

Visible light-mediated catalyst-free radical arylations using arenediazonium salts

Pia Wenisch^a, Meret Kuschow^a, and Markus R. Heinrich^{a,*}

^aDepartment of Chemistry and Pharmacy, Pharmaceutical Chemistry, Friedrich-Alexander Universität Erlangen-Nürnberg, Nikolaus-Fiebiger Straße 10, 91058 Erlangen, Germany

Email: markus.heinrich@fau.de

Dedicated to Prof. Samir Z. Zard

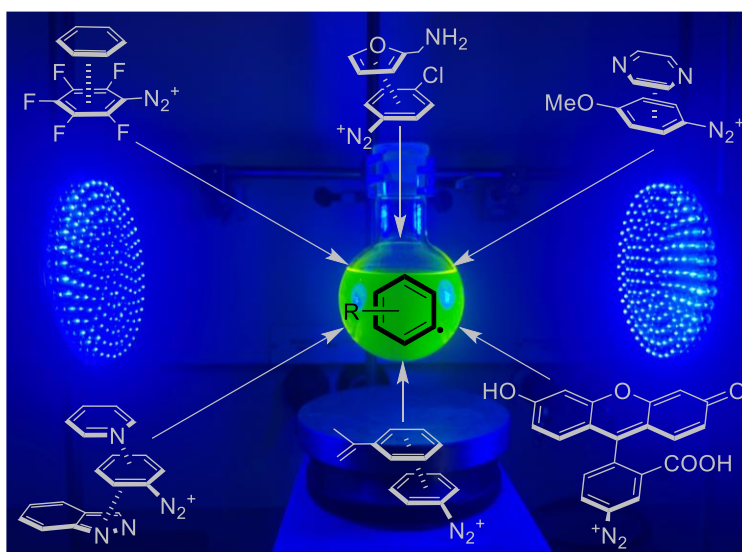
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Abstract

Radical arylation reactions based on arenediazonium salts have a long history in organic chemistry. While early methods to generate aryl radicals relied on metals, metal catalysts or basic conditions, more recent developments focused on the use of photoredox catalysts. As such catalysts are nevertheless additives, and they thus have to be separated during work-up, an even more attractive option is to exploit charge-transfer complexes between the arenediazonium ion and its substrate to enable aryl radical generation under visible light irradiation. In this review, we summarize recent developments in this particular field of visible light-promoted, additive-free radical arylation reactions.



Keywords: Arenediazonium, radical reactions, arylation, charge transfer, photochemistry

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1. Introduction

Since their first description by Peter Griess in 1859¹, arenediazonium salts have not only emerged as widely applicable reactants and reagents in organic chemistry, but also – and mainly due to the most often clean diazotization of anilines – for many analytical purposes.^{2,3,4} Regarding synthesis, it is in particular the option to generate aryl radicals and aryl cations under versatile and often mild conditions which accounts for much of the attractiveness of aryl diazonium salts. Besides, they have meanwhile been used in a variety of organometallic cross coupling reactions,^{5,6,7} and have been employed as scavengers for a range of nucleophiles and radicals,^{8,9} thereby leading to highly important compound classes such as azo compounds or triazenes, among others. Taking a closer look at aryl radical generation from arenediazonium salts, the related transformations include the well-known Sandmeyer (1897) reaction,^{10,11} the Pschorr cyclization (1899),¹² the Gomberg-Bachmann reaction (1924)¹³ as well as the Meerwein arylation (1939).¹⁴ While these reactions appeared for a long time to have a valuable, but also somehow limited substrate and product scope, especially the last two decades have now revealed the until then hidden power of these radical transformations. Among these advances, and in parallel to the general development of novel reaction conditions for radical generation and capture, the broad emergence of photoredox chemistry has had a strong impact on arenediazonium-based radical reactions.

While the addition of small amount of photoredox catalyst is certainly beneficial when replacing a stoichiometric amount of reductant, such catalyst is nevertheless an additive which has to be removed later on. An even more ideal reaction would thus rely on radical generation by direct optical excitation of the diazonium ion to give, upon single electron transfer and cleavage of dinitrogen, the desired aryl radical. As common aromatic diazonium ions however show no or at best only weak absorption in the visible wavelength range, early approaches to catalyst-free radical generation relied on the use of UV irradiation. A second, and far more attractive strategy to circumvent the low absorbance of diazonium ions in the visible range is to exploit charge-transfer interactions between the diazonium ion and its reaction partner. In this way, visible light-induced radical reactions can be performed without any further additive. As a third option to achieve additive-free arylation reactions, the absorbance of the diazonium ion in the visible wavelength range can be increased, which has however only scarcely been put into practice so far.

In this review, we will focus on additive-free, visible light-induced radical arylations of alkenes and arenes using arenediazonium salts, as such reactions can be highly attractive contributions to modern synthetic organic chemistry in several aspects. At this point, it is also important to note that besides visible light irradiation, aryl radicals may be readily generated from diazonium salts under weakly basic and even at neutral conditions, which can be a valuable synthetic alternative as well. For a significant number of substrates, however, such conditions also favor side reactions among which azo coupling is the most important.

2. Aryl-aryl Coupling – Gomberg-Bachmann Type Reactions

Seminal work on light induced radical arylations, in which charge transfer complexes play a key role for initiation, was published by Kochi.¹⁵ The formation of the charge-transfer complexes could be readily recognized by the change of color of the diazonium salt solution upon addition of the aromatic substrate. The UV spectra summarized in Figure 1 give an impression on the magnitude of the charge-transfer related absorption depending on the nature of the substrate. While benzene or toluene lead to only weak, but still remarkable bathochromic shifts, naphthalene and 1,4-dimethoxybenzene cause strong absorptions in the visible range.

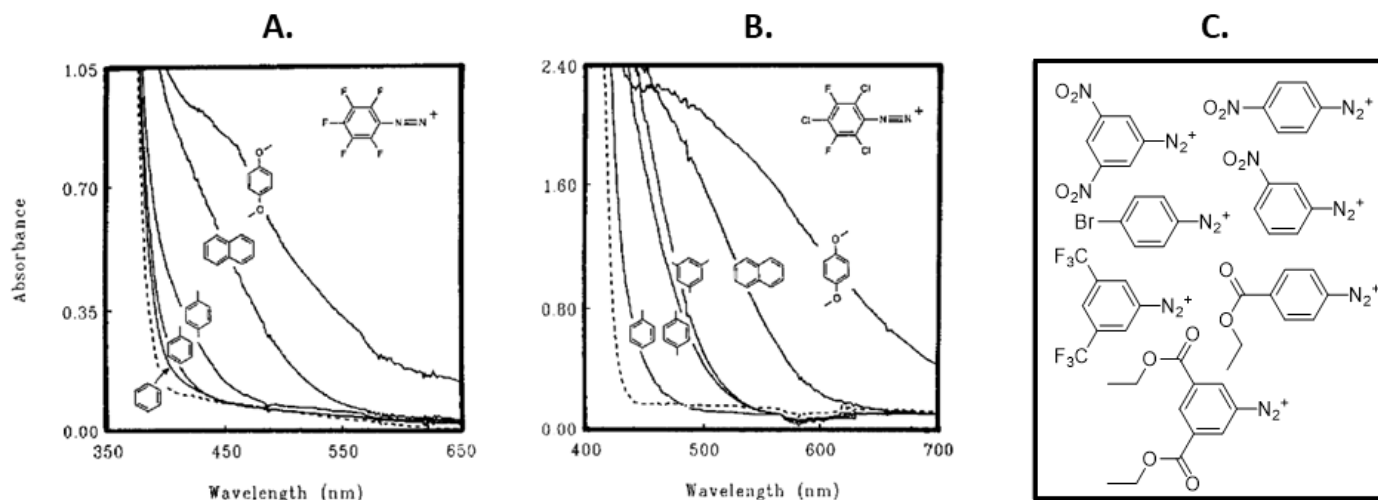
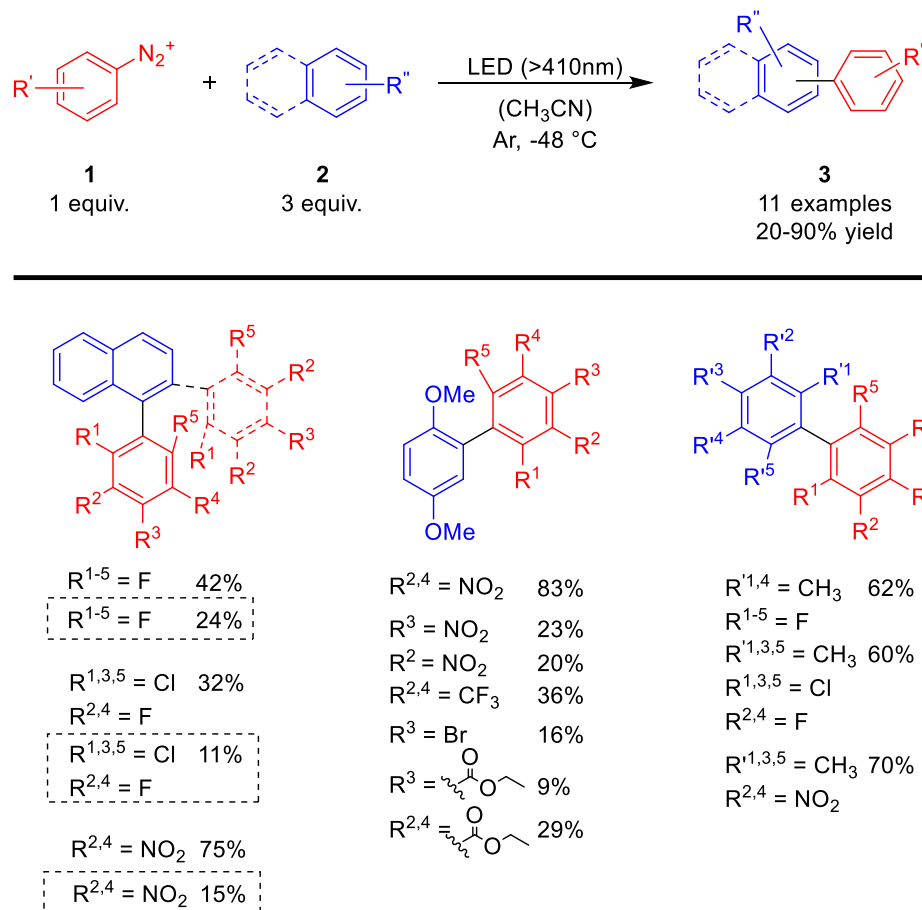


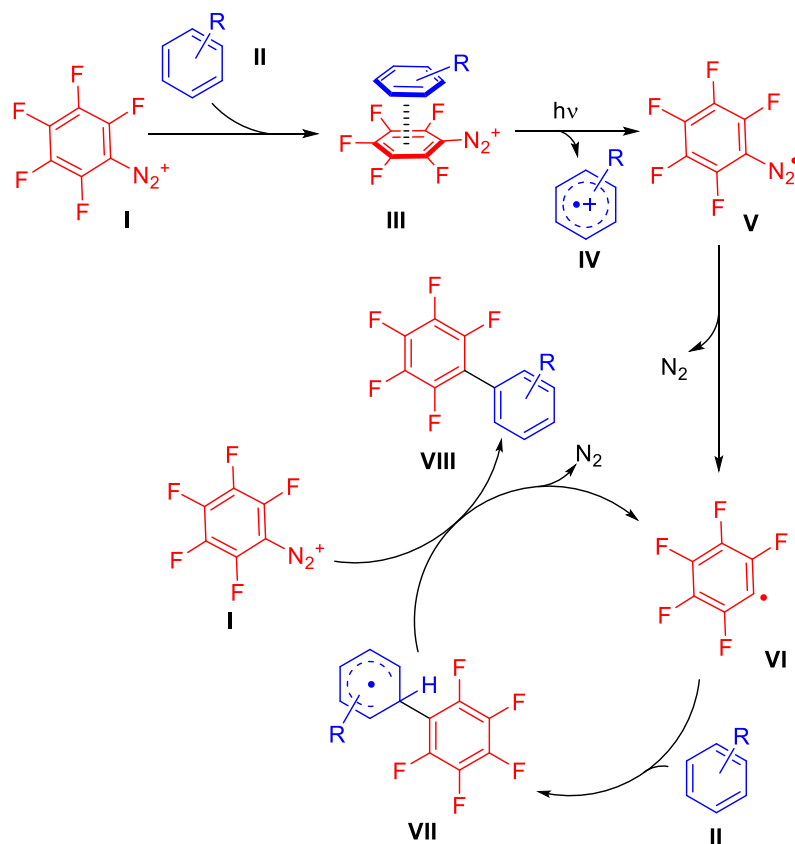
Figure 1. Charge-transfer spectra of 2,3,4,5,6-pentafluorophenyldiazonium tetrafluoroborate and 2,4,6-trichloro-3,5-difluorophenyldiazonium hexafluorophosphate combined with various aromatic substrates. The dashed lines indicate the absorption of the diazonium ions in absence of the substrates. Adapted with permission from Kosynkin, D.; Bockman, T. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1997**, Copyright 1997 American Chemical Society.

