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## Catalyst-Free Arylation of Tertiary Phosphines with Diarylodonium Salts Enabled by Visible Light

Dmitry I. Bugaenko, Alexey A. Volkov, Mikhail V. Livantsov, Marina A. Yurovskaya, Alexander V. Karchava\*<sup>[a]</sup>

**Abstract:** The visible-light-induced arylation of tertiary phosphines with aryl(mesityl)iodonium triflates to produce the quaternary phosphonium salts occurs under mild, metal, and catalyst-free conditions. Photo-excited EDA-complexes between diaryliodonium salts and phosphines supposedly enable this transformation, that is difficult to achieve through the traditional ground-state reactions. Demonstrating high functional group tolerance, broad scope, and complete selectivity of the aryl group transfer, particularly the method is compatible with sterically congested phosphines, which are challenging under metal-based catalytic methods.

Metal-free reactions of diaryliodonium salts are of great practical importance as they can be used as an alternative to the "traditional" metal-based cross-coupling reactions, thereby eliminating heavy-metal-related issues (high cost, toxicity, residues, etc.).<sup>[1]</sup> Initial association between a diaryliodonium salt and a nucleophile typically produces an electron-donor-acceptor (EDA) complex (Scheme 1), that can occasionally be isolated or detected by spectroscopy.<sup>[1,2]</sup> The EDA-complex, normally under thermal activation, undergoes a concerted ligand coupling at the I(III)-center, delivering an arylation product and an iodoarene.<sup>[1]</sup> Alternatively, the EDA-complexes could serve as photonabsorbing species that enable the further transformation to occur under visible light irradiation without any exogenous photosensitizer. In this scenario, excitation of the EDA-complexes by harvesting light induces an intrasystem single electron transfer (SET), eventually generating aryl radicals.<sup>[3]</sup> While metal-free arylation with diaryliodonium salts under thermal activation represents a powerful methodology developed in the last decade,<sup>[1]</sup> only few examples of synthetically useful light-induced reactions of these reagents have been reported to date.[4] However, the photo-induced reactions are of high interest because they could provide transformations that are impossible or difficult to occur through the traditional thermal reactions.

Quaternary phosphonium salts are an important class of organophosphorus compounds whose applications have been extended well beyond the classic Wittig olefination and phase-transfer catalysis (Figure 1A).<sup>[5]</sup> Organocatalysts,<sup>[6a]</sup> arylating<sup>[7]</sup> and other practically useful reagents<sup>[6b]</sup> include an

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arylphosphonium cation. Moreover, these compounds have found application in a variety of industrially relevant areas, serving as corrosion inhibitors,<sup>[8a]</sup> conjugated polyelectrolytes,<sup>[8b]</sup> electron transporting materials,<sup>[8c]</sup> nonlinear optical chromophores,<sup>[8d]</sup> ionic liquids,<sup>[8e]</sup> and antimicrobial polymeric materials.<sup>[8f]</sup>



Scheme 1. Metal-free arylation with diaryliodonium salts: thermal and photo activation modes.

Furthermore, delocalized lipophilic arylphosphonium cations can readily pass through the lipid bilayer of the cell membrane and accumulate within mitochondria inside cells.<sup>[9]</sup> Introducing an arylphosphonium moiety into biomolecules to make them "mitochondriotropic"<sup>[9b]</sup> is currently a widely used strategy for developing of mitochondria-targeted drugs, agents for imaging, probes, and sensors.<sup>[5,9]</sup>

Commonly employed methods toward quaternary arylphosphonium salts from tertiary phosphines are based on Pd-,<sup>[10]</sup> or Ni-catalyzed<sup>[11]</sup> arylations with haloarenes and a photoredox-reaction with diaryliodonium salts mediated by a Ru-based photosensitizer (Figure 1B).<sup>[12]</sup> While mainly effective, these methodologies raise issues related to the high cost of catalysts and trace toxic metal contaminations present in the end products, which limits their industrial and biomedical applications.<sup>[13]</sup> Furthermore, multi-halogenated and sterically congested substrates are challenging for the metal-catalyzed assembly of C<sub>A</sub>-P-bond.<sup>[10,11]</sup> Among metal-free methods are quaternization with arynes<sup>[14]</sup> and the recently developed hydrogen-bondingassisted reaction with bromoarenes.<sup>[15]</sup> However, the regioselectivity problems inherent to the former and high temperature required in the latter substantially limit these methodologies. A highly specific metal-free method for introducing the Ph<sub>3</sub>P-moiety on the pyridine ring has also been developed recently.<sup>[7c]</sup> Although quaternary arylalkylphosphonium salts are traditionally available via alkylation reaction, both active alkylating agents and

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Figure 1. Examples of useful molecules featuring arylphosphonium moiety (A), current status of methods for arylation of tertiary phosphines (B).

sterically innocent phosphines are normally required for the reaction to proceed with high efficiency.<sup>[16]</sup>

We report here on the employing aryl(mesityl)iodonium triflates, bearing a variety of substitution patterns, for a broadly applicable visible-light-driven arylation of tertiary phosphines under mild, metal-, and photocatalyst-free conditions. The new protocol circumvents the above issues and is suitable for the late-stagediversification of tertiary phosphines to make valuable quaternary arylphosphonium salts.

