**/**42** (Scheme 18).

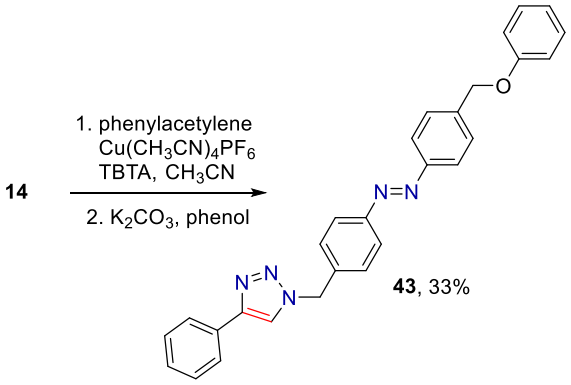


Scheme 18: Syntheses of heterobifunctional azobenzenes **39**/**41** and stilbenes **40**/**42**: (i) NBS, PPh_3, THF, rt; (ii) NaN_3, acetone/H_2O, rt.

One-pot syntheses using novel heterofunctional cores

The possibility of step-wise functionalization of novel azobenzenes and stilbenes is quite obvious given the appropriate conditions are used in each step. So instead, we opted for showing that selected functionalities could be modified in a one-pot approach, thus benefitting from lower amounts of purification steps.

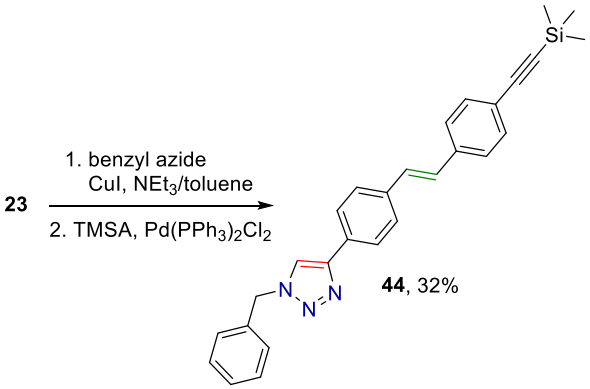
For the heterobifunctional core with the azidomethyl and chloromethyl groups, modification by means of CuAAC and alkylation reactions was tried. As other reactants, phenylacetylene and phenol were selected and a CuAAC-then-alkylation reaction sequence was used. To ensure the absence of side reactions with the chloromethyl group, $Cu(CH_3CN)_4PF_6$/TBTA catalytic system was chosen while acetonitrile was used as a solvent fitting for both reaction steps. The CuAAC step of modification of azobenzene **14** was done after stirring at 60 °C for 6.5 h as was shown by TLC, so K_2CO_3 and phenol were introduced and after 10 h no spot of an intermediate chloride was seen on a TLC plate. The reaction mixture was then worked-up by means of extraction, column chromatography and re-crystallization from methanol successfully yielding bifunctional azobenzene **43** (Scheme 19).



Scheme 19: One-pot synthesis using heterobifunctional azobenzene **14** with azidomethyl and chloromethyl groups.

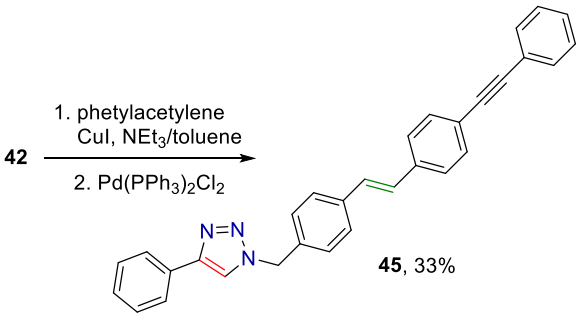
Next, the core having the ethynyl and iodo groups, namely, stilbene **23**, was subjected to a one-pot modification in CuAAC and Sonogashira cross-coupling reactions. In this case, the other reactants were phenylacetylene and TMSA, CuI and $Pd(PPh_3)_2Cl_2$ were used as catalysts. As in previous case, the TLC analysis showed that the CuAAC step conducted in toluene/NEt_3 was over after 6.5 h at 60 °C. Another portion of NEt_3 and $Pd(PPh_3)_2Cl_2$ were then added and the cross-coupling step was conducted at

80 °C finishing in 11 h. A similar to previously used work-up sequence smoothly afforded stilbene **44** (Scheme 20).