Nine different diazonium ions shown in Figure 1A, B and C were investigated in photoinduced arylations of 1,4-xylene, mesitylene, naphthalene and 1,4-dimethoxybenzene (Scheme 1). As it can be expected from the results summarized in Figure 1, especially combinations of particularly electron-poor phenyldiazonium ions such as 3,5-dinitrophenyldiazonium and 2,3,4,5,6-pentafluorophenyldiazonium and electron rich arenes like *p*-dimethoxybenzene and naphthalene led to the best yields.



Scheme 1. Visible light mediated radical arylation based on charge-transfer initiation. 500 W high-pressure mercury lamp in combination with pyrex sharp cutoff filter and IR water filter used for $\lambda_{\text{exc}} > 410 \text{ nm}$.¹⁵

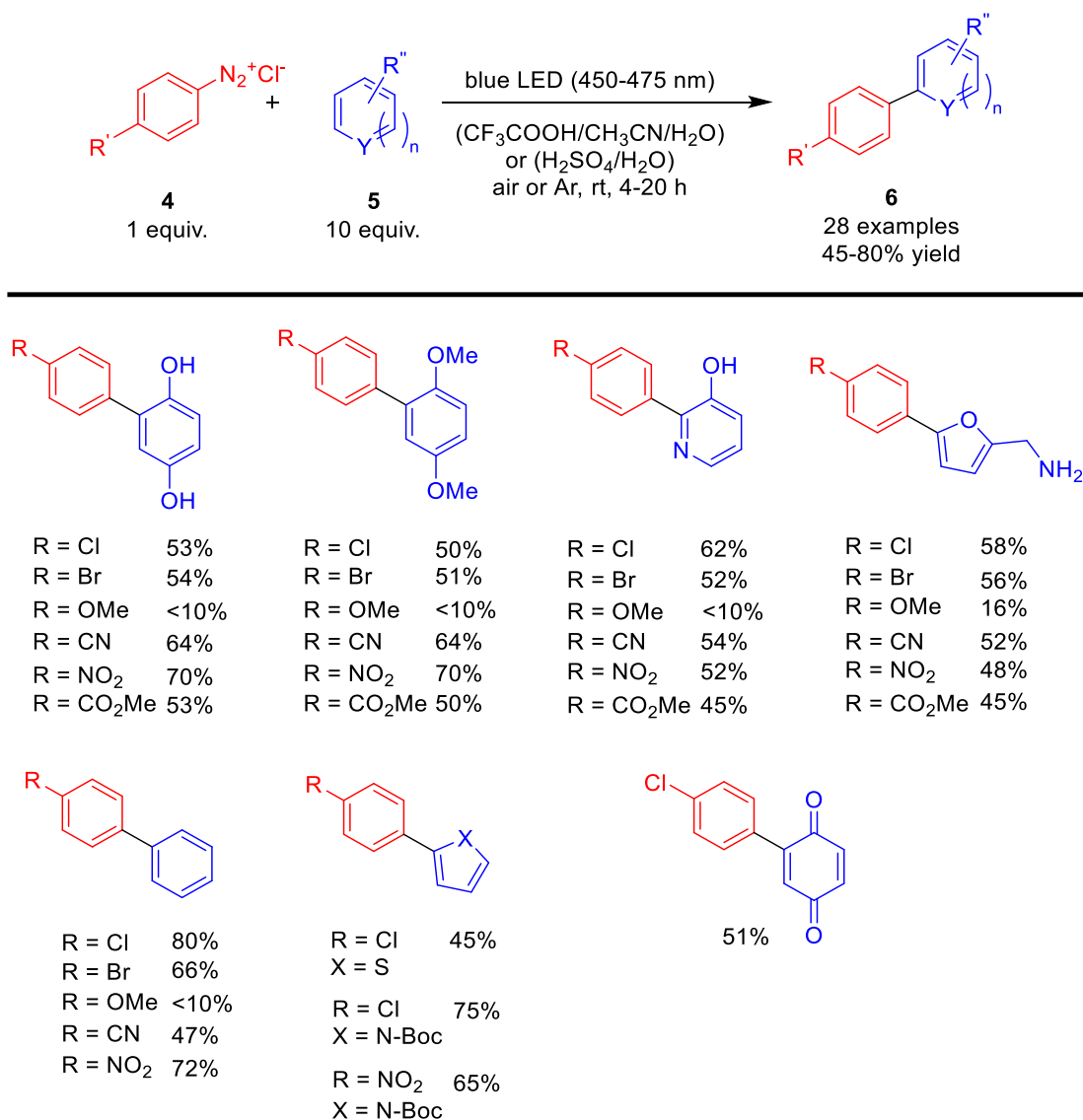
To rule out thermal initiation, the arylations were conducted at low temperature ($-48 \text{ } ^\circ\text{C}$). Strong support for the radical mechanism was gained by control reactions, in which haloalkanes were added to the reaction mixture. Diiodomethane or tetrabromomethane redirected the reaction course from biaryl synthesis towards the related halogenated arenes. As shown in Scheme 2, light-induced formation of the aryl radical **VI** from diazonium salt **I** is strongly facilitated by the charge transfer complex **III**, of which the decay at first generates radical cation **IV** and diazenyl radical **V**. Besides enabling strong charge transfer complexes, the pronounced electron deficiency of the diazonium also promotes radical chain propagation from the cyclohexadienyl intermediate **VII** to biaryl **VIII** and a new aryl radical **VI**.



Scheme 2. Plausible reaction mechanism for light-induced radical arylations based on the initiation resulting from charge-transfer complexes.¹⁵

Although representing a highly valuable starting point, the full potential of radical arylations based on charge-transfer initiation from arenediazonium complexes remained unrecognized for quite long time. A plausible reason for this appears to be that only low yields and conversions were achieved with diazonium ions not bearing one or more strong acceptor substituents, such as 4-bromophenyldiazonium tetrafluoroborate (see Scheme 1). In turn, this may have led to the conclusion that only particularly electron-deficient arenediazonium ions are suitable for charge-transfer initiation – thus representing a significant limitation of the reaction scope.

As shown in a more recent study by Fürst et al.,¹⁶ the scope of charge-transfer initiated arylations is indeed much broader and only donor substituted phenyldiazonium salts (e.g. 4-methoxyphenyldiazonium) now turned out as difficult to convert (Scheme 3).



Scheme 3. Visible-light induced arylations using arenediazonium chlorides.¹⁶

Besides the difference to Kochi's study¹⁵ that more or less electron neutral substituents on the phenyldiazonium salt (e.g. 4-chloro, 4-bromo) are now also well tolerated, the reactions summarized in Scheme 3 further demonstrate that less energetic visible light in the range from 450-475 nm is fully sufficient for initiation. This can be considered as a valuable prerequisite towards broader application, in particular in biological settings. However, and representing a certain drawback for some substrates, the light induced arylations had to be conducted under acidic conditions to prevent side reactions of the diazonium ion such as azo coupling. Substrates, which are not or only less sensitive to azo coupling, such as *N*-Boc pyrrole, did not require the addition of acid. For all arylations, constant cooling of the reaction mixtures was again applied to avoid thermal initiation.

Taking a closer look at the difference spectra resulting from the charge transfer interaction of 4-chlorophenyldiazonium chloride and the four aromatic substrates 1,4-hydroquinone, 1,4-dimethoxybenzene, 3-hydroxypyridine and furfurylamine revealed the additional importance of a second factor regarding reaction outcome (Figure 2).

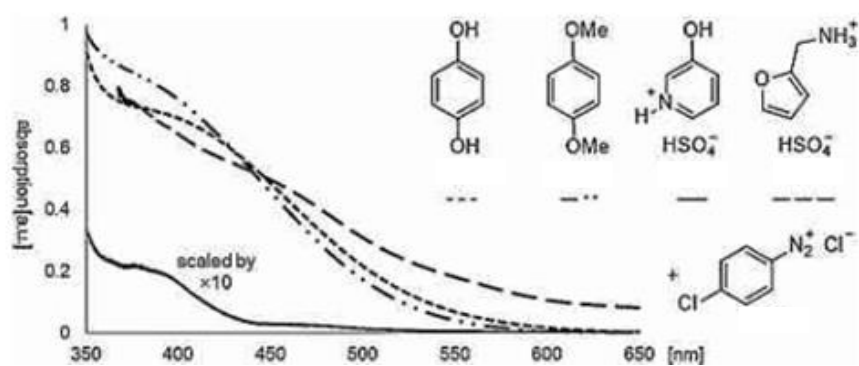
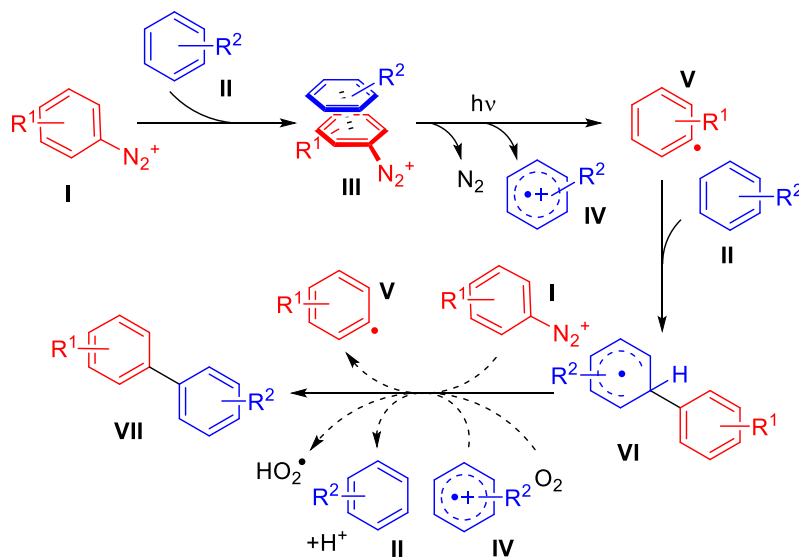


Figure 2. Difference spectra resulting from charge-transfer interactions between aromatic substrate and the 4-chlorophenyldiazonium ion. Adapted with permission from Fürst, M. C. D.; Gans, E.; Böck, M. J.; Heinrich, M. R. *Chem. Eur. J.* **2017**, Copyright 2017 European Chemical Society.

While the electron-rich benzene derivatives and furfurylamine (Figure 2) showed strong interactions and remarkable bathochromic shifts in the absorption spectra, the charge transfer complex resulting from protonated 3-hydroxypyridine and the 4-chlorophenyldiazonium ion was difficult to detect by UV-Vis measurements. Nevertheless, arylations starting from 3-hydroxypyridine led to comparably good yields (Scheme 3). A plausible explanation for this observation is that arylations with 3-hydroxypyridine benefit from a fast aryl radical attack on the substrate (leading to a captodatively stabilized cyclohexadienyl radical) and probably also a facilitated chain propagation generating a new aryl radical (step VI>VII, Scheme 4). In turn, and due to more a more reliable radical chain, even a weakly efficient charge-transfer initiation can thus be sufficient for successful arylation reactions.



Scheme 4. Plausible reaction mechanism for the visible-light induced radical arylation by Fürst et al.¹⁶

Similar to the earlier study by Kochi,¹⁵ the radical mechanism could be further supported by a trapping experiment with diiodomethane as additive, which inhibited biaryl formation and led to an iodobenzene as major product. Control experiments under initiation with a catalytic amount of iodide confirmed that radical

chain transfer (step VI->V) is most probably only of importance for particular aromatic substrates such as 3-hydroxypyridine.

The general effect that unprotonated pyridine and its derivatives show strong charge transfer interactions with aromatic diazonium salts was later exploited by de Oliveira¹⁶ to enable catalyst-free, visible light-induced radical arylations. As shown in Figure 3, both pyridine and its hydrochloride salt led to a change in absorption, whereat the charge transfer band shows – not surprisingly – a much stronger bathochromic extent in the case of pyridine.

