

# Arylation Reactions: The Photo-S<sub>N</sub>1 Path via Phenyl Cation as an Alternative to Metal Catalysis

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## ABSTRACT

Photo(sensitized) cleavage of benzenediazonium salts as well as, when an electron-donating substituent is present, of aryl chlorides, fluorides, mesylates, triflates, and phosphates leads to the corresponding phenyl cations in the triplet state. These otherwise unavailable intermediates add selectively to alkenes, alkynes, and (hetero)arenes, giving arylation products in a good yield. The reactions are photochemical alternatives of metal-catalyzed Heck and cross-coupling reactions and bear some mechanistic analogy with them.

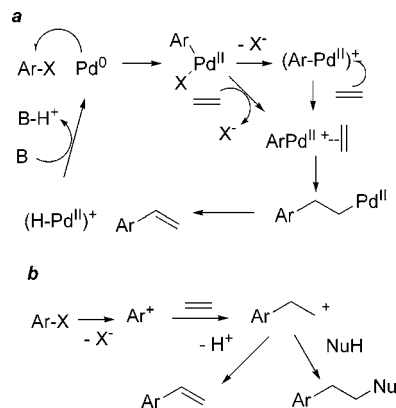
## Introduction

While S<sub>N</sub>2 substitutions are a main path for the formation of carbon–carbon bonds in alkylation reactions, no analogous facile path is available for arylation reactions. Actually, S<sub>N</sub>2Ar substitutions, e.g., with enolates, are restricted to electron-withdrawing-group-substituted derivatives. This limitation has led to the extensive development of metal (in particular palladium) catalyzed arylation methods in the past few years.<sup>1,2</sup> In these reactions, the metal acts as a nucleophile and the first step is the oxidative addition of the aryl derivative to the metal center. Ligand exchange and reductive elimination then lead to the product. Appropriate examples are the Heck reaction with alkenes (see Scheme 1a) and cross-coupling reactions with organometallics and anions such as those introduced by Stille, Suzuki, Negishi, Hiyama, and Kumada.<sup>1,2</sup> The activation mechanism can be envisaged in two phases. First, donation from the metal to the antibonding (either π\* or close-lying σ<sub>C–X</sub>\*) orbital of the reagent weakens the aryl–X bond and allows oxidative addition. Second, in the key step, ligand X is exchanged with a nucleophile, e.g., an alkene. In an extreme view, X<sup>–</sup> is detached and an aryl–metal cationic complex is the electrophile (a sort of metal-assisted S<sub>N</sub>1 process). This

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Scheme 1



ionic mechanism has actually been demonstrated to apply for the case of X = N<sub>2</sub><sup>+</sup> in a Heck reaction.<sup>3</sup>

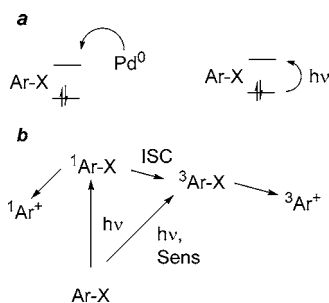
Looking at Scheme 1a, a simple question is whether the same reactivity might be more directly attained by heterolysis of the aryl–X bond, viz., through an actual S<sub>N</sub>1 process via an aryl cation (Scheme 1b). There are two objections. First, devising a precursor for the proposed heterolysis is a difficult task. When an excellent leaving group is present, such as nitrogen in diazonium salts, a phenyl cation is indeed the intermediate in solvolysis reactions, as supported by various pieces of evidence,<sup>4</sup> including the quite early recognized constancy of the decomposition rate under different conditions.<sup>5</sup> Apart from this case, however, phenyl cations<sup>6</sup> are intermediates in solution only in the solvolysis of 2,4-bis(*tert*-butyl)-4-trimethylsilylbenzene<sup>7</sup> and of some silylated dienyne.<sup>8</sup> Furthermore, the desired addition to alkenes and aromatics is easily carried out from diazonium salts via the Meerwein and Gomberg reactions, but these involve previous reduction of the salt (by Cu<sup>I</sup>) and take place via phenyl radicals, not cations.<sup>9</sup> This determines the chemoselectivity of these processes; i.e., only electrophilic alkenes react. Second, even if it were possible to generate phenyl cations easily, their reactivity would be too high, leading to indiscriminate attack on any nucleophile, e.g., the solvent.