We began our investigation by exploring the reaction of Ph(Mes)IOTf (**1a**) and Ph<sub>3</sub>P under different conditions (Scheme 2).<sup>[17]</sup> When **1a** and Ph<sub>3</sub>P were reacted in a 1:1.5 ratio in MeCN at 80 °C for 12 h a poor conversion was observed and the expected Ph<sub>4</sub>POTf (**2a**) was obtained in only 19% yield. Inspired by an early report from Reutov and co-workers<sup>[18a]</sup> and other isolated reports,<sup>[12,18b]</sup> we next examined the ability of light to drive the reaction to full conversion. After evaluating a wide set of reaction parameters,<sup>[17]</sup> we found that 90% yield of **2a** was achieved when **1a** (1 equiv) and Ph<sub>3</sub>P (1.5 equiv) in MeCN were irradiated with a 6 W blue LED (400–410 nm) for 2 h at. Importantly, arylation with **1a** lead to the exclusive formation of **2a**; while a transfer of the mesityl-group is also possible, the corresponding phosphonium salt was not detected.

After establishing the optimal reaction conditions, we applied this new protocol to a series of substituted aryl(mesityl)iodonium triflates **1a-t** having diverse electronic and steric effects (Scheme 3A). A variety of **1a-t** reacted smoothly with Ph<sub>3</sub>P, producing the corresponding aryltriphenylphosphonium triflates bearing either electron-donating (**2b**–**2i**) or electron-withdrawing (**2k**–**2s**) groups

at different positions of the phenyl ring in 44-94% yields and with excellent selectivity of the aryl group transfer. The reaction exhibits a good functional group compatibility; methyl (2d-f, k), trifluoromethoxy (2j), trifluoromethyl (2l,m), cyano (2p), methoxycarbonyl (2q), sulfamide (2s), nitro (2k,r) groups and the pyridine ring (2t) were well tolerated. Halo-substituted phosphonium salts 2n,o could also be obtained in good yields, which would be challenging using most current methods.[17] Remarkably, ortho-substituted iodonium salts, regardless of the electronic nature of the substituents, were successfully reacted giving 2e,k,I in 85-90% yields. For all aryl(mesityl)iodonium salts tested, aryls with substituents of different electronic nature are exclusively transferred, while the mesityl group serves as a "dummy" group. Notably, the reaction required prolonged irradiation time to reach synthetically useful yields when electronrich aryls were transferred (2b,f,g,i). Arylation with 4methoxyphenyl(mesityl)iodonium triflate (1i) produced 2i as the only detectable outcome, though in a moderate (44%) vield achieved in 5h. When di(mesityl)iodonium triflate (1f) was employed, however, 2f was obtained in 72% yield despite the steric hindrance. Reaction (pyridine-3-yl)(4of methoxyphenyl)iodonium triflate (1t) gave 2t exclusively in 87% vield. The chemoselectivity observed allows us to assume the reaction shows electronic preferences, suggesting that the more electron-deficient aryl group should be transferred. Considering the result obtained for 1i, however, one could conclude that steric interactions probably also contribute to the reaction outcome, though do not prevent the reaction from occurring.



Scheme 2. Selected optimization results. [a] Yields by 1H NMR, isolated yield in parentheses.

Our next challenge was to apply this method to different tertiary phosphines (Scheme 3B). All tested phosphines reacted efficiently delivering 2u-z in 66–91% isolated yields. Importantly, *tert*-butyl[bis(*o*-tolyl)]phosphine readily produced 2x in 91% yield, highlighting the utility of the developed method for arylation of sterically demanding phosphines in sharp contrast to the previous metal-based protocols.<sup>[17]</sup> Notably, the steric hindrances do not necessitate to alter the established reaction conditions. Additionally, arylation of other organophosphorus (III) compounds, namely phosphinous and phosphonous amides, also lead smoothly to **2aa,bb** in 86% and 71% isolated yields respectively with no traces of the *N*-quaternization products. Conversely, **2aa** was formed in only 17% yield with a low conversion of starting

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materials when a mixture of reagents was refluxed in MeCN for 12 h,<sup>[17]</sup> thereby highlighting the difference between ground- and excited-state reactions of the EDA-complex.