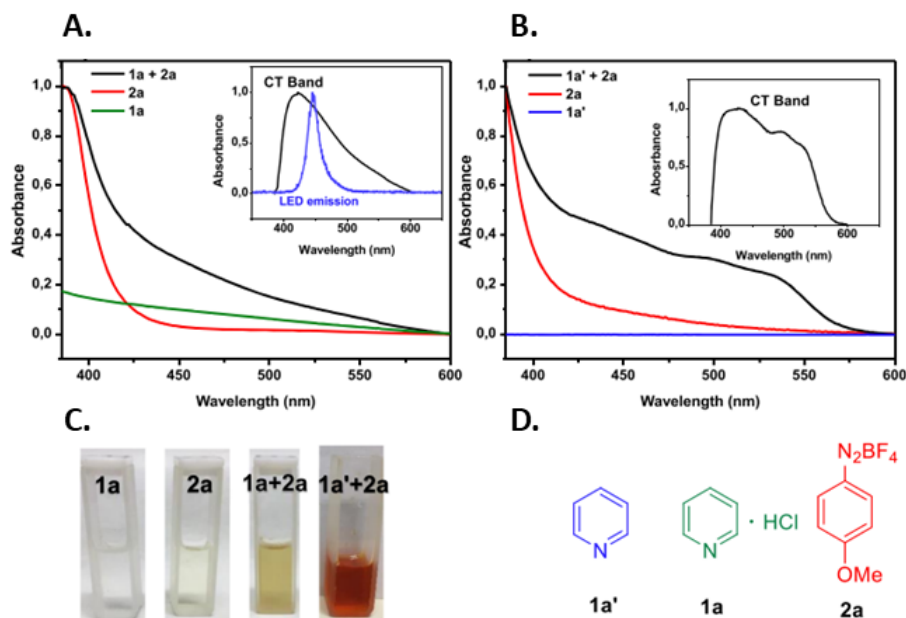
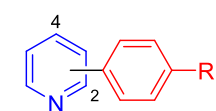
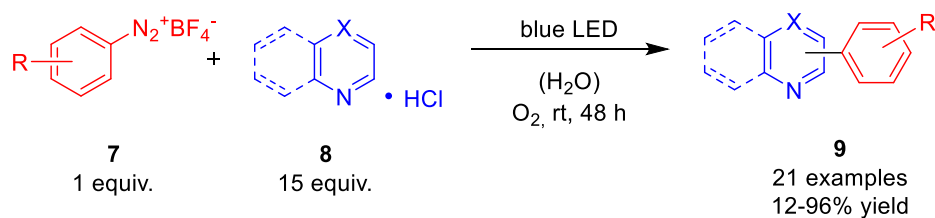


Figure 3. Charge transfer interactions of pyridine and its hydrochloride salt in combination with 4-methoxyphenyldiazonium tetrafluoroborate. CT bands (shown as insets) correspond to difference spectra from compound mixture and individual components. Adapted with permission from Bartolomeu, A. de A.; Silva, R. C.; Brocksom, T. J.; Noël, T.; de Oliveira, K. T. *J. Org. Chem.* **2019**, Copyright 2019 American Chemical Society.

Despite these observations, which might at first point to pyridine as more suitable substrate than its hydrochloride, optimization of the reaction conditions demonstrated that significantly higher yields can be achieved with pyridine hydrochloride (84% vs. 20% for pyridine as free base). Further experiments aimed at optimized conditions led to the choice of water as the favorable solvent compared to MeOH, EtOH, DMF, DMSO and related mixtures, which can be explained by far reduced hydrogen atom transfer.¹⁸ The fact that oxygen atmosphere turned out as more suitable than argon, is most probably due to facilitated rearomatization (see Scheme 6).

An overview over the products prepared from pyridine hydrochloride and its derivatives is shown in Scheme 5.



R = H 62%

2-aryl/4-aryl, 71:29

R = Cl 80%

2-aryl/4-aryl, 68:32

R = F 53%

2-aryl/4-aryl, 59:41

R = NO₂ 66%

2-aryl/4-aryl, 64:36

R = Me 80%

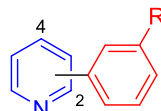
2-aryl/4-aryl, 68:32

R = Et 75%

2-aryl/4-aryl, 68:32

R = N(Me)₂ 14%

2-aryl/4-aryl, 1:0



R = F 58%

2-aryl/4-aryl, 62:38

R = CF₃ 49%

2-aryl/4-aryl, 63:37

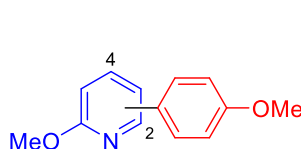
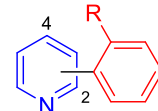
R = NO₂ 49%

2-aryl/4-aryl, 61:39

R = OMe 13%

2-aryl/4-aryl, 67:33

R = Et 0%

15%
2-aryl/4-aryl, 60:40

R = F 31%

2-aryl/4-aryl, 64:36

R = CF₃ 23%

2-aryl/4-aryl, 23:0

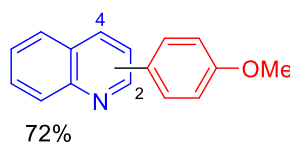
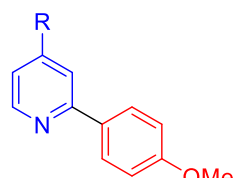
R = NO₂ 52%

2-aryl/4-aryl, 60:40

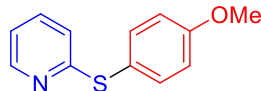
R = OMe 57%

2-aryl/4-aryl, 66:34

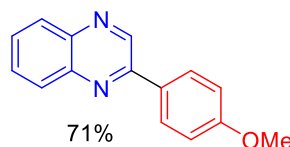
R = Et 0%

72%
2-aryl/4-aryl, 41:59R = CF₃ 41%

R = OMe 12%



38%



71%

Scheme 5. Visible light induced, catalyst-free arylation of pyridinium hydrochlorides exploiting a charge transfer interaction for initiation.¹⁷

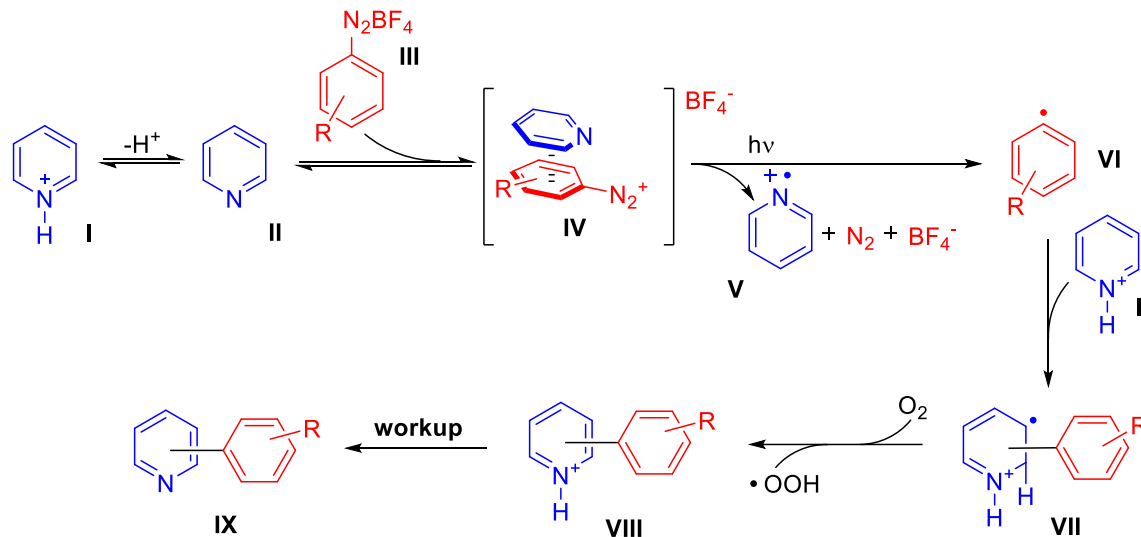
Pyridines with no blocking substituents generally led to mixtures of 2- and 4-substituted products. In contrast to the study by Fürst et al.,¹⁶ electron donating and more or less electron neutral diazonium salts now led to higher yields than those substituted with electron acceptor groups. A donor substituent (e.g. R = OMe) at the position 3 or an acceptor substituent (e.g. R = F, CF₃) at the position 2 of the diazonium salt decreased the product yield significantly to 13-31%. The protonated 4-dimethylaminophenyldiazonium salt only led to 2-arylated product in 14% yield.

Complete absence of the expected biaryls was observed for 2-ethyl and 3-ethyl substituted diazonium salts. As no biaryls were formed but 56% and 55% the corresponding phenols, respectively, these side products point to the option that some reactions may apparently be directed to a cationic pathway.

Besides these exceptions, almost all employed substrates showed biaryl product formation in medium to high yields. Especially good yields were obtained for quinoline (72%) and quinoxaline (71%) as substrates. The

reaction between 4-methoxyphenyldiazonium and 2-methoxy- or 4-methoxypyridine as a substrate yielded the biaryl products only in low yields (12%, 15%). Only the pyridine-2-thiol led to a product arylated at the thiol position instead of an arylation at the aromatic ring.¹⁹

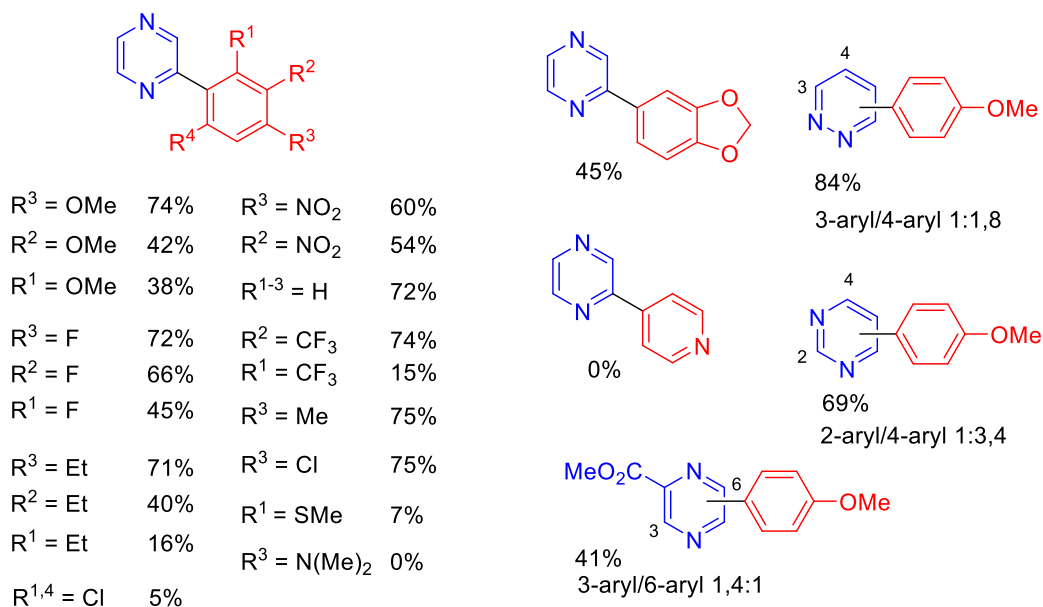
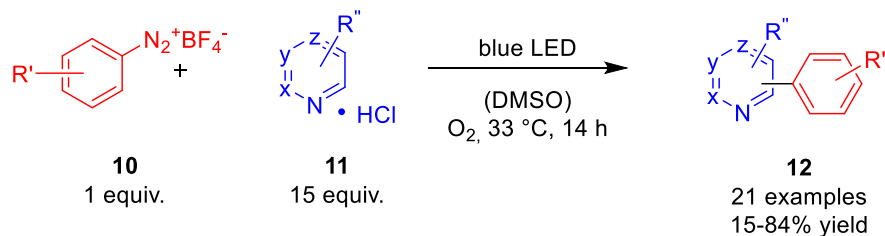
Based on the observations from the optimization experiments and further control reactions, the following reaction mechanism was proposed.¹⁷



Scheme 6. Radical arylation based on visible light sensitive charge transfer complexes between arenediazonium salts and pyridine.¹⁷

While the necessity of light irradiation was shown by control reactions in the dark, the addition of the radical scavenger TEMPO led only to a partial inhibition of reaction, which can however be due to the low solubility of TEMPO in water. Besides employing UV-Vis measurements (see Figure 3), the interaction between pyridine or its hydrochloride salt and 4-methoxybenzenediazonium tetrafluoroborate could also be shown by 1H-NMR aggregation studies. In these experiments, mixtures of diazonium salt and pyridine free base or hydrochloride at high concentration showed a slight change of the chemical shifts.