As a matter of fact, the second objection can be in part lifted considering that phenyl cations come in two spin states, either the singlet (<sup>1</sup>Ar<sup>+</sup>) or the triplet (<sup>3</sup>Ar<sup>+</sup>).<sup>10</sup> The singlet is a localized cation expected to react as an indiscriminate electrophile, while the triplet has a carbene character at C1 and may exhibit some selectivity. Indeed, the following will show that this is actually the case and that the latter intermediate is useful for C–C bond forming reactions.

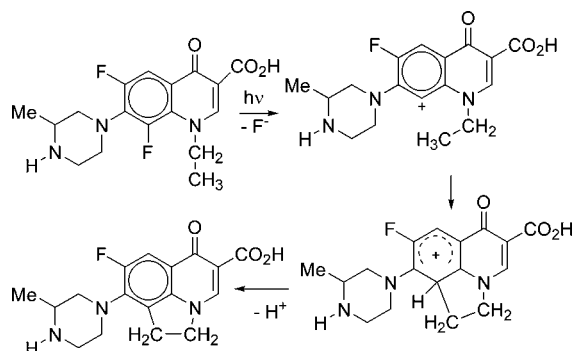
As for the first objection, given that activation of the Ar–X bond by the metal involves population of the antibonding orbitals, an alternative path is skipping the metal and promoting an electron from a bonding orbital of the molecule itself, i.e., having recourse to photochem-

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Scheme 2



Scheme 3



istry (Scheme 2a). Importantly, when the excited state cleaves, the fragments conserve the multiplicity of the state they come from. Thus, the singlet phenyl cation  $^1\text{Ar}^+$  is obtained from the cleavage of the precursor in the singlet excited state, as initially formed by light absorption, while the triplet  $^3\text{Ar}^+$  is generated either when spontaneous intersystem crossing is sufficiently fast or by triplet photosensitization (Scheme 2b).

This 2-fold possibility is analogous to the well-known photogeneration in either spin state of carbenes from diazo compounds and of nitrenes from azides. Photochemistry offers a convenient entry to triplet phenyl cations and thus introduces a simplified, though roughly mechanistically related, alternative to metal catalysis for cross-coupling arylation reactions, since these intermediates selectively add to carbon nucleophiles. In this Account, the photogeneration and the intriguing chemoselectivity of these intermediates are first discussed, and then the synthetic applications are exemplified in comparison with thermal catalytic processes.

## Origin of the Study

We came to this chemistry in an entirely serendipitous way. When studying the photodecomposition of the (considerably phototoxic) fluoroquinolone antibacterial drugs in water, we found that generally fluoride is liberated.<sup>11</sup> Mechanistic studies revealed that with some derivatives the reaction gives the corresponding phenols through an  $\text{S}_{\text{N}}2\text{Ar}^*$  process from the triplet. With other members of the series, e.g., lomefloxacin (see Scheme 3), the triplet is very short lived, apparently due to fast unimolecular fragmentation, and the product formed is not a phenol. Rather, efficient ( $\Phi = 0.5$ ) insertion into a neighboring C–H bond occurs. Little was known about

phenyl cations in solutions, but Schuster had found<sup>12</sup> that photodecomposition of a 4-piperidinobenzenediazonium salt in methanol gives the methyl ether, via the singlet phenyl cation, while the 4-acetyl analogue gives products resulting from hydrogen abstraction from the solvent, via the triplet phenyl cation.

