Modulation of Azobenzenes by Cross-Coupling Reactions

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Abstract
Azobenzenes are among the most extensively used molecular switches for many different applications. The need to tailor them to the required task often requires further functionalization. Cross-coupling reactions are ideally suited for late-stage modifications. This review provides an overview of recent developments in the modification of azobenzene and its derivatives by cross-coupling reactions.

1 Introduction

Azobenzene and its derivatives are among the most investigated molecular switches. They can interconvert photochemically and thermally between their metastable (E)- and (Z)-isomers (Figure 1).

Several physicochemical characteristics are affected by this photoisomerization, e.g., geometry and end-to-end distance, electronic properties, and polarity. Whereas (E)-azobenzene is planar and without a dipole moment, (Z)-azobenzene shows a non-planar geometry and a dipole moment of 3.0 D. Consequently, azobenzene derivatives have gained great interest, for example for applications in data storage materials, dynamic molecular devices, or in photonics.

Thus, manifold synthetic procedures have been developed for the preparation of azobenzene derivatives, most with the formation of the diazenyl group as the key step. Methods to obtain symmetric azobenzenes range from reductive coupling of nitrobenzenes or oxidative coupling of anilines. The Mills reaction or azo-coupling reactions can be used to prepare asymmetric azobenzene derivatives. However, functionalized azobenzenes obtained in this way usually require prefunctionalized starting materials which limits the synthetic modification possibilities. An additional problem is the susceptibility of the diazenyl group towards oxidizing and reducing agents. Therefore, late-stage modification through cross-coupling reactions provides a valuable alternative to access a wider variety of azobenzene derivatives. This short review aims to give a broad, but not exhaustive, overview of the synthetic possibilities offered by cross-coupling reactions on azobenzenes and diazocines. In this short review, we distinguish between azobenzenes as formally electrophilic and formally nucleophilic components.

Key words: azobenzene, diazocine, molecular switches, cross-coupling reactions, C–H activation, metal-catalyzed
philic components because of the different requirements and the corresponding difficulties in the synthesis of the azobenzene precursors, especially for nucleophilic derivatives.

2 Azobenzenes as Formally Electrophilic Components

(Pseudo)halogenated azobenzenes are used as an electrophilic component in cross-coupling reactions with a large variety of organometallic (nucleophilic) coupling partners. These (pseudo)halogenated species are usually obtained by employing prefunctionalized building blocks. There are very few reported examples of the direct halogenation of azobenzene derivatives. The relatively low reactivity of azobenzenes towards electrophilic halogenation reactions results from the electronic properties of the diazenyl group, which can form adducts with halogen halides leading to low yields. The use of elemental halogens often results in inseparable mixtures of mono-, di-, tri-, and tetrahalogenated products. Due to the lone-electron pairs on the nitrogen atoms, the diazenyl group can coordinate to metal catalysts facilitating substitution in the ortho-position. ortho-Halogenation is thus possible via metal-catalyzed C–H activation. However, different coordination patterns of the metal catalyst on the azobenzene moiety have been detected. Thus, selective halogenation remains challenging.

2.1 Palladium Catalysis

Palladium catalysts are the most frequently used catalysts in cross-coupling reactions. Therefore, the high number of palladium-catalyzed cross-coupling reactions of azobenzene derivatives that serve as a formally electrophilic component is no surprise.

2.1.1 Suzuki–Miyaura Cross-Coupling Reactions

The Suzuki–Miyaura cross-coupling reaction of (pseudo)halogenated azobenzenes with boronic acids or esters is one of the most frequently used cross-coupling reactions for the modification of azobenzenes. Due to its convenience, reliability, and high yields, it is often used as the final synthetic step to combine large building blocks. Of the many available examples, in this review we place a certain focus on polymers or molecules that self-assemble: such larger molecules are often not easy to prepare and this is where the benefits of the Suzuki–Miyaura cross-coupling are most relevant. Consequently, the Suzuki–Miyaura cross-coupling reaction gives access to many azobenzene derivatives with new applications in self-assembled materials or many liquid crystals, compounds that show tunable fluorescence, photoswitchable porphyrin systems, dendrimers, polymers, metal-organic frameworks (MOFs), as well as molecular machines such as rotaxanes.
The first successful Suzuki–Miyaura cross-coupling reaction of an azobenzene derivative was described in a polymerization reaction (Scheme 1); different conjugated polymers were synthesized with molecular weights up to $M_n = 9700$ (in yields of 80–99%).