In a follow-up study by Oliveira,²⁰ the substrate scope of the charge transfer-based, visible light induced arylation of pyridines could be extended to further nitrogen-containing heterocycles (Scheme 7).



Scheme 7. Visible-light induced, charge-transfer based arylation of pyrazine, pyrimidine and pyridazine.²⁰

Scheme 7 also gives an overview over scope and limitations resulting from the use of different diazonium salts. High product yields (60-75%) were obtained when 4-substituted diazonium salts were applied, regardless whether the substituent was electron donating (e.g. R³ = OMe), more or less electron neutral (e.g. R³ = Cl) or electron-withdrawing (e.g. R³ = NO₂). Diazonium salts with 2- and 3-substitution led to moderate yields (15-66%), except for the 3-trifluoromethylphenyldiazonium which yielded 74% of the biaryl product in contrast to the low yield resulting from the 2-trifluoromethylphenyldiazonium (15%). Attempts with the 2-mercaptobenzenediazonium or the 2,6-chlorophenyldiazonium led to very low yields (5-7%). Similar to Oliveira's previous work¹⁷ (Schemes 5, 6), the reaction with 4-dimethylaminobenzenediazonium did not provide any product. In addition to the substituents and substitution pattern on the diazonium salts, the regioselectivity was investigated for a substituted pyrazine, pyrimidine and pyridazine (Scheme 7).

Compared to Oliveira's earlier study¹⁷ discussed above, a key difference is the use of DMSO as solvent instead of water. This can be rationalized by the UV-Vis studies summarized in Figure 4. In water, hardly any charge-transfer interaction was detectable, whereas remarkable absorption bands were observed in DMSO. Since the heteroaromatic substrates pyrazine, pyrimidine and pyridazine are more polar than the previously used pyridine, a more stable water shell is now likely to hinder significant charge transfer complex formation. When changing to DMSO, in contrast, the less stable solvent shell still enables CT complexes suitable for initiation. In addition, the formation of excited states might be improved by using DMSO as a solvent.

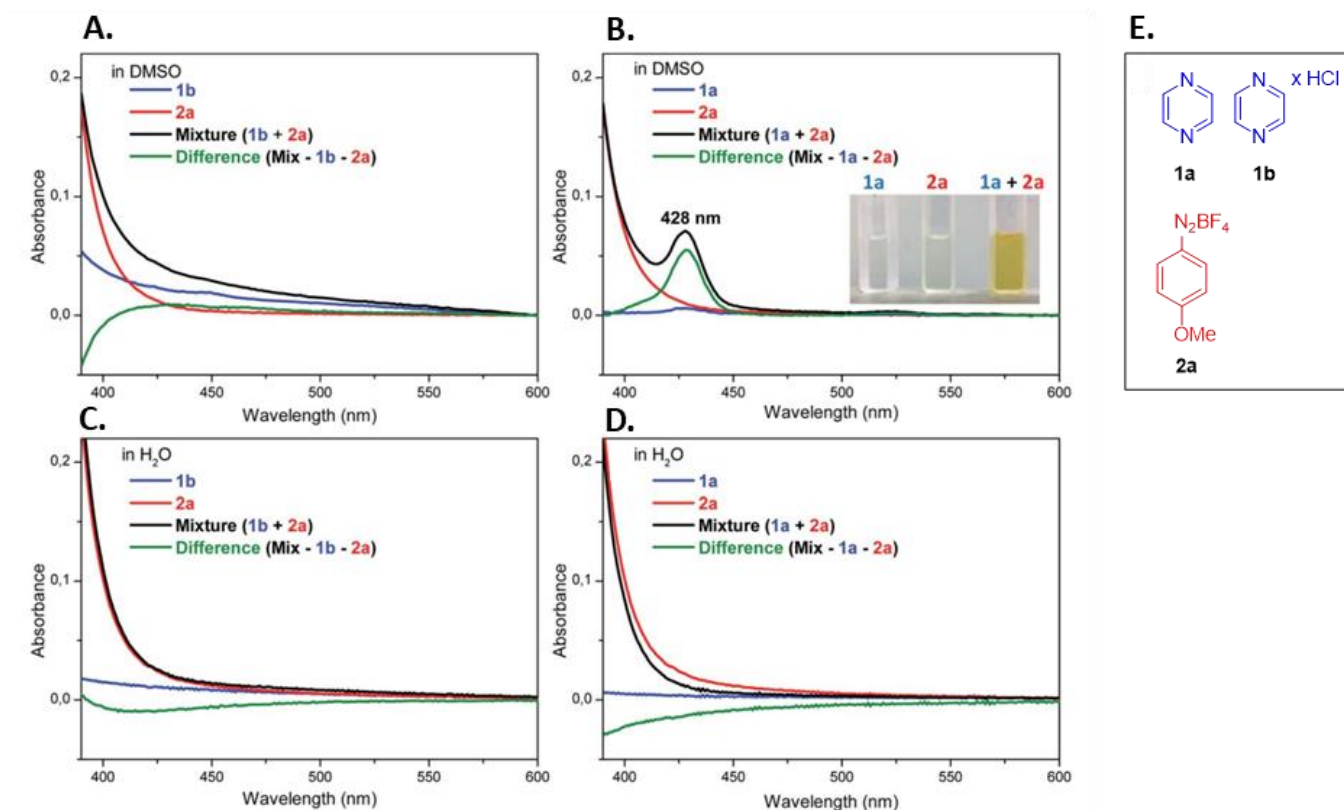
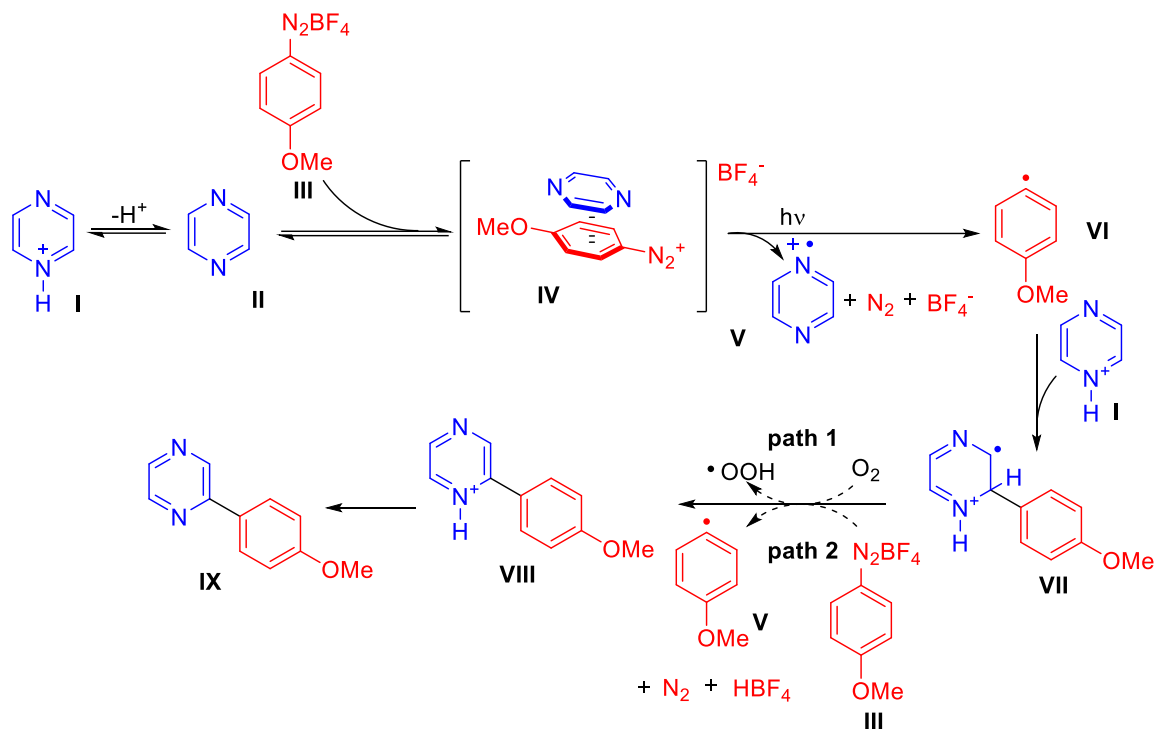


Figure 4. UV-Vis studies on charge transfer complex formation: comparison of water and DMSO as solvents. Adapted with permission from Silva, R. C.; Villela, L. F.; Brocksom, T. J.; de Oliveira, K. T. *RSC Adv.*; **2020**, Copyright 2020 Royal Society of Chemistry.

Regarding the reaction course, a similar mechanism is plausible as previously described for pyridines (Scheme 8).

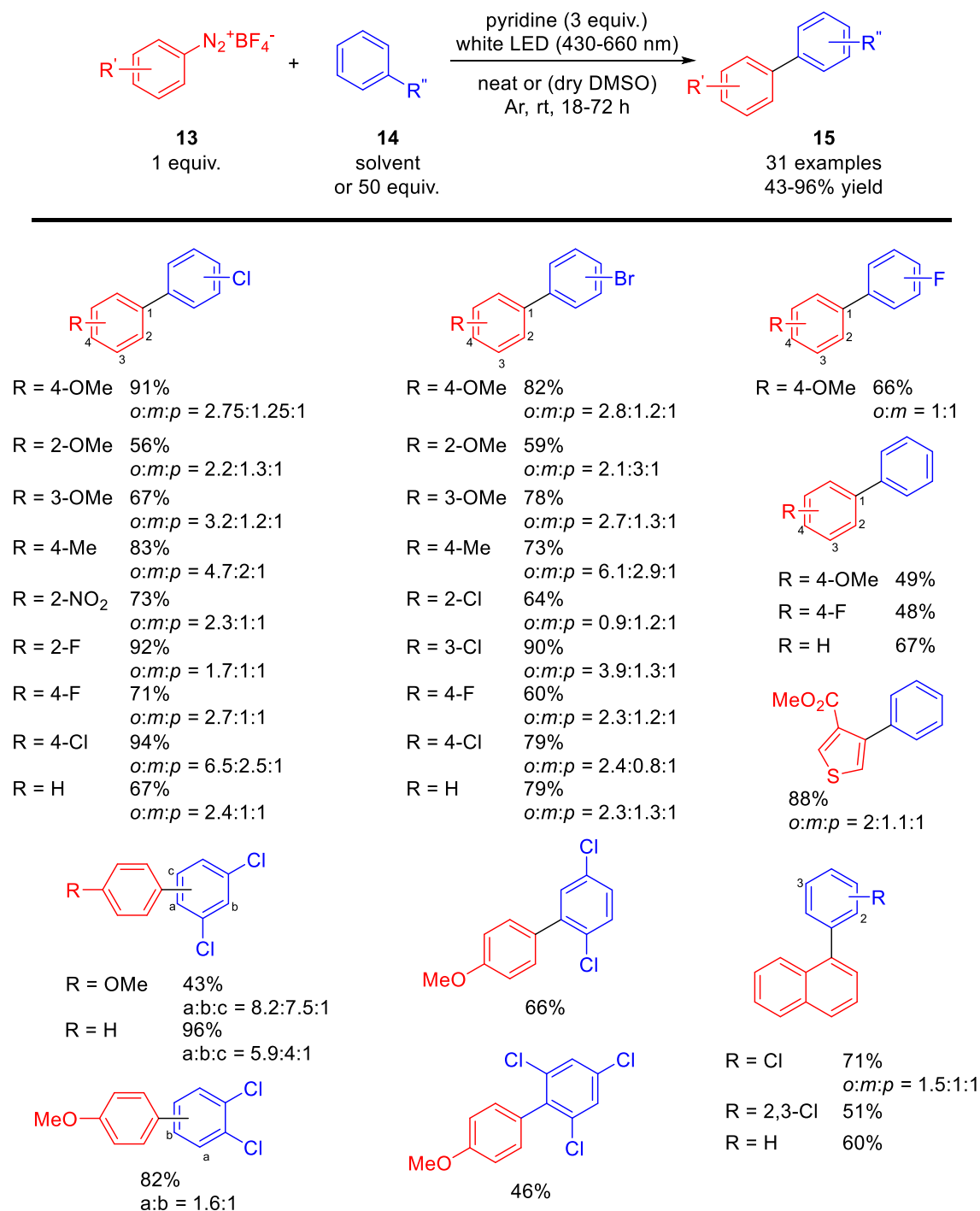


Scheme 8. Plausible reaction mechanism for the visible light induced, charge transfer based arylation of pyrazine.²⁰

In control experiments, the intermediacy of aryl radicals could be supported by trapping with TEMPO. In addition to the points mentioned above, the mechanistic proposal in Scheme 8 provides a further reason for the superiority of DMSO as solvent compared to water, as the lower dielectric constant of DMSO can lead to a more favorable equilibrium between the protonated species **I** and the free base **II** thereby promoting the formation of the crucial CT complex **IV**.