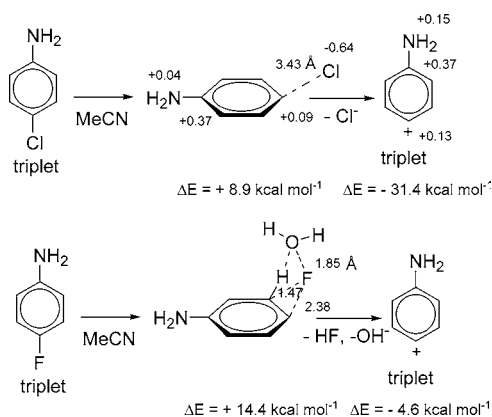
The fact that C–C bond formation rather than solvolysis was observed with lomefloxacin suggested that a triplet cation may undergo an unusual chemistry, a point that was later explored with this and related drugs.<sup>11</sup> Since the fluoroquinolone derivatives we were studying bear an amino group on the same ring as the fluorine, we surmised that a similar photoheterolysis might take place with simpler models such as fluoro- and chloroanilines. The thus formed triplet phenyl cation might be trapped by nucleophiles, in particular by  $\pi$ -nucleophiles, according to Scheme 1b. In the event, photolysis of the 4-substituted anilines in the presence of alkenes and benzene was found to give smoothly arylated products that were well rationalized as involving a cationic attack.<sup>13</sup> The various steps of the overall process are sequentially discussed in the following.

## Photogeneration of the Aryl Cation

Different fragmentation modes are known for aromatic derivatives. Thus, aryl iodides and bromides (as well as other derivatives, e.g., aryl thioethers and selenoethers) cleave (with modest quantum yield) homolytically, though electron transfer within the initially formed radical pair may lead to the formation of ionic products along with (or in the place of) radical products depending on the choice of the medium.<sup>14</sup> The stronger bond makes aryl chlorides and fluorides much less prone to homolysis, in particular from the lower lying triplet state. More important is the photo- $\text{S}_{\text{RN}}1$  process, where electron transfer from the nucleophile generates the radical anion of the aryl halide and this cleaves to give a radical.<sup>15</sup> The synthetic potential of this reaction is relevant, though it requires a weak Ar–X bond and a good donor. As for nonradical processes, there are several examples of  $\text{S}_{\text{N}}2\text{Ar}^*$  substitutions via an excited state,<sup>14</sup> while unimolecular heterolysis to give an aryl cation, though envisaged as a possible path since the pioneering work by Havinga,<sup>16</sup> has been deemed a rare occurrence and has actually been invoked only in a couple of cases.<sup>17</sup>

However, we found that the  $\text{S}_{\text{N}}1$  process dominates with electron-donating-group-substituted aryl halides in polar media, where both ionic fragments are stabilized. This has been shown in a detailed study of 4-haloanilines.<sup>18</sup> While the iodo and bromo derivatives cleave inefficiently ( $\Phi \leq 0.05$ ) in any solvent, the chloro and fluoro analogues shift from almost unreactive in apolar solvent ( $\Phi \leq 0.003$ ) to highly reactive in polar solvents (for the chloro analogue,  $\Phi_{-\text{Cl}} = 0.77$  in MeCN and 0.68 in MeOH) or in protic solvents (for the fluoro analogue,  $\Phi_{-\text{F}} = 0.48$  in MeOH but only 0.04 in MeCN). Flash photolysis confirmed that cleavage occurs in every case from the triplet. Support for the mechanism was obtained

Scheme 4



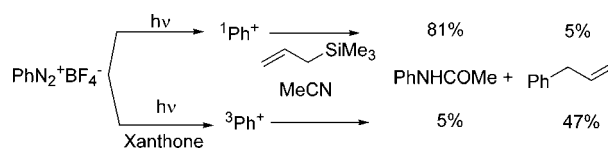
by UB3LYP/6-31G(d) calculations. These showed that heterolytic cleavage of the chloro derivative is exothermic in polar media (while homolysis remained endothermic) and actually indicated that elongation of the C–Cl bond in the triplet occurs with localization of the negative charge on the halogen atom in the quite accessible transition state (Scheme 4).