Besides a benzene ring, more complex motifs such as a fluorene ring or a carbazole ring were successfully integrated in the conjugated main chain.

For the synthesis of rotaxanes, azobenzene derivatives were connected with two $\beta$-cyclodextrin units resulting in a [3]-rotaxane, and later on a [1]-rotaxane. The azobenzene motif was either trapped in or bonded directly to the $\alpha$-cyclodextrin units and subsequently capped by benz[de]isoquinoline derivatives via cross-coupling.

Further possibilities are demonstrated by the implementation of two consecutive Suzuki cross-coupling reactions. Starting from a 4,4'-diiodoazobenzene, initial coupling with 4-bromophenylboronic acid gave a 4,4'-bis(4-bromophenyl)azobenzene that underwent a second cross-coupling reaction with a 4-substituted phenylboronic acid to give an azoterphenyl derivative (37–54% over 2 steps).

Since 2016, several cross-coupling reactions have been performed using asymmetric azobenzene derivatives; in this way, molecules capable of precise self-assembly with additional non-covalent interactions were prepared in yields ranging from 26% to 94% (Scheme 2, A–C). Suzuki–Miyaura cross-coupling was also applied to functionalize nickel porphyrin systems with azobenzene moieties in excellent overall yields (Scheme 2, D). Pd(PPh$_3$)$_4$ served as Pd(0) catalyst with K$_2$CO$_3$ as base and the reaction was carried out in a toluene/EtOH/water mixture at 90 °C leading to good and sometimes excellent yields. The coupling was even successful with an azopyridine and with adjusted conditions for an azimidazole unit. For the latter, the free amine of the imidazole was N-methylated to prevent a possible side reaction with PdCl$_2$(dppf) as the Pd(II) catalyst.
2.1.2 Sonogashira Cross-Coupling Reactions

The palladium-catalyzed cross-coupling reaction of a terminal alkyne with halogenated azobenzenes represents another widely used functionalization possibility. In this way, an azobenzene unit can be connected with relatively long, rigid, and π-conjugated linkers in good to excellent yields.20 The incorporated linkers then serve a specific function in the molecule: For example, the functionalization of ethynyl-1,6-methano[10]annulenes with azobenzene demonstrated the synthesis of electron-donor/acceptor systems that are suitable substrates for nonlinear optics or liquid crystals (Scheme 3, A).20a In different azobenzene systems for the synthesis of photochromic self-assembled monolayers, the rigid linker ensures sufficient control over the distance from the headgroup to the surface and features a cooperative switching behavior of the azobenzene units.20b–d Hydrophobic fluorescent azobenzenes were transformed into water-soluble fluorescent 2-borylazobenzenes by incorporating ionic functional groups via Sonogashira coupling.20e Employing 4,4′-diodoazobenzene as the starting material enabled a double cross-coupling; in this way, an azobenzene moiety containing two paramagnetic nitroxide spin labels was synthesized in which the ethynyl groups supported the formation of spin exchange coupling (Scheme 3, B left).20f Low-molecular organogelators were obtained by double cross-coupling of 3,3′-diiodoazobenzenes with acetylene derivatives (Scheme 3, B right).20g The two urethane moieties were required for strong hydrogen bonding, whereas the two cholesterol units led to relatively weak van der Waals interactions.20h Moreover, an azobenzene bisporphyrin system20i as well as different para-alkylazobenzene ligands and their corresponding organometallic cobalt complexes were obtained.20j As azotolanes usually show liquid crystallinity as well as highly birefringent features, this method was utilized for the synthesis of several azotolane monomers20j or polymers with azobenzene in the side chain or main chain (Scheme 3, C), respectively. Additionally, photosensitive and fluorescent co-polymers (Scheme 3, D),20k polyamide-phenylethynylethynylenes20l or a semiconducting colloidal porous organic polymer20m were obtained. The scope of electrophilic azobenzene cross-coupling partners was successfully broadened to bistriﬂates for the synthesis of rigid dendrimers in an acceptable yield.20n,21