Based on the successful arylations of pyridine, pyrazine and its isomers (Schemes 7, 8), showing that such heterocycles are suitable substrate to form charge transfer complexes with a broad variety of diazonium salts, Lee et al.²¹ explored the feasibility of arylations in which pyridine was only added for initiation. A plausible rationale supporting this approach is that aryl radical addition to pyridine is comparably slow^{22,23} ($3.7 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$) so that a more reactive aromatic substrate can be successful in competing with pyridine. Besides exploiting relative reactivity, an aromatic substrate being a comparably reactive to pyridine can be used in excess to direct the radical arylation to this substrate and away from the “initiator” pyridine.

An overview over the scope of the aryl-aryl coupling reactions, in which pyridine is used as an initiator enabling charge transfer complex formation, is given in Scheme 9. Since the substrates used as aryl radical scavengers are in a similar reactivity range as pyridine,^{24,25} these substrates had to be present in excess (50 equiv.) or even had to be used as solvents.



Scheme 9. Visible light promoted radical arylation based on charge transfer complexes between diazonium salts and pyridine.²¹

Regarding the substrate scope - and similar to the earlier work by de Oliveira¹⁷ - electron-donating, electron-neutral as well as electron-withdrawing substituents on the diazonium salt were well tolerated. In the case of chlorobenzene, this is nicely evidenced by the successful formation of the related 4-methoxy-, 2-nitro- and 4-chlorobiphenyl derivatives. Furthermore, this observation points to a certain generality of charge transfer complex formation between aromatic diazonium salts and pyridine, which is required for initiation. In

addition to a variety of substituted benzenes, the method proved also effective for the methyl thiophene-3-carboxylate and naphthalene.

The radical reaction course could be supported by a control experiment in which TEMPO was added to the reaction mixture, thereby suppressing product formation. Moreover, visible light irradiation and the presence of pyridine were shown to be required, which strongly supports the assumption of a charge transfer complex between the diazonium salt and pyridine. For 4-methoxyphenyldiazonium, complex formation was studied in detail (Figure 5). Besides the remarkable bathochromic shift resulting from complex formation (Figure 5A), a Job plot revealed a 1:1 ratio of 4-methoxyphenyldiazonium and pyridine in the complex (Figure 5B). Based on a Scott plot (Figure 5C), a K value of 18 could be determined for complex formation (Figure 5C).

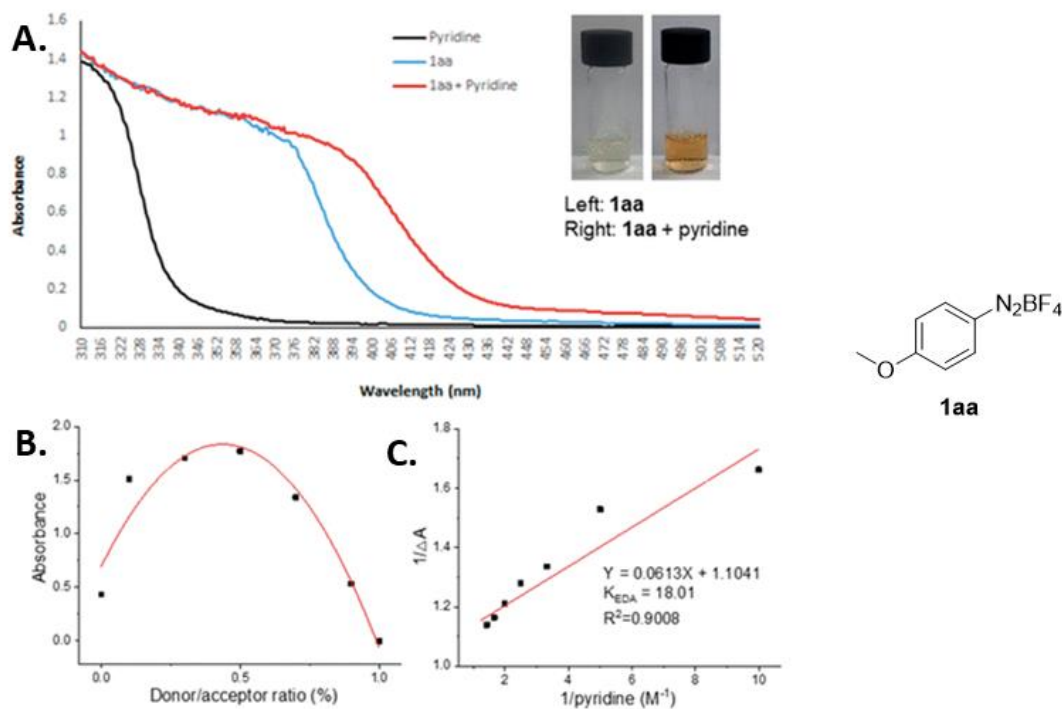
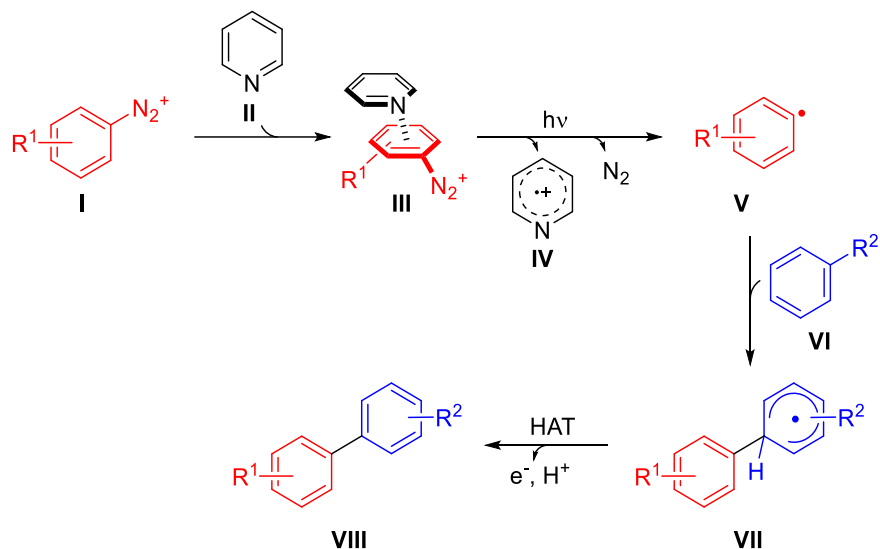


Figure 5. Characterization of charge transfer complex formation between 4-phenyldiazonium ions and pyridine in acetonitrile. Adapted with permission from Lee, J.; Hong, B.; Lee, A. *J. Org. Chem.*; **2019**, Copyright 2019 American Chemical Society.

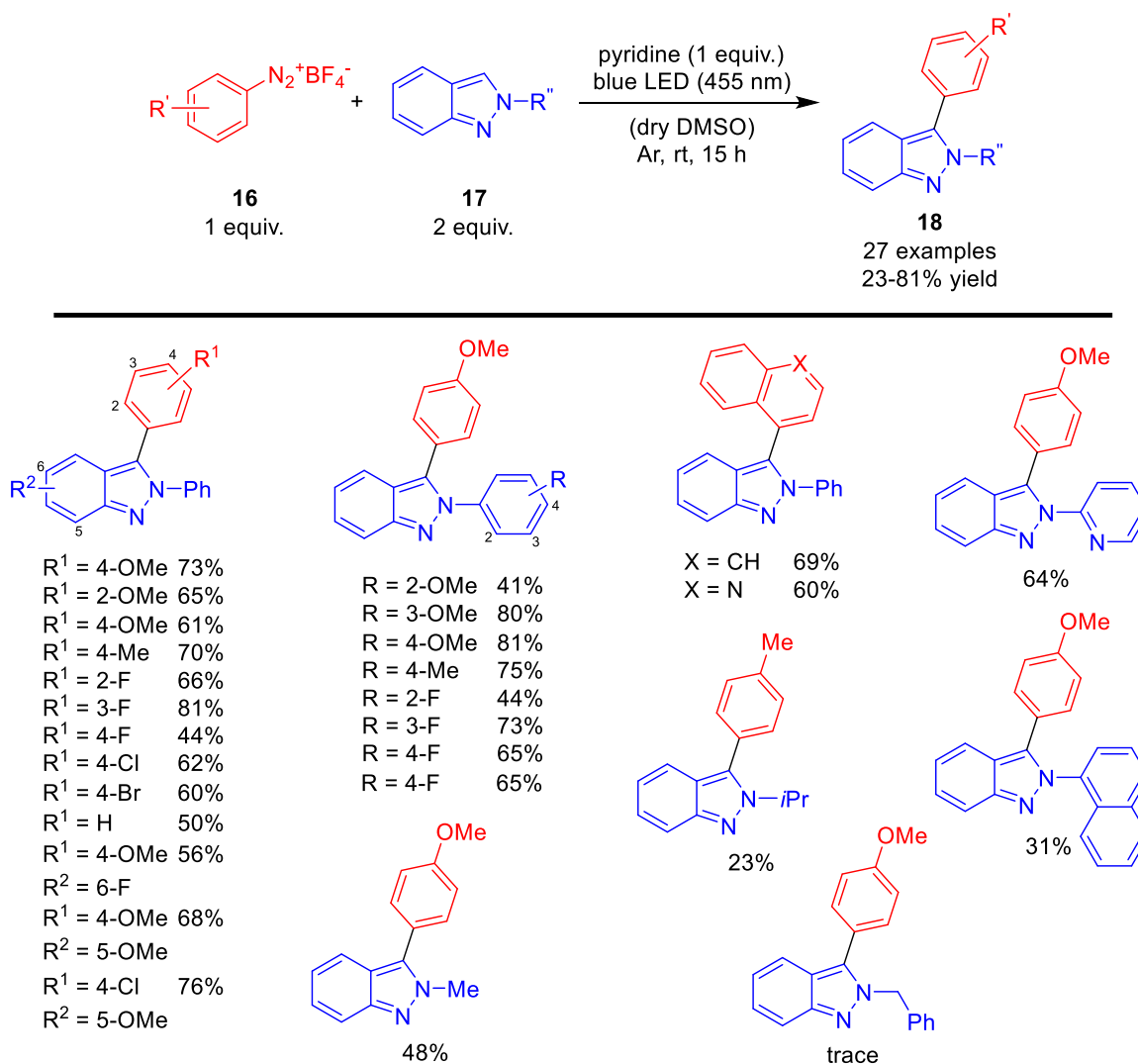
In agreement with all results and observations, a mechanism as shown in Scheme 10 was proposed. Again, the key to aryl radical formation is the irradiation of the charge transfer complex **III**. Due to the large excess of the substrate **VI**, the arylation is then mainly directed towards the substrate **VI** and not to pyridine. The electron liberated in the rearomatization step (**VII**->**VIII**) may either be transferred to the pyridinium radical cation **IV** or generate a new aryl radical from diazonium ion **V**, whereat the latter pathway is equivalent to a radical chain mechanism.



Scheme 10. Visible light promoted arylation based on charge transfer complex formation between diazonium salts and pyridine.²¹

As discussed above, and related to the relative reactivity of aromatic substrates towards aryl radicals, a large excess of substrate is not required if the particular substrate shows as significantly higher reactivity towards aryl radicals than pyridine. This option has been nicely exploited by the Lee group in a follow-up study,²⁶ in which 2H-indazoles were employed as reactive aryl radical scavengers in combination with pyridine to promote initiation by visible light irradiation.

The comparably high reactivity of the 2H-indazoles towards aryl radicals can thereby directly be derived from the optimized reaction conditions comprising an only two-fold excess of 2H-indazole relative to the diazonium salt and pyridine (Scheme 11).