Heterolysis is exothermic also from the bromo derivative, but there the heavy atom effect shortens the lifetime of the triplet, making the cleavage inefficient. As for the fluoride, calculations showed that the requirement of a protic, not merely polar, solvent is due to the fact that only the formation of the strong H–F bond makes heterolysis exothermic. 4-Chlorophenols and anisoles also cleave efficiently in polar media.<sup>19</sup> Thus, irradiation of electron-donating-group-substituted aryl chlorides and fluorides is a convenient entry to the corresponding phenyl cations in ion-stabilizing media.<sup>20</sup>

As mentioned above, benzenediazonium salts have been known for a long time as photochemical precursors of phenyl cations, besides having a role in thermal solvolysis. Most of the photochemical work, however, has been carried out in a matrix at low temperature for spectroscopic characterization,<sup>21</sup> rather than looking for synthetic applications, though examples of spin-selective chemistry of these intermediates in solution have been found.<sup>12</sup> This point was systematically examined by photolyzing a series of 4-substituted benzenediazonium fluoroborates in acetonitrile as a non-hydrogen-donating solvent. In most cases, fragmentation proceeds from the singlet excited state and the singlet phenyl cation (Scheme 2b) is trapped by the solvent to give iminium cations and finally acetamides.<sup>22</sup> Only when the substituent makes ISC faster than cleavage (nitro, cyano, acetyl) is the triplet cation obtained. However, also in the other cases, the triplet can be easily obtained by using triplet photosensitization (xanthone performs well) rather than direct irradiation. Scheme 5 shows that singlet- or triplet-derived products are obtained in the two cases from parent benzenediazonium fluoroborate.

Another useful class of precursors are electron-donating-group-substituted phenyl esters. Organic esters undergo homolytic cleavage of the RCO–OAr bond by irradiation, finally yielding phenols and hydroxyphenyl

Scheme 5

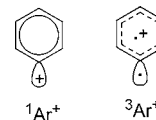


ketones (photo-Fries rearrangement),<sup>23</sup> but several inorganic esters ZOAr, such as mesylates, triflates, and phosphates were found to undergo heterolytic cleavage of the ZO–Ar bond (in polar solvents), giving phenyl cations in the triplet state.<sup>24</sup>

As seen above, a detailed mechanistic picture has been obtained in a few cases. On this basis and after (not yet systematic) explorative studies, we suggest that aromatics bearing an electron-donating group (NR<sub>2</sub>, OR, SR) in position 2 or 4 with respect to a nucleofugal (X<sup>−</sup>, ZO<sup>−</sup>) group photofragment and give triplet phenyl cations with reasonable efficiency in polar solvents.<sup>25</sup> The following presentation shows that the resulting chemistry is unmistakably cationic, though with peculiarities due to the triplet multiplicity.

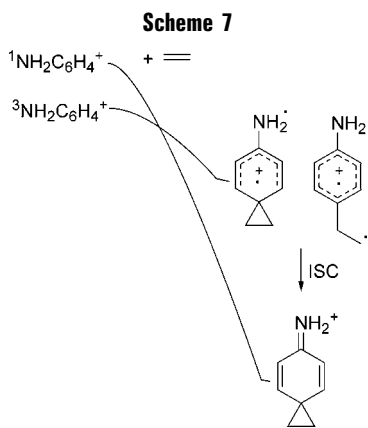
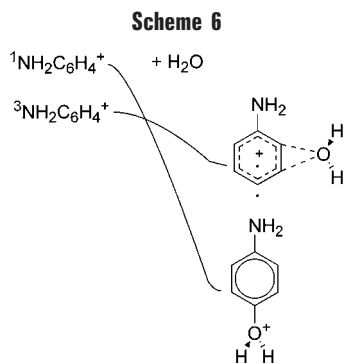
## Structure of the Phenyl Cation