2-Iodoazobenzene reacted with (trimethylsilyl)acetylene under Sonogashira conditions, but even after optimization of the reaction conditions the yield of 2-[(trimethylsilyl)ethynyl]azobenzene remained 50%.21 Additionally, the product decomposed during workup because of the lability of the protecting group and the instability of the deprotected diazene. Coupling with more robust (triisopropylsilyl)- and (triethylsilyl)acetylene solved both problems and the product 2-[(trialkylsilyl)ethynyl]azobenzenes were obtained in 97% and 87% yield, respectively.21

### Scheme 3
Pd-catalyzed Sonogashira cross-coupling reactions of halogenated azobenzenes

- **A** Neidlein 1997
- **B** Wachtveitl/Prisner 2017, Koumura/Tamaoki 2004
- **C** Kuciauskas/Wright 2003 and 2005
- **D** Das 2019

R = NO2 48%  H 33%  OMe 46%

m = 4, n = 1 32%
m = 3, n = 2 23.8%
m = 4, n = 2 79%
2.1.3 Buchwald–Hartwig Cross-Coupling Reactions

This type of cross-coupling reaction is used to form C–N bonds. In 2020, the coupling of 3,5-dibromoazobenzene with N-Boc-N-(4-methoxyphenyl)hydrazide to give 3,5-bis[N′-Boc-N′-(4-methoxyphenyl)hydrazino]azobenzene in 58% yield was reported (Scheme 4). The obtained product was then oxidized to yield a C2-symmetric 3,5-bis(4-methoxyphenylazo)azobenzene. Unsymmetric tris(arylazo)benzenes were accessible by sequential coupling.

![Scheme 4 Pd-catalyzed Buchwald–Hartwig cross-coupling reaction of 3,5-dibromoazobenzene](image_url)

2.1.4 Heck Reactions

The Heck reaction can be employed in order to preserve double bonds within the starting material for later functionalization. As with the Suzuki–Miyaura cross-coupling, we mainly discuss reports of larger functional polymers and assemblies. One interesting example is the functionalization of cage silsesquioxanes with azobenzene units via the Heck reaction (Scheme 5). The synthesis of new azobenzene-doped hybrid porous polymers was thus possible.

![Scheme 5 Pd-catalyzed Heck reaction of 4-bromoazobenzene](image_url)

Poly(phenylenevinylene)-based conjugated polymers with azobenzene derivatives incorporated directly in the \( \pi \)-conjugative building units were prepared in quantitative yield and with a high molecular weight (M > 10000) by coupling polymerization of divinylbenzenes with 4,4'-di-haloazobenzenes. The Heck reaction of nipecotic acid (piperidine-3-carboxylic acid) derivatives with azobenzene triflates and iodides yielded vinyl ethers in good yields. However, the coupling was not possible for ortho-substituted azobenzenes. In this case, the Heck reaction needed to be performed with 1-iodo-2-nitrobenzene with the formation of the azobenzene by an azo coupling in a later step.

2.1.5 Stille Reactions

In a Stille cross-coupling reaction, an organotin compound is reacted with a halide. Organostannanes are easy accessible and stable in air and moisture so that a broad range of functional groups can be used under mild conditions. In this way, 4,4'-dibromoazobenzene was coupled with tributylvinyltin to yield 4,4'-divinylazobenzene in 70% yield. It was also possible to introduce heteroaromatic compounds into a polymer backbone via a Stille cross-coupling: The monomer 4,4'-diiodoazobenzene was reacted with four different bis(trimethylstannyl)-substituted heteroaromatic compounds to give poly(phenylene) based polymers that were soluble in common organic solvents in moderate to excellent yields (Scheme 6). Due to the extended main-chain conjugation, the thiophene-, furan-, and N-methylpyrrole-containing poly(phenylenes) showed strongly red-shifted absorptions in the visible region. Only the pyridine-containing poly(phenylene) had a low degree of main-chain conjugation, but contrary to other examples, it showed in solution reversible photoisomerization of azobenzene units with an accompanied change of the electrochemical properties. The \( (Z) \)-enhanced polymer was less susceptible to oxidation.