Scheme 11. Visible light promoted arylation of 2H-indazoles with arenediazonium salts using pyridine for enhanced charge transfer complex formation.²⁶

Experiments aimed at optimization and mechanistic insights revealed that product formation also occurs in the absence of pyridine, but that higher yields are achieved if pyridine is present. This led to the conclusion that charge transfer complex formation is also possible between the 2H-indazole and the diazonium ion, but that the additional presence of pyridine leads to a ternary complex enabling even more effective initiation. The substrate scope points to a particular suitability of diazonium salts bearing electron-donating and more or less electron neutral substituents. The question whether acceptor-substituted diazonium salts might also be applied is to a certain extent answered by the successful use of a quinoline-derived diazonium salt leading to 60% of the related biaryl compound. On the 2H-indazole, aryl groups on the nitrogen in 2-position were mainly tolerated whereas the naphthyl derivative is likely to suffer from competitive arylation. In contrast, the alkyl-substituted indazoles gave lower yields and the benzyl derivative gave only traces, which is however plausible with regard to competing hydrogen atom transfer from the benzylic position to the aryl radical intermediate.

While the radical pathway was once more proven by a successful trapping experiment with the scavenger TEMPO, the assumed ternary complex comprising the diazonium ion, the 2H-indazole and pyridine could be

supported by UV-Vis measurements (Figure 6A). The related spectra showed bathochromic shifts for both binary complexes, namely diazonium and indazole as well as diazonium and pyridine, but an even stronger shift for the ternary mixture including all three components. Moreover, the overall absorption could be further increased through the addition of more equivalents of pyridine (Figure 6B). By investigating the chemical shift of the methoxy group of **2aa** by ^1H NMR spectroscopy, the 4-methoxyphenyldiazonium ion could be unambiguously identified as electron acceptor in the charge transfer complex (Figure 6C). Based on UV spectroscopy of varying mixtures of 2-phenyl-2H-indazole and 4-methoxyphenyldiazonium and Job plot analysis, a 1:1 ratio in the binary diazonium-indazole could be determined. For complexes between 4-methoxyphenyldiazonium ions and pyridine, the 1:1 ratio had been observed earlier (see Figure 5).

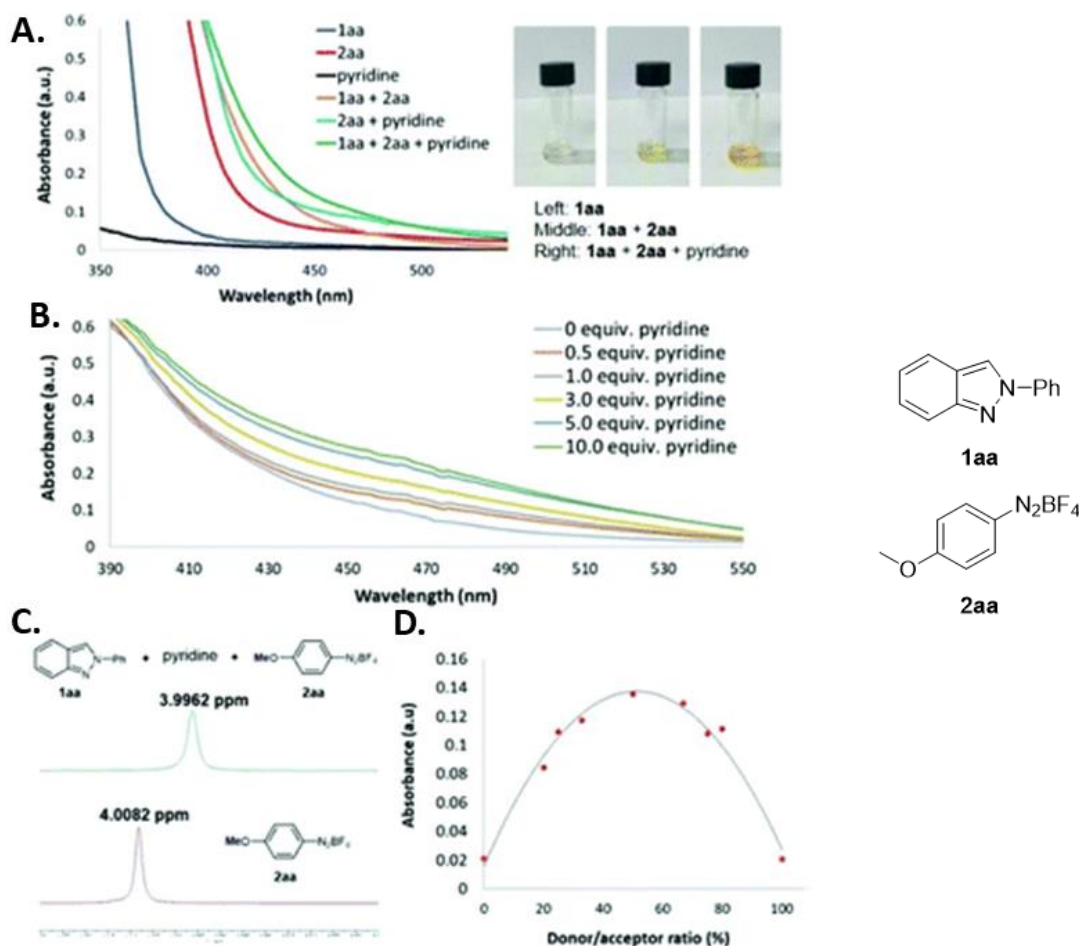
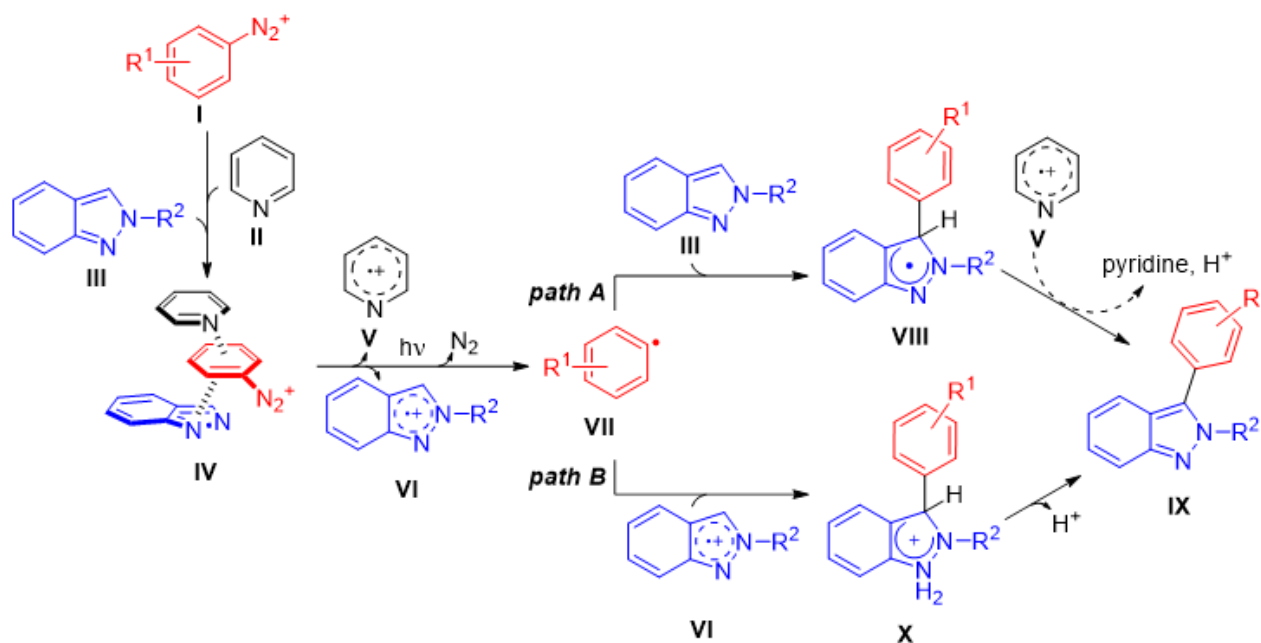


Figure 6. Investigations on the ternary complex comprising 2-phenyl-2H-indazole and 4-methoxyphenyldiazonium ions and pyridine. Adapted with permission from Aganda, K. C. C.; Kim, J.; Lee, A. *Org. Biomol. Chem.* **2019**, Copyright 2019 Royal Society of Chemistry.

Due to the formation of a ternary complex between the indazole, the diazonium ion and pyridine, light induced electron transfer to the diazonium moiety can now either occur from pyridine or from the indazole. As a result, a pyridinium radical cation **V** or an indazolium radical cation **VI** is generated along with the aryl radical **VII**. Following path A, the aryl radical **VII** is trapped by an indazole **III** to give **VIII**, from which rearomatization occurs via electron and proton transfer. Alternatively, the aryl radical **VII** may add to the indazole radical cation **VI** to give **X**, which only requires deprotonation for rearomatization (path B).

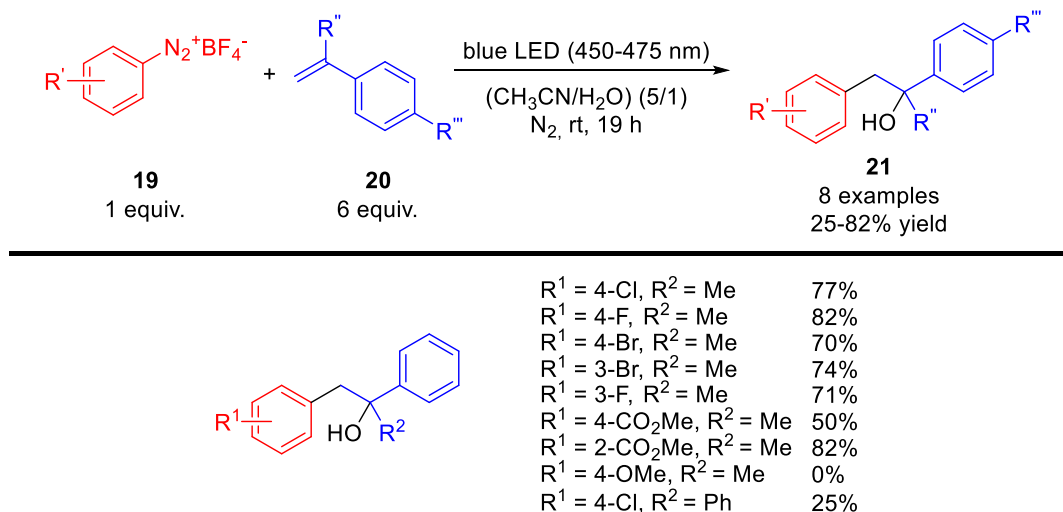


Scheme 12. Arylation of 2H-indazoles based on ternary indazole-diazonium-pyridine complexes **IV**.²⁶

3. Aryl-alkene Coupling – Meerwein Type Reactions

In addition to the radical arylation of aromatic substrates leading to the formation of biaryl compounds, visible light promoted reactions based on charge transfer initiation further turned out as highly useful to conduct Meerwein-type arylations for the functionalization of alkenes. In comparison to aromatic and even heteroaromatic substrates, styrenes are particularly suitable aryl radical scavengers since the rate of addition to such substrates is around $k = 10^8 \text{ M}^{-1}\text{s}^{-1}$ whereas the aryl radical addition to arenes and heteroarenes typically occurs at lower rate constants ranging from $k = 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $10^7 \text{ M}^{-1}\text{s}^{-1}$.

Based on the initial observation by Altmann²⁷ that the reaction of various diazonium tetrafluoroborates **19** with styrenes **20** to give the carbohydroxylation products **21** is accelerated by irradiation with blue LEDs (450–475 nm), the underlying effects were studied in more detail (Scheme 13).



Scheme 13. Visible light promoted Meerwein-type carbohydroxylation of styrenes.²⁷

The assumption that a charge transfer complex might play a key role in initiation was first supported by the substrate scope, since only the donor-substituted 4-methoxyphenyldiazonium salt failed to undergo the reaction, which can be rationalized by insufficient charge-transfer interactions with the styrene acting as a comparably weak donor. But also for the diazonium salts showing increased reaction rates under irradiation, the respective charge-transfer complexes to α -methyl styrene could hardly be detected (Figure 7).