Scheme 20: One-pot synthesis using heterobifunctional stilbene **23** with ethynyl and iodo groups.

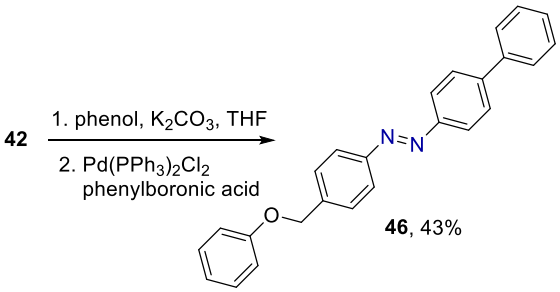
For the one-pot modification of stilbene **42** bearing azidomethyl and iodo groups, the CuAAC and Sonogashira cross-coupling reactions were selected, the other reactant for both steps being phenylacetylene. Both steps were conducted in the toluene/NEt_3 solvent mixture at 60 °C. After the CuAAC step catalyzed by CuI was done in 6.5 h, the excess of NEt_3, the second portion of phenylacetylene and $Pd(PPh_3)_2Cl_2$ were added and the Sonogashira coupling proceeded for another 10 h. The reaction was worked-up in the same fashion as previously used affording stilbene **45** (Scheme 21).



Scheme 21: One-pot synthesis using heterobifunctional stilbene **42** with azidomethyl and iodo groups.

Finally, the alkylation and Suzuki cross-coupling reactions were used as steps to carry out the one-pot modification of the core possessing bromomethyl and iodo groups,

namely, azobenzene **39**. The other reactants were phenol and phenylboronic acid and THF was utilized as a medium appropriate for both steps while K_2CO_3 served as a base. After the first step, the alkylation of phenol with azobenzene **39**, was over upon stirring at 60 °C for 20 h, $Pd(PPh_3)_2Cl_2$ and phenylboronic acid were added to the mixture and the Suzuki coupling took place for another 24 h. Due to the absence of a triazole ring, the polarity of the product of this reaction appeared to be much lower than that of compounds **43**–**45**. So, a hexane/CH_2Cl_2 system was used for column chromatography after the separation of inorganics. Subsequent re-crystallization of the residue from a hexane/CH_2Cl_2 solvent mixture allowed us to obtain azobenzene **46** (Scheme 22).



Scheme 22: One-pot synthesis using heterobifunctional azobenzene **39** with bromomethyl and iodo groups.

It should be noted that despite the moderate yields of all above-mentioned one-pot reactions such results are still noteworthily given the reduce of purification steps and the fact that there was no tuning the reaction conditions whatsoever. Thus, these results encourage us to believe that the presented cores can indeed be successfully used for the facile construction of bifunctional molecules, in which two components possessing different functions are linked by the photo-sensitive bridge, in either one-pot or step-wise fashion.

Conclusion

In summary, we have described the rational syntheses of novel azobenzene and stilbene heterobifunctional cores, possessing pairs of azidomethyl/chloromethyl, iodo/ethynyl, iodo/bromomethyl and iodo/azidomethyl groups in 4,4'-positions, from available precursors. The introduction of these groups enables stepwise or one-pot functionalization of presented building blocks via CuAAC, cross-coupling and nucleophilic substitution reactions as was shown by a series of model reactions. Developed synthetic strategies can be applied to azobenzenes and stilbenes having auxiliary substituents and different substitution patterns allowing for the broadening of the scope of available photo-sensitive building blocks. We hope that these results will encourage further studies in the fields of both azobenzene and stilbene chemistry and facilitate the construction of new bifunctional molecules having two components connected by a photo-sensitive linker.

Experimental

Materials and Methods

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 instrument at 20 ºC and chemical shifts are reported as ppm referenced to solvent signals. ESI and APPI mass spectra were obtained from Sciex TripleTOF 5600+ spectrometers. Chemicals received from commercial sources were used without further purification. Compounds **1** [23,24], **5** [26], **18** [32], **24** [35], **29** [31], **30** [37], **34** [39], **35** [40], **36** [41] were synthesized according to published procedures. The synthetic procedures for novel azobenzene and stilbene building blocks are presented in the Supporting Information File 1.