![Scheme 6 Pd-catalyzed Stille cross-coupling reactions of diiodoazobenzenes](image_url)

2.2 Nickel Catalysis

Although palladium complexes are the most common catalysts in cross-coupling reactions, attempts have been made to replace palladium by less expensive metals such as nickel. For example, a nickel-catalyzed Heck reaction of aryl...
triflates with vinyl ethers proceeded under mild reaction conditions, using a catalytic system consisting of bis-
(cyclooctadiene)nickel(0), 1,1'-bis(diphenylphosphino)fer-
rocene (DPPF), and tertiary amine Cy2NMe, followed by hy-
drolysis to give the corresponding acetyl-substituted prod-
ucts with good functional group tolerance. It was also pos-
sible to incorporate a photoswitchable unit by the
olefination of an azobenzene triflate followed by hydrolysis
to give the corresponding acetyl derivative (Scheme 7).28

2.3 Copper Catalysis

Copper catalysts are another alternative to palladium
catalysts in cross-coupling reactions to obtain substrates
otherwise not accessible.

2.3.1 Cadiot–Chodkiewicz Reactions

The copper-catalyzed Cadiot–Chodkiewicz reaction en-
ables the formation of conjugated dienes. A synthetic route
towards large-scale highly ordered porous structures from
organometallic precursors via spontaneous self-assembly
was established by using a two-step Cadiot–Chodkiewicz
cross-coupling. Several neutral platinum–acetylide com-
plexes with azobenzene groups in the center and long alkyl
chains on both ends of the molecule were obtained in ex-
cellent to quantitative yields (Scheme 8).29 In a similar fash-
on, poly(platinaynes) were synthesized with both meta-
or para-substituted azobenzene spacers to compare their op-
toelectronic properties. In these complexes, the acetylide-
functionalized azobenzene ligands could still undergo pho-
toisomerization reversibly, although the switching process
appeared to be more facile for para-substituted systems
and with lower photoisomerization in solution in compari-
sion to smaller systems.30

2.3.2 Ullmann Reactions

The Ullmann reaction is a powerful tool for C–N bond
formation. The Ullmann coupling of 4,4’-dibromoazoben-
zene with 3,6-bis(9H-carbazol-9-yl)-9H-carbazole gave a
bis(tercarbazole)azobenzene derivative in 46% yield that
was used as a precursor for photoresponsive microporous films (Scheme 9).31

2.4 Cobalt Catalysis

Another alternative to palladium catalysis is the use of
cobalt as an inexpensive metal. For example, the C(sp3)–P
cross-coupling of vinyl, styryl, and aryl halides with diphe-
nyl phosphine oxide and dialkyl phosphinate using a
unique Co/Cu catalytic system gave the corresponding
phosphoryl-substituted products. This protocol showed robust functional group tolerance that enabled the coupling of 4,4′-diiodoazobenzene with diisopropyl phosphite to give 4,4′-bis(diisopropoxyphosphoryl)azobenzene in 76% yield (Scheme 10).32

3 Azobenzenes as Formally Nucleophilic Components

In cross-coupling reactions, the formal nucleophile is an (organo)metallic species. Organometallic, nucleophilic azobenzene derivatives can be obtained either by halogen-metal exchange of the (pseudo)halogenated azobenzene or by applying an appropriate cross-coupling reaction with a dimetallic reagent (Scheme 11, A) (see later for C–H activation).7b,33 However, in the case of azobenzenes, halogen-metal exchange can lead to the reduction of the azo group as a dominating side reaction (Scheme 11, B).34 From the perspective of the formally nucleophilic azobenzene, the main limitation is access to the azobenzene starting material. There has been very little research performed in this area in terms of systematic investigations and thus, it is difficult to distill common principles or indeed select the most seminal papers.

3.1 Palladium Catalysis

Palladium catalysts are also most commonly used in cross-coupling reactions involving azobenzene derivatives as the formally nucleophilic component. In terms of the obtained product structure, the same criteria apply for the selection of the specific cross-coupling reaction as are utilized for electrophilic azobenzene derivatives. However, a key consideration is the availability of the metalated azobenzene.