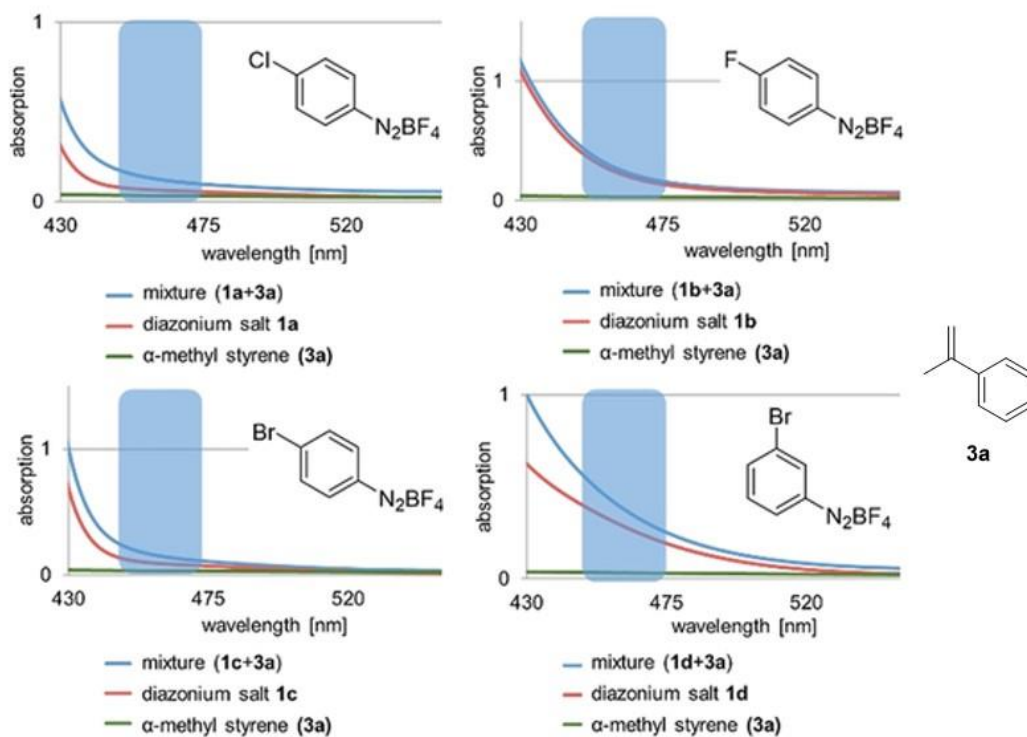
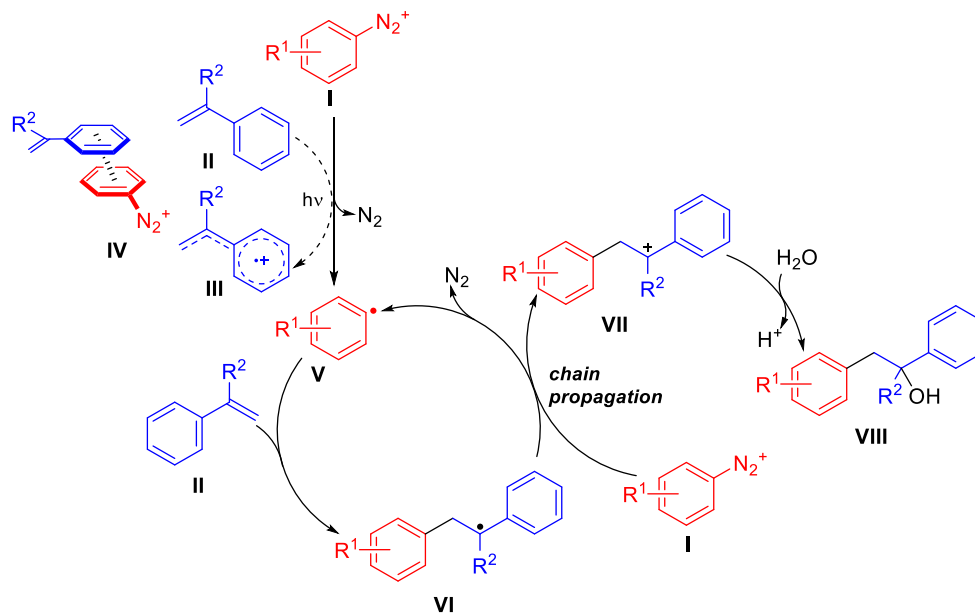


Figure 7. UV-Vis measurements of charge-transfer complexes formed between α -methyl styrene and fluoro-, chloro- and bromobenzenes. Adapted with permission from Altmann, L.-A.; Zantop, V.; Wenisch, P.; Diesendorf, N.; Heinrich, M. R. *Chem. Eur. J.* **2020**, Copyright 2020 Wiley-VCH GmbH.

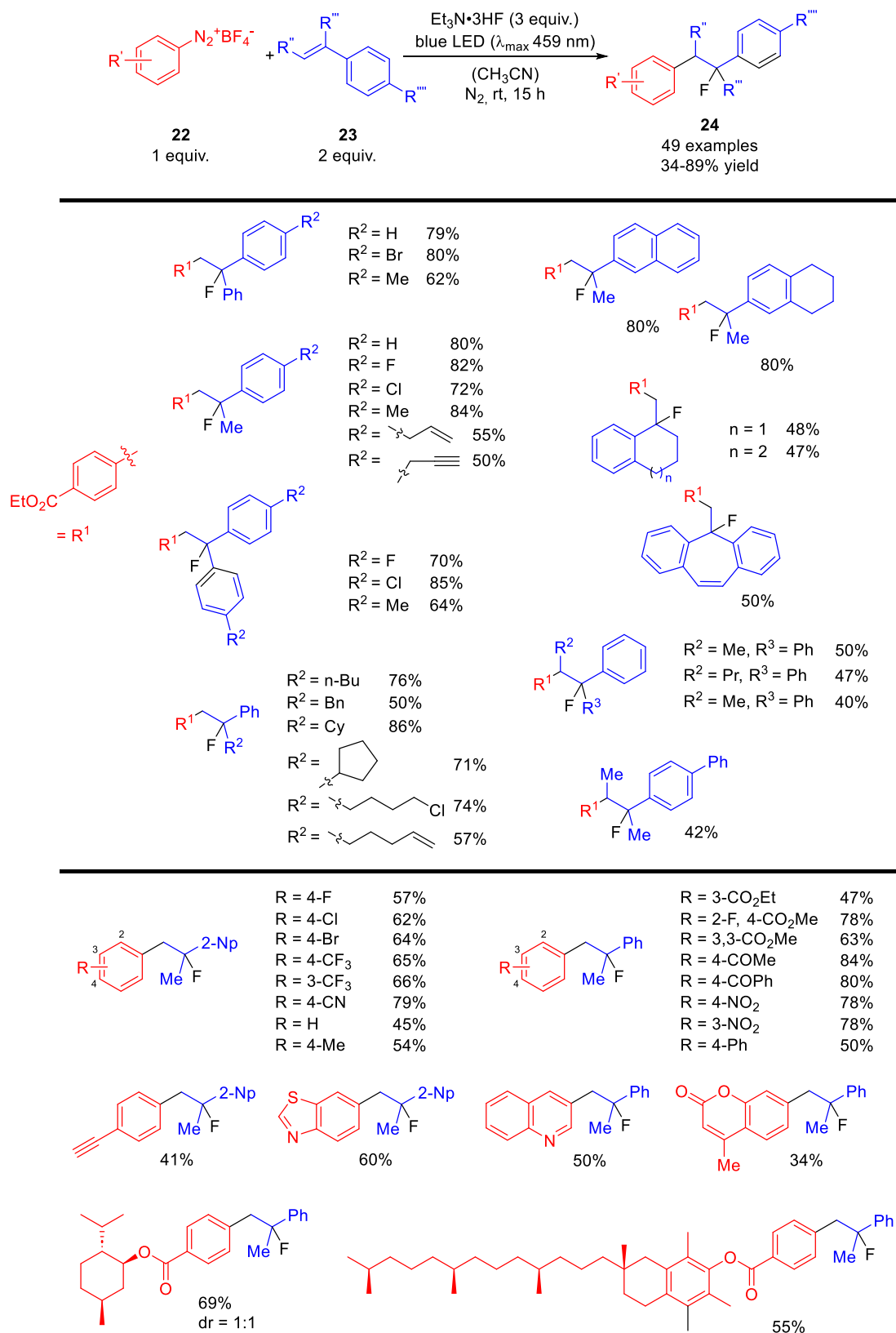
In turn, and since radical initiation via the optical absorption of the charge transfer complex is probably weak, the overall reaction has - in return - to benefit from a highly reliable radical chain leading to comparably few chain-breaking events. One aspect making the chain reliable is certainly the high rate of aryl radical **V** addition to the styrenes **II** (see above and Scheme 14). The second vital part of the chain is the propagation step, in which the diazonium ion **I** oxidizes the benzylic radical **VI** to the cation **VII** which finally forms **VIII** upon trapping with water. That the chain propagation is indeed highly efficient can be derived from the observation that control reactions in the dark (e.g. for diazonium salts **1a** and **1d** combined with α -methylstyrene (**3a**), Figure 7), where only every limited radical initiation occurs, also reach high conversions after 19 h reaction time.



Scheme 14. Plausible reaction mechanism for the visible light promoted carbohydroxylation of styrenes.²⁷

Taking together all observations in this study, it is interesting to note that the impact of visible light irradiation on the Meerwein carbohydroxylation of styrenes is strong although the charge transfer complexes between diazonium ions and styrenes are weak. The disadvantage of weak CT complexation is however counterbalanced by a very efficient radical chain, which can turn comparably few aryl radicals from initiation into a considerable amount of carbohydroxylation product **VIII**.

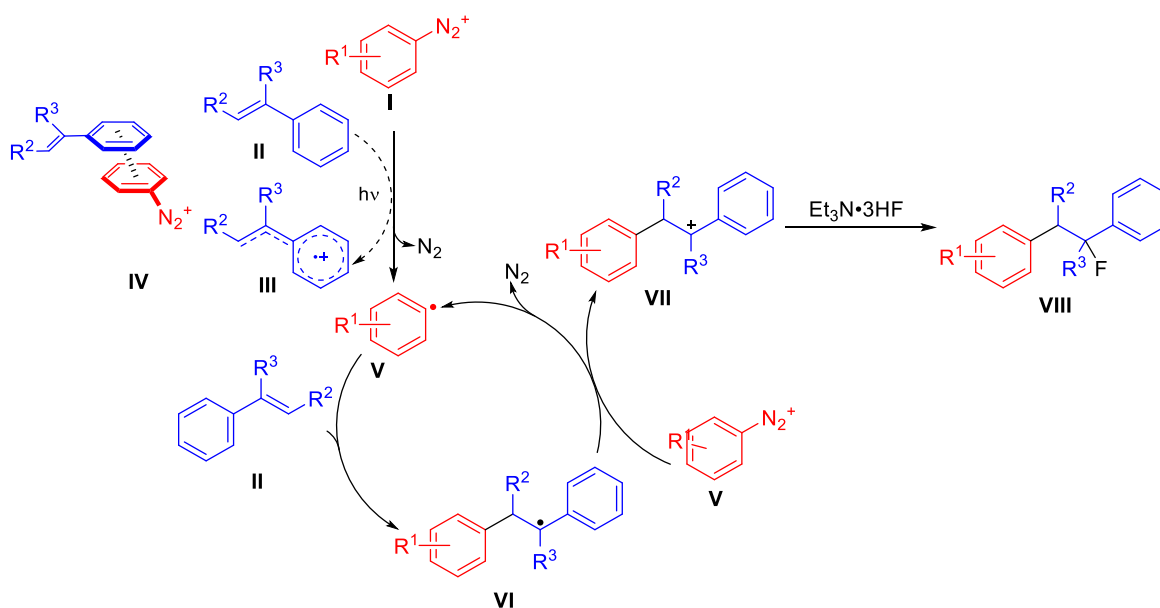
A similar reaction mechanism and the - albeit weak - sensitivity of diazonium-styrene complexes towards visible light irradiation was later on applied by Feng²⁸ for the carbofluorination of styrenes (Scheme 15). As in the Meerwein-type carbohydroxylation (Scheme 13), blue light irradiation was applied and the styrene required an alkyl or aryl substituent in α -position to ensure a sufficiently efficient chain transfer (**VI**->**VII**, Scheme 14). To introduce the fluorine atom instead of the hydroxy group, triethylamine trihydrofluoride was used as nucleophilic fluorinating reagent.

Scheme 15. Visible light promoted Meerwein-type carbofluorination of styrenes.²⁸

The broad applicability of the carbofluorination protocol was demonstrated through a large number of examples comprising both a wide range of α -substituted styrenes and aromatic diazonium salts. Notably, no

examples were reported for a diazonium salt bearing a strong electron donor. This aspect is also in agreement with the failed carbohydroxylation employing a 4-methoxyphenyldiazonium salt (Scheme 13), where the charge transfer complex as well as the chain propagation step can be considered as too unfavourable to achieve useful conversions.