(*E*)-4-phenoxymethyl-4'-(4-phenyl-1,2,3-triazol-1-yl)methylazobenzene (43)

A mixture of azobenzene **14** (28.6 mg, 0.1 mmol), phenylacetylene (21.9 mL, 0.1 mmol), TBTA (31.8 mmol), $[Cu(CH_3CN)_4]PF_6$ (11.2 mg, 0.03 mmol) and CH_3CN (0.5 mL) was stirred at 60 °C for 6.5 h. Phenol (18.8 mg, 0.2 mmol) and K_2CO_3 (27.6 mg, 0.2 mmol) were added and the stirring continued for 10 h. The mixture was diluted with CH_2Cl_2 and washed with HCl (2 M). The organic layer was separated, washed with brine and concentrated to dryness. The residue was subjected to column chromatography (gradient from CH_2Cl_2 to CH_2Cl_2/EtOH 100:1). Fractions containing the product were collected, the solvent was removed *in vacuo* and the residue was re-crystallized from methanol. Yield 19.0 mg (43%), orange solid. M.p. 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 4H; ArH_{azo}), 7.85–7.79 (m, 2H; ArH_{Ph}), 7.71 (s, 1H; ArH_{Trz}), 7.62–7.56 (m, 2H; ArH_{azo}), 7.49–7.43 (m, 2H; ArH_{azo}), 7.44–7.36 (m, 2H; ArH_{Ph}), 7.36–7.26 (m, 3H; ArH_{Ph}), 7.03–6.95 (m, 3H; ArH_{Ph}), 5.67 (s, 2H; CH_2N), 5.16 (s, 2H; CH_2O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.54, 152.72, 152.12, 140.59, 137.27, 130.42, 129.54, 128.83, 128.75, 128.25, 127.91, 125.73, 123.57, 123.21, 121.19, 119.50, 114.88 (C_{Ar}, CH_{Ar}), 69.36 (CH_2O), 53.84 (CH_2N) ppm. ESI-MS *m*/*z*: 446.1978 $[M+H]^+$ for $C_{28}H_{23}N_5O$ (446.1975).

(*E*)-4-(1-benzyl-1,2,3-triazol-4-yl)methyl-4'-trimethylsilylethynylstilbene (44)

A mixture of stilbene **23** (33.0 mg, 0.1 mmol), benzyl azide (25.0 mL, 0.2 mmol), CuI (5.7 mg, 0.03 mmol), toluene (0.4 mL) and NEt_3 (0.1 mL) was stirred at 60 °C for 6.5 h. NEt_3 (1 mL) was added followed by TMSA (27.6 µL, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol). The mixture was heated to 80 °C and the stirring continued for 11 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl. The organic layer was separated, washed with brine and concentrated to dryness. The residue was subjected to column chromatography (gradient from CH_2Cl_2 to

CH_2Cl_2/EtOH 100:1). Fractions containing the product were collected, the solvent was removed *in vacuo* and the residue was re-crystallized from methanol. Yield 14.0 mg (32%), off-white solid. M.p. 234–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.76 (m, 2H; ArH_{stil}), 7.66 (s, 1H; ArH_{Trz}), 7.73–7.65 (m, 2H; ArH_{stil}), 7.57–7.50 (m, 2H; ArH_{stil}), 7.48–7.42 (m, 4H; ArH_{stil}), 7.42–7.35 (m, 3H; ArH_{Ph}), 7.35–7.29 (m, 2H; ArH_{Ph}), 7.12 (d, 1H, ^3J = 16.5 Hz; CH), 7.07 (d, 1H, ^3J = 16.5 Hz; CH), 5.58 (s, 2H; CH_2), 0.26 (s, 9H; $Si(CH_3)_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.34, 136.85, 134.62 (C_{Ar}), 132.29 (CH_{Ar}), 129.95 (C_{Ar}), 129.16, 129.08 (CH_{Ar}, CH_{stil}), 129.01 (C_{Ar}), 128.80, 128.09, 128.07, 127.02, 126.26, 125.96 (CH_{Ar}, CH_{stil}), 122.14 (C_{Ar}), 119.44 (CH_{Ar}), 105.14, 95.15 (C≡C), 54.25 (CH_2), -0.03 ($Si(CH_3)_3$) ppm. ESI-MS *m*/*z*: 434.2046 $[M+H]^+$ for $C_{28}H_{27}N_3Si$ (434.2047).