3.1.1 Suzuki–Miyaura Cross-Coupling Reactions

The first use of an azobenzene derivative as a nucleophile in a Suzuki–Miyaura cross-coupling reaction was reported in 2007;36 the coupling of a boronic acid pinacol ester functionalized azobenzene with diverse iodoarenes gave arylation azobenzenes in 41–72% yields.36 While the cross-coupling reactions themselves are relatively unremarkable, the importance is in the synthesis of the starting material by cross-coupling of a (pseudo)halogenated azobenzene with the boronic ester.36,37 A second approach is the condensation of a nitrosobenzene and aniline boronic acid ester; the boronic acid ester is unaffected by the condensation reaction.36 Due to the efficiency of this method, a number of synthetic targets36 were assessed. Moreover, an azobenzene-4-boronic acid pinacol ester derivative was used as the nucleophile and 4-bromo-2,2,2′,2′-tetrafluoroazobenzene derivatives as the electrophile, which enabled the use of azobenzene as both cross-coupling components. The resulting product undergoes orthogonal switching, where the azobenzene units are switched separately to give 4 different isomers by green, blue, or ultraviolet light or electrocatalytic isomerization (Scheme 12).37
3.1.2 Sonogashira Cross-Coupling Reactions

In 2014, the preparation of an azobenzene liquid crystal was reported by the Sonogashira cross-coupling reaction of an ethynyl-substituted azobenzene with 1-bromooctane. This protocol was utilized in 2017 for the coupling of an azobenzene derivative with aryl bromides (Scheme 13, A). The Sonogashira cross-coupling reaction has also been used for the synthesis of artificial helical oligomers or polymers in which the photoisomerization of the azobenzene moieties triggers a geometric change. Novel azobenzene-containing hydroxyphenylglycine-derived poly-(m-phenyleneethynylene)s were synthesized by polymerization through the Sonogashira couplings (thus formally a polycondensation) of 3,5-diethynylazobenzenes with various diiodinated amides (Scheme 13, B).

Furthermore, the Sonogashira reaction was used to prepare a hairy-rod like \( \pi \)-conjugated polymer with a fluorene unit in the backbone. The late-stage functionalization of poly(aryl ethers) with azobenzene moieties was feasible, in which polymer bromo side groups react with 4-(dimethylamino)-3’-ethynylazobenzene.

3.1.3 Buchwald–Hartwig Cross-Coupling Reactions

The Buchwald–Hartwig cross-coupling reaction can be used to form C–N bonds. The Buchwald–Hartwig amination of various polystyrene and poly(Iminoarylene) derivatives was reported to give the corresponding products with aminoazobenzene groups in the side chain (Scheme 14). The absence of characteristic stretching vibrations of the starting materials in the IR spectrum indicated a full loading of the obtained polymer.

This methodology was applied to the synthesis of amorphous materials such as branched triarylamino derivatives, a spiro-linked bifluorene as well as a perfluorocyclobutane (PFCB) aryl ether polymer or a poly(arylalmine) derivative. It was even possible to prepare ferrocenophanes with azobenzene derivatives in the ligand and to use them as a redox-active and chromophore site showing potential as electron- or acid-responsive organic materials.

3.1.4 Heck Reactions

The Heck reaction of dihaloazobenzenes with divinylarenes as well as the reverse case, the coupling of 4,4’-divinylazobenzene with dihaloarenes, to produce photoresponsive poly(phenylenevinylene)s was investigated. However, the obtained polymers were largely insoluble in common organic solvents, hence this route was discarded.

3.1.5 Stille Reactions

An efficient microwave-assisted method to prepare stannylated azobenzenes was developed to circumvent the possible reduction of the diazenyl group during halogen-metal exchange. These organostannyl-substituted azobenzenes subsequently served as nucleophiles in high-yielding Stille cross-coupling reactions (Scheme 15).
3.2 Copper Catalysis

A copper-catalyzed Ullmann cross-coupling reaction was the method of choice for the synthesis of bis[4-(phenyldiazenyl)phenyl]amine and tris[4-(phenyldiazenyl)phenyl]amine by varying the stoichiometric quantities of the electrophilic component (Scheme 16).50

Scheme 16  Cu-catalyzed Ullmann cross-coupling reaction of 4-iodo-azobenzene with amino-azobenzene

The Ullmann cross-coupling reaction is also useful for generating phenol ethers through C–O bond formation. In this way, a series of azobenzene-functionalized poly(ether sulfone)s were prepared, using a catalyst system of CuI and 2,2,6,6-tetramethylheptane-3,5-dione (TMHD), that had high glass transition temperatures (Tg >199 °C) (Scheme 17).51 Irradiation and writing/erasing experiments indicated a large photoinduced birefringence and good stability of the photoinduced orientation of the polymers. This makes them interesting for applications in reversible optical storage.51

This synthetic procedure was expanded to the synthesis of an azobenzene-containing poly(aryl ether) with carboxyl side groups capable of coordination to rare earth complexes.43

3.3 C–H Activation Reactions

C–H Activation reactions catalyzed by different transition metals have played an important role especially in the functionalization of azobenzene derivatives in the ortho-position.