To obtain information about the reaction mechanism we performed several experiments (Scheme 4). Mixing starting compounds in different combinations and ratios did not result in the appearance of the EDA complex that could be determined by <sup>1</sup>H or <sup>31</sup>P NMR. In a UV-Vis experiment, however, the mixture of 1p and Bu<sub>3</sub>P (1:1) exhibited a weak but notable absorption between 350 and 450 nm compared to the separated compounds,<sup>[17]</sup> which can be attributed to the formation of the EDA-complex. The addition of TEMPO (1 equiv) completely suppressed the formation of 2a, implying that this reaction involved radical pathway [Eq. (1)]. In this case, similarly to the reaction performed under air conditions (Scheme 2c), Ph<sub>3</sub>PO was produced as the main product, with 1a being quantitatively recovered. Importantly, neither air nor TEMPO were able to oxidize Ph<sub>3</sub>P to Ph<sub>3</sub>P=O in the absence of **1a** under otherwise identical conditions [Eq. (2, 3)]. However, loading even only 0.1 equiv of 1a gave Ph<sub>3</sub>P=O in 13% yield after 5 h, and in 51% yield after 15 h irradiation [Eq. (4)], thus pointing to the key role of 1a in the oxidation process. Notably, 1a turned out fully stable upon exposure to visible light under both argon and air atmosphere [Eq. (6, 7)]. Irradiation of a mixture of iodobenzene and Ph<sub>3</sub>P (3 equiv) did not lead to the phosphonium salt in any detectable amount [Eq. (8)]. Finally, an on/off visible-light-irradiation experiment demonstrated that the continuous irradiation is necessary for the reaction completion.[17]

Combining the above results and literature precedents, we propose the following rationale for the reaction (Scheme 5). Initially, the interaction between a tertiary phosphine and an aryl(mesityl)iodonium salt leads to the formation of an EDAcomplex, serving as a photo-absorbing species. This complex is characterized by only a weak absorption band; however, it has been previously reported that the strong absorption of an EDAcomplex is not mandatory for a successful reaction induced by visible light.<sup>[19]</sup> Next, an excited EDA-complex is formed upon photo-irradiation. The following single electron transfer from the phosphorous atom to the iodonium center brings about decomposition of the above complex to form the aryl radical and the phosphorous radical cation with the simultaneous elimination of Mesl. Eventually, combination the above radical species leads to the resulting phosphonium salts. In the presence of oxygen, the excited EDA\*-complex changes its duty and acts as an energy transfer (EnT) agent.<sup>[20]</sup> The energy transfer process occurs between the excited EDA\*-complex and triplet oxygen <sup>3</sup>O<sub>2</sub> to give a singlet oxygen <sup>1</sup>O<sub>2</sub>., which reacts with Ph<sub>3</sub>P finally furnishing Ph<sub>3</sub>PO as the product.<sup>[21]</sup> The addition of Co(acac)<sub>3</sub>, a singlet oxygen quencher,[22] completely suppresses the formation of Ph<sub>3</sub>PO [Eq. (5), Scheme 4], thereby supporting our assumption on the key role of  ${}^{1}O_{2}$  in this oxidation process.

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Scheme 4. Control experiments.



Scheme 5. Mechanistic rationale.

While both diaryliodonium and tetraarylphosphonium salts are electrophilic species and susceptible to attack from nucleophiles, phosphonium salts being initially activated by nucleophiles could behave as nucleophilic agents,<sup>[7b]</sup> delivering of those substituents most stable as an anion.<sup>[23]</sup> The transformation of diaryliodonium salts into tetraarylphosphonium salts thus may be thought as a polarity inversion ("umpolung") of the aromatic substituent, which provides new opportunities for synthetic application of diaryliodonium salts and could be of interest for medicinal chemists. To demonstrate this concept, we prepared 3-deuteronitrobenzene (3) employing sequences merging our new and the McNally's<sup>[7d]</sup> protocols (Scheme 6).



In summary, we have developed a general method for producing quaternary arylphosphonium salts employing a visiblelight-driven reaction of aryl(mesityl)iodonium triflates and tertiary phosphines. The possibility of introducing aryl groups of different electronic and steric nature and applicability to sterically congested tertiary phosphines are the features of this protocol. In contrast to thermal reaction, the photo-induced transformation occurs with good to excellent yields under mild, metal- and catalyst-free conditions with an exceptional selectivity of the aryl group transfer governed by electronic factors.

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**Keywords:** diaryliodonium salts • hypervalent compounds • phosphonium salts • photochemistry• synthetic methods

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**Just a light is enough!** Arylation of tertiary phosphines with aryl(mesityl)iodonium salts occurs under visible light irradiation without any catalyst or additives. The new protocol allows for an easy access to valuable quaternary arylphosphonium salts, bearing substituents of different electronic and steric nature, including those challenging to current catalytic methods.

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