(*E*)-4-(4-phenyl-1,2,3-triazol-1-yl)methyl-4'-phenylethynylstilbene (45)

A mixture of stilbene **42** (36.1 mg, 0.1 mmol), phenylacetylene (21.9 mL, 0.2 mmol), CuI (5.7 mg, 0.03 mmol), toluene (0.4 mL) and NEt_3 (0.1 mL) was stirred at 60 °C for 6.5 h. Phenylacetylene (21.9 mL, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) and NEt_3 (0.5 mL) were added and the stirring continued for 10 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl. The organic layer was separated, washed with brine and concentrated to dryness. The residue was subjected to column chromatography (gradient from CH_2Cl_2 to CH_2Cl_2/EtOH 100:1). Fractions containing the product were collected, the solvent was removed *in vacuo* and the residue was re-crystallized from methanol. Yield 14.6 mg (33%), off-white solid. M.p. 247–249 °C (subl.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.79 (m, 2H; ArH_{stil}), 7.68 (s, 1H; ArH_{Trz}), 7.59–7.45 (m, 8H; ArH), 7.45–7.26 (m, 8H; ArH), 7.14 (d, 1H, ^3J = 16.6 Hz; CH), 7.06 (d, 1H, ^3J = 16.6 Hz; CH), 5.59 (s, 2H; CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.76, 136.86, 134.00 (C_{Ar}), 131.97, 131.59 (CH_{Ar}), 130.52 (C_{Ar}), 129.05,

128.81, 128.51, 128.47, 128.37, 128.32, 128.19 (CH_{Ar}, CH_{stil}), 127.25, 126.52, 125.72 (CH_{Ar}), 123.23, 122.64 (C_{Ar}), 119.41 (CH_{Ar}), 90.50, 89.43 (C≡C), 53.99 (CH_2) ppm. ESI-MS *m*/*z*: 438.1965 $[M+H]^+$ for $C_{31}H_{23}N_3$ (438.1965).

(*E*)-4-phenoxymethyl-4'-phenylazobenzene (46)

A mixture of azobenzene **39** (40.1 mg, 0.1 mmol), phenol (18.8 mg, 0.2 mmol), K_2CO_3 (27.6 mg, 0.2 mmol) and THF (1 mL) was stirred at 60 °C for 25 h. Phenylboronic acid (24.4 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol) were added and the stirring continued for 24 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl. The organic layer was separated, washed with brine and concentrated to dryness. The residue was subjected to column chromatography (gradient from hexane to hexane/CH_2Cl_2 1:1). Fractions containing the product were collected, the solvent was removed *in vacuo* and the residue was re-crystallized from CH_2Cl_2/hexane. Yield 15.5 mg (43%), orange solid. M.p. 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–7.99 (m, 2H; ArH_{azo}), 7.99–7.93 (m, 2H; ArH_{azo}), 7.81–7.73 (m, 2H; ArH_{azo}), 7.72–7.65 (m, 2H; ArH_{Ph}), 7.64–7.57 (m, 2H; ArH_{azo}), 7.53–7.45 (m, 2H; ArH_{Ph}), 7.44–7.37 (m, 1H; ArH_{Ph}), 7.36–7.28 (m, 2H; ArH_{Ph}), 7.07–6.92 (m, 3H; ArH_{Ph}), 5.17 (s, 2H; CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.59, 152.39, 151.77, 143.80, 140.19, 140.11 (C_{Ar}), 129.54, 128.90, 127.91, 127.90, 127.78, 127.19, 123.40, 123.09, 121.15, 114.91 (CH_{Ar}), 69.44 (CH_2) ppm. ESI-MS *m*/*z*: 365.1652 $[M+H]^+$ for $C_{25}H_{20}N_2O$ (365.1648).

Supporting Information

Supporting Information File 1

Synthetic procedures for novel azobenzene and stilbene building blocks, NMR spectra of all novel compounds.

Acknowledgements

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