3.3.1 Palladium-Catalyzed C–H Activation Reactions

The ortho-directing property of the azo group has been exploited in palladium-catalyzed C–H activation reactions.14e,52 In many such reactions, the azobenzene is transformed by reaction with the diazenyl group. For example, azobenzenes were used for the synthesis of indazole backbones through palladium-catalyzed C–H functionalization and subsequent intramolecular cyclization.52a In a similar approach, 3H-indazol-3-ones were prepared from azobenzene derivatives using formic acid as carbon monoxide source (Scheme 18, A).52g ortho-C–H Amination of azoarenes with trimethylsilyl azide yielded 2-aryl-2H-benzotriazoles (Scheme 18, B).52b In this reaction, electron-donating substituents (alkyl, alkoxy) give higher product yields (58–87%) than electron-withdrawing groups, such as CF3 (8%).

Late-stage functionalization of azobenzenes in the ortho-position was reported by the Trauner group (Scheme 19, A).14e These tetra-ortho-chlorinated azobenzenes are of
special interest because of their redshifted isomerization to cis at $\lambda \approx 560$ nm. Azoarenes were functionalized with phenylhydrazine using a Pd(II) catalyst with atmospheric oxygen as the oxidant (Scheme 19, B). Wu, Wang, and co-workers reported the acylation of azobenzene derivatives with benzylic ethers (Scheme 19, C).

### 3.3.2 Rhodium-Catalyzed C–H Activation Reactions

Rhodium has been shown to be a potent ortho C–H activator of azobenzene derivatives. There are several reported examples of the formation of C–N bonds, similar in yields to the palladium-catalyzed reactions. A very useful reaction is the ortho-heteroarylation of azobenzenes by rhodium-catalyzed cross-dehydrogenative coupling (Scheme 20). Such conjugated biaryls might be of special interest for luminescent materials.

### 3.3.3 Ruthenium-Catalyzed C–H Activation Reactions

Ruthenium-catalyzed C–H activation reactions of azobenzene derivatives have been reported. Of particular interest is the meta/ortho-selective C–H alkylation of azobenzenes. Using a carboxylic acid promoted Ru(II)-catalyzed CAr–H alkylation reaction of 4,4′-substituted azobenzenes with secondary and tertiary alkyl bromides gave selectively the meta-product (Scheme 21), while under the same reaction conditions, primary alkyl groups gave the ortho-product. To our knowledge this is the only reported reaction so far which allows C–H activation in the meta-position. Coupling with alkyl chlorides was unsuccessful. Furthermore, bulky groups, such as tert-butyl ($Y = t$-Bu), on the azobenzene, prevented the reaction.
3.3.4 Cobalt-Catalyzed C–H Activation Reactions

Cobalt-catalyzed C–H activation reactions are largely unknown on azobenzene derivatives and only a few examples exist. A synthetic procedure for the azo-directed selective 1,4-addition of maleimides by Co(III)-catalyzed C–H activation was reported (Scheme 22). Worth noting is the use of low amounts of additives, as well as the fact that it does not require the use of a copper source.

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\begin{align*}
\text{Scheme 22} & \quad \text{Co-catalyzed C–H activation reactions of azobenzene derivatives}\end{align*}
\]

3.3.5 Iridium-Catalyzed C–H Activation Reactions

The Ir(III)-catalyzed [4+2] cyclization of azobenzenes with diazotized Meldrum's acid via a two-step reaction with an initial C–H alkylation, followed by intramolecular annulation gave 3-oxo-2,3-dihydrocinnoline-4-carboxylic acids or esters depending on the solvent used (Scheme 23).

\[
\begin{align*}
\text{Scheme 23} & \quad \text{Ir-catalyzed C–H activation reaction of azobenzene derivaties}\end{align*}
\]

3.3.6 Copper-Catalyzed C–H Activation Reactions

Azobenzenes can be functionalized by a Cu(II)-catalyzed aerobic oxidative amidation with amides yielding the corresponding 2-(acylamino)azobenzenes in moderate to excellent yields (Scheme 24).