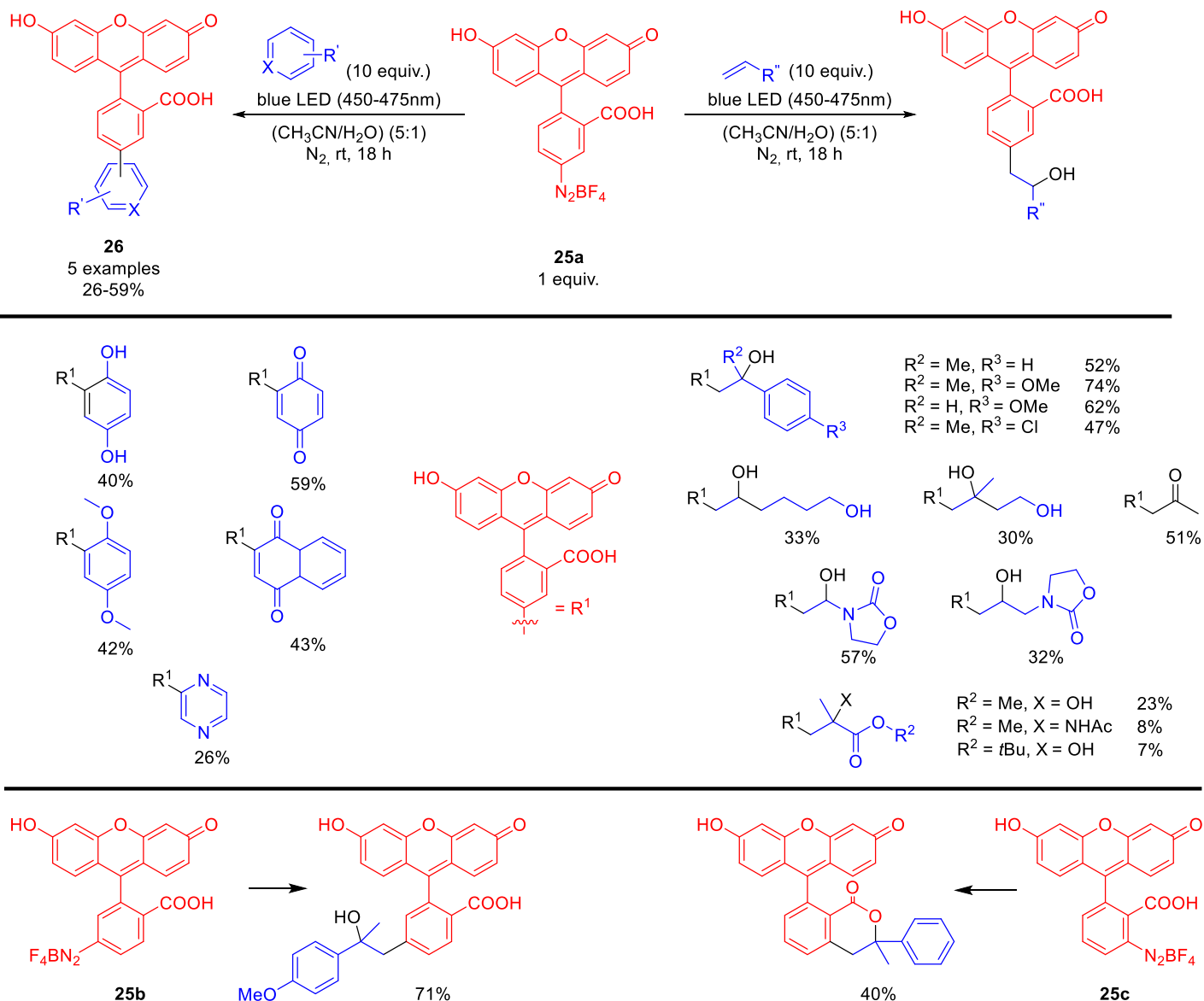
In mechanistic studies and control experiments, a styrene lacking the α -substituent failed to give the carbofluorination product, which again highlights the importance of the propagation step (VI→VII, Scheme 16). While the addition of TEMPO provided further support for the radical polar crossover mechanism, a control reaction in the absence of the nucleophilic fluorinating agent led to arylation the styrene and formation of a stilbene. Due to the manifold similarities to the previously described carbohydroxylation,²⁷ the mechanism of the carbofluorination is identical with the only exception of the final trapping of cation VII by nucleophilic fluoride (Scheme 16).



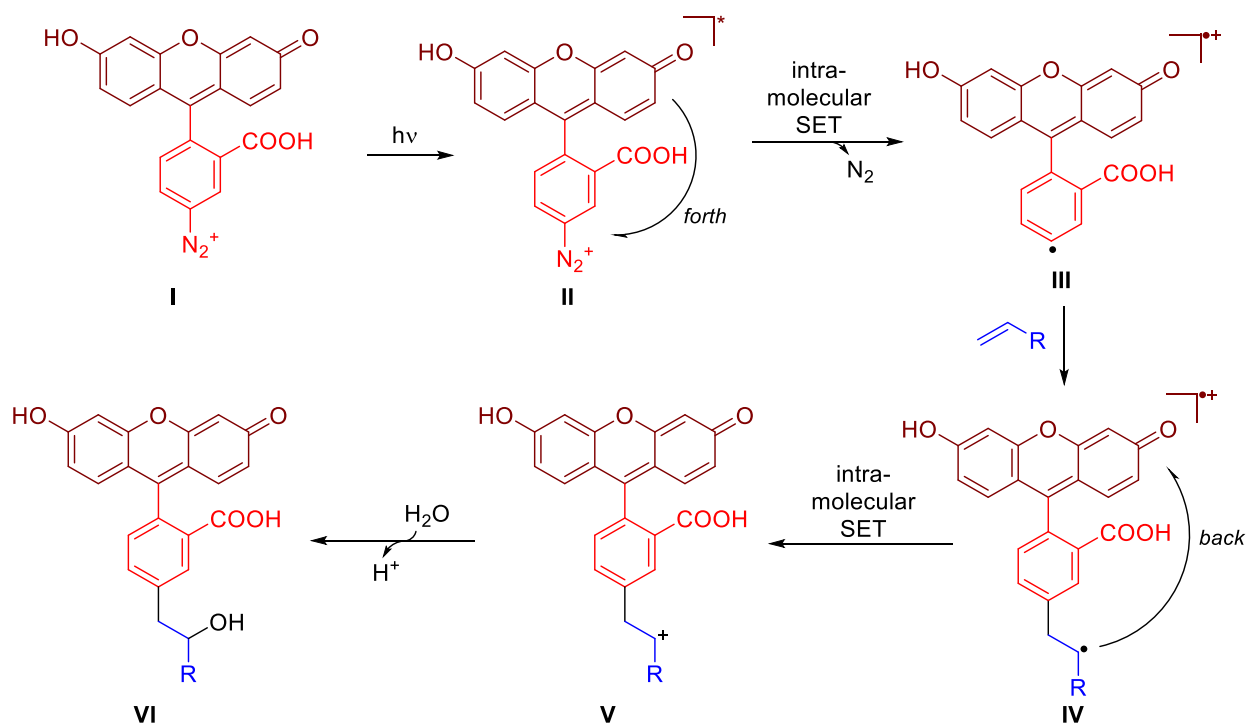
Scheme 16. Plausible reaction mechanism for the visible light promoted Meerwein-type carbofluorination of styrenes.²⁸

4. Fluorescein-derived Diazonium Salts

Having shown that the sensitivity of diazonium salts can be increased even through hardly detectable charge transfer complexes, a further option to implement catalyst-free radical arylations is employ diazonium salts which are sensitive to visible light due to their aromatic moiety. The feasibility of such arylations has recently been investigated by Diesendorf²⁹ (Scheme 17). Diazonium salts derived from the well-known dye fluorescein, such as **25**, were previously used in azo coupling reactions,^{30,31} but no generation of the related aryl radicals had been reported. An overview over the products accessible from **25a**, **25b** and **25c** via Gomberg-Bachmann- and Meerwein-type reactions is given in Scheme 17.



The reason why carbohydroxylation of non-activated and electron-deficient alkenes is nevertheless possible, is outlined in Scheme 18. Starting with optical excitation of **I** to give **II**, intramolecular single electron transfer triggers the cleavage of nitrogen and the formation of the aryl radical **III**. This aryl radical **III** is more precisely a diradical cation as the xanthene moiety remains oxidized. Upon addition to the alkene to provide the alkyl radical **IV**, the previously oxidized xanthene unit now offers an intramolecular oxidation pathway through which even difficult oxidations from radical to cation become possible. With a restored xanthene moiety, the cation **V** is finally trapped by water to furnish the carbohydroxylation product **VI**.



Scheme 18. Meerwein arylation using the fluorescein-derived diazonium salt **25a** featuring a forth and back electron transfer mechanism.²⁶

While the hydroxy group's origin from water could be verified through the use of H_2^{18}O as solvent, the mechanistic steps involving forth (**II**->**III**) and back (**IV**->**V**) electron transfer were supported by an alternative initiation method. When treating diazonium salt **25a** with the reductant iron(II) sulfate,³² cleavage of nitrogen and formation of an aryl radical also occurs, but with the crucial difference that the xanthene moiety of **III** is then not in an oxidized state. In turn, the transient aryl radical can well add to the alkene to give an intermediate comparable to **IV**, but the following intramolecular back electron transfer to the xanthene will be impossible. As a result, no oxidation to the cation (c.f. **V**) occurs and the alkyl radical is trapped by an available scavenger – such as another diazonium ion – to give an azo compound as main product.³²

Besides providing first illustrative examples for reactions of fluorescein-derived diazonium salts, which can – for example – be useful for the attachment of fluorescent moieties to a broad range of target molecules, the unique forth-and-back electron transfer mechanism offers a new option to generate cations from radicals at positions, which are otherwise difficult to oxidize.

Conclusions

In conclusion, visible light mediated aryl radical generation from arenediazonium salts, which is enabled by the formation of charge-transfer complexes with the respective substrates or a readily removable additive such as pyridine, offers a valuable alternative for initiation. Besides the fact that a broad range of diazonium salts and substrates are suitable for such strategy, the herein presented studies show that even very weak charge transfer interactions to an arene or alkene can be sufficient to achieve high conversions if the overall reaction proceeds via a reliable radical chain. In addition, additive-free, visible light mediated radical arylations can be readily put into practice by using diazonium salts derived from dyes. As demonstrated for the first time for a short series of fluorescein-derived diazonium salts, such reactions are not only useful to attach fluorescent moieties to larger substrates, but also offer the possibility to generate cations at unusual positions through a unique forth-and-back electron transfer.

Regarding the overall attractiveness of such charge-transfer based radical arylation techniques, it will be interesting to see to which further CT complex-forming compounds and visible light sensitive aryl diazonium derivatives this strategy can be extended. While the development of light sensitive diazonium salts may be complicated by significant homocoupling of the aryl radical to the conjugated system of the dye, the major challenge for CT complex-forming additives is their simple removal during workup.

Acknowledgements

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Authors' Biographies



Pia Wenisch started her studies in molecular science at the Friedrich-Alexander Universität Erlangen Nürnberg in 2015. She finished her bachelor studies in 2018 and obtained her master's degree in 2020 with a master's thesis on the synthesis of photoswitchable inhibitors prepared in the Heinrich research group. Shortly after, and aiming at a Ph.D. degree, she continued her research work in the same group, now further focusing on ligands for the TRPM7 receptor as well as *Meerwein* reactions with fluorescein.



Meret Kuschow began her studies in pharmacy 2015 at Friedrich-Alexander Universität Erlangen Nürnberg. During her practical trainings for pharmacists she worked in a Pharmacy in Nürnberg and at the Dr. Pfleger

GmbH in Bamberg. After obtaining the license to practice pharmacy 2020 she started working on her PhD thesis on radical arylation reactions with diazonium salts in the research group of Prof. Dr. Markus Heinrich.



Markus R. Heinrich studied chemistry with a particular focus on pharmaceutical chemistry at the Ludwig-Maximilians-Universität München. After receiving his diploma (2000) and his PhD degree (2003), he moved to the group of Prof. Dr. Samir Zard as a postdoctoral researcher. Back to Germany in 2005, he started his habilitation at the Technische Universität München. Since 2009, he has been a professor for pharmaceutical chemistry at the Friedrich-Alexander-Universität Erlangen-Nürnberg.

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