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\begin{align*}
\text{Scheme 24} & \quad \text{Cu-catalyzed C–H activation reactions of azobenzene derivatives}\end{align*}
\]

3.3.7 Iron-Catalyzed C–H Activation Reactions

To date only one example of an iron-catalyzed C–H activation reaction has been reported. An iron hydride complex bearing a 2,5-bis(di-tert-butylphosphinomethyl)pyrroli dine ligand reacted with azobenzene. However, further functionalization was unsuccessful since the pentacoordinated ary1–iron complex was inert toward various reagents (Scheme 25).

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\begin{align*}
\text{Scheme 25} & \quad \text{Fe-catalyzed C–H activation of azobenzene}\end{align*}
\]

4 Azobenzenes as Ligands in Catalysts

In addition to their use as a reactant in cross-coupling reactions, azobenzene derivatives can be also employed as ligands for catalysts in cross-coupling reactions. Here, the N-donor capability of the diazenyl group (due to the lone electron pair on the nitrogen atoms) is used to form transition metal complexes. The incorporation of azo chromophores has enabled the synthesis of complexes with interesting physicochemical properties such as photoluminescence. Complexes with multidentate azoaromatic ligands are significantly stabilized because of the enhanced \( \pi \)-acceptor behavior compared to monnocyclopalladated azobenzenes. Although the synthesis of azo-containing phosphine Pd(II) and Pt(II) complexes was reported in 1999, and the first results of their catalytic use were demonstrated in Heck reactions, it took a further decade before this possibility was explored in more detail.

In 2010, the synthesis of a polystyrene-anchored Pd(II) azo complex (Figure 2, A) and its application in the Suzuki–Miyaura as well as Sonogashira cross-coupling reactions was reported; various aryl halides were reacted with phen-
ylboronic acids or terminal alkynes in excellent yields (68–100% yield, 27 examples) under phosphine-free and aerobic reaction conditions in aqueous medium. A similar catalytic system showed comparable recyclability, but, in addition, it could even be employed in Heck reactions (89–96% yield, 5 examples).

A single core palladacyclic azobenzene catalyst with CNCN chelation was successfully synthesized (Figure 2, B) and used successfully in Suzuki–Miyaura and Heck reactions. However, it was only moderately active (27–70% yield, 4 examples) and required high temperatures that led to decomposition of the catalyst.

A symmetric bisazobenzene derivative was used as chelating ligand to obtain unsymmetric CNN pincer palladacycles (Figure 2, C) that showed high turnover numbers (TONs) even under the harsh conditions of the Heck reaction (60–93% yield, 9 examples, TONs up to 93000).

Phosphine-free Pd(II) complexes with 2,2′-bis(alkylamino)azobenzene ligands were obtained in good yields by reaction of the ligands with sodium tetrachloropalladate. In this work, the benzyl derivative (Figure 2, D) showed high catalytic activity in Suzuki–Miyaura and Heck reactions under mild conditions in the presence of air and moisture (65–93% yield, 22 examples).

It should be noted that the photoswitchability of the azobenzenes in Figure 2 was not exploited.

5 Diazocines

(Z)-11,12-Dihydrodibenzo[c,g][1,2]diazocines (diazocines) are ethylene-bridged azobenzenes that can be switched from their thermodynamic stable (Z)- to the metastable (E)-isomer by using blue light at λ ≈ 370–400 nm and back from the (E)- to the (Z)-isomer by green light at λ = 480–550 nm (Figure 3).

The switching properties of unsubstituted diazocines are different to unsubstituted azobenzenes. Diazocines show better resolution of absorption bands between the two isomeric states and switching is possible with light in the visible range. However, the substituents have a great impact on the switching properties of both azobenzenes and diazocines. For example, tetra-ortho-chlorinated azobenzenes can be switched to (Z) at λ ≈ 560 nm, which exceeds the redshift of regular diazocines. Amino substituents on diazocines have also been shown to reduce the separation of the absorption bands yielding low amounts of (E)-isomers (25–30%). The synthesis of diazocines is more demanding compared to azobenzenes, which is why only few applications have been reported to date.

5.1 Synthesis

The key step in any diazocine synthesis is the cyclization to form the diazene moiety. This has been performed by reduction of 2,2′-dinitrobibenzyls, or the oxidation of 2,2′-ethylenedianilines (Figure 4).

A novel route involving a cross-coupling reaction has been introduced by connecting the C–N bond instead of the N–N bond (Scheme 26). The diazocine ring in this route is formed via consecutive cross-coupling reactions between a 2,2′-dihalobenzyl and di-fert-butyl hydrazidocarboxylate.
5.2 Cross-Coupling Reactions

To date there are only a few reports of palladium-catalyzed cross-coupling reactions of diazocines. Therefore, a comparison with cross-coupling reactions of azobenzenes is, at present, of little informative value. Due to the different electronic and geometric structures of azobenzenes and diazocines, a different reactivity can be expected (as the lone pairs in diazocine are not aligned with the π-systems of the aromatic rings). At first glance the yields seem to be lower for cross-coupling reactions on diazocines, but this might be misleading since it is unknown if the reaction conditions were optimized. The Heck reaction of an 8-substituted 3-bromodiazocine with a glutamate derivative yielded diazocine ligands capable of light-controlling neural receptors (Scheme 27).67c

Turn-on fluorescence diazocines were prepared by a Stille cross-coupling reaction (Scheme 29, A).72 Furthermore, it was possible to obtain a pyroglutamate diazocine derivative via the Stille cross-coupling reaction (Scheme 29, B).67e

6 Conclusion

Cross-coupling reactions have proved to be a powerful tool for the late-stage modification of both electrophilic and nucleophilic azobenzene derivatives, with palladium catalysis being most prevalent. The Suzuki–Miyaura and Sonogashira cross-coupling reactions are the most widely used. First examples of cross-coupling reactions catalyzed by other transition metals than palladium, such as nickel or cobalt, have been published thus broadening the scope of cross-coupling reactions towards new bond formations that are not possible with palladium catalysts. At present, the number of examples of the use of azobenzenes as formally electrophilic reactants is much greater than that for their use as formally nucleophilic reactants. Most likely, this does not reflect intrinsic problems with nucleophilic azobenzenes, but rather that their accessibility is limited at present.
and requires more research. The reported yields do not significantly differ for cross-coupling reactions with azobenzene as formally the electrophilic or as nucleophilic component. However, due to the difficulties in the synthesis of nucleophilic azobenzene derivatives, cross-coupling reactions involving formally electrophilic azobenzene derivatives are favored. Normally, cross-coupling reactions with formally nucleophilic azobenzene derivatives are only used if the the nucleophilic coupling partner in the reaction of electrophilic azobenzene derivative cannot be synthesized. Most reported examples of cross-coupling reactions involving azobenzene derivatives employ the para-isomer; there are few examples of the use of the meta- or even the ortho-isomer. In fact, some groups specifically pointed out that cross-coupling reactions on ortho-azobenzene derivatives were unsuccessful. So cross-coupling reactions in the ortho-position of azobenzenes are almost, but not completely, unknown. The different reaction behavior of ortho-azobenzene derivatives in comparison to their corresponding meta- and para-isomers can be attributed to the nature of the diazenyl group; due to the adjacent lone electron pair on the nitrogen atoms, the diazenyl group can interact with substituents in the ortho-position. For example, ortho-halogenated precursors that are easily accessible can be directly lithiated because the ortho-lithiated species is significant stabilized by N-Li coordination. Although the diazenyl group has this directing and stabilizing effect also for transition metal insertions, only very few examples of metalated ortho-azobenzenes exist. C-H Activation is, therefore, a valuable alternative especially for the modification of ortho-azobenzenes. In almost all examples of C-H activation on azobenzenes, the ortho-position was functionalized. Here, the use of palladium complexes as catalysts was not as dominant as for the cross-coupling reactions. Another promising field is the use of complexed azobenzene derivatives acting as ligands or promoters for catalysts. New synthetic procedures for the preparation of diazocene derivatives means that they are accessible in good yields. Therefore, further functionalization possibilities through cross-coupling reactions can now be explored.

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**References**