The singlet is the low-lying state for the phenyl cation and for its 4-substituted derivatives, except when the substituent is OH (nearly degenerate states) or NH<sub>2</sub> (the triplet is the lowest).<sup>10</sup> However, if the (sensitized) irradiation generates the triplet cation, an efficient trap will scavenge this state, preventing ISC to the singlet when this is the lowest state. As hinted above, the electronic structure of phenyl cations depends on the multiplicity.<sup>10,18</sup> The triplet state is planar, scarcely deformed from the benzene hexagonal geometry; the charge is mainly on the ring, while the divalent carbon resembles a triplet carbene, with the difference that the second (orthogonal) electron is delocalized on the ring (strong contribution by a  $\pi^5\sigma^1$ -structure). The singlet is slightly puckered with shortened bonds and an empty orbital at divalent C1 (localized cation,  $\pi^6\sigma^0$ -structure).



The situation is more complex with substituted derivatives; e.g., for the 4-aminophenyl cation a multideterminant configuration is required for an accurate description of the singlet, but this does not deter from the applicability of the generalization that the singlet is a localized cation and the triplet rather has a carbene character at C1 (and the positive charge mainly on the ring and on the substituent when this is an electron donor such as the amino group; see Scheme 4).<sup>26</sup>

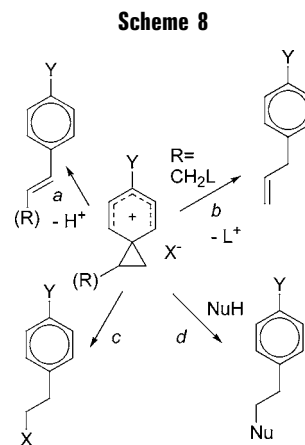
Gas-phase calculations on the two cations rationalized the different reactivities. In the case of the 4-aminophenyl cation (and the result has probably general application), B3LYP-calculated potential energy surfaces predict easy



addition of the singlet to  $\pi$ -nucleophiles. As an example, with water protonated phenol is formed through a strongly exothermic reaction (Scheme 6). However, the triplet gives no stable product, while forming reversibly a complex where a molecule of water is held perpendicularly in front of the C2–C3 bond.<sup>27</sup> Likewise, with alcohols no ether is formed; rather, hydrogen atom transfer takes place, yielding the aniline radical cation, which is finally reduced to aniline.<sup>26</sup>

By contrast, both singlet and triplet phenyl cation reacts with  $\pi$ -nucleophiles. Calculations taking ethylene as a model show that the triplet correlates with reasonably stable adducts (both a spirocyclopropylbenzenium–phenonium–ion and an open-chain structure were located) and the singlet correlates with a phenonium ion, which is by far the most stable structure (92.0 kcal mol<sup>-1</sup> below the reagents; see Scheme 7). Since triplet adducts have a geometry rather similar to that of the singlet adduct cation, intersystem crossing to the latter occurs easily.<sup>27</sup>

To summarize, since a polar (and thus to some degree nucleophilic) solvent is required for the photoheterolysis to occur, the unselective singlet attacks the solvent, while the triplet adds selectively to  $\pi$ -nucleophiles, e.g., alkenes, and ensuing ISC then leads to a singlet adduct cation (phenonium ion from an alkene). The experiments showed indeed that singlet phenyl cations add to the solvent (giving acetamides in acetonitrile, see Scheme 5, and ethers in alcohols). When generated in the triplet state, however, the cation rather abstracts a hydrogen atom from alcohol solvents and in the presence of a  $\pi$ -nucleophile is selectively trapped (Scheme 5). The latter reaction is a very fast process; in the case of 4-hydroxyphenyl cation with allyltrimethylsilane as the trap, the rate constant was



measured as  $2 \times 10^8 \text{ mol}^{-1} \text{ s}^{-1}$  and the adduct cation was detected by flash photolysis.<sup>28</sup> Indeed, when alkenes (and arenes) are present in a sufficient amount (0.2–1 M), arylation is the major or only process even in alcohol solvents. When reduction is still important, changing from methanol to less hydrogen donating media such as trifluoroethanol, acetonitrile, or MeCN/H<sub>2</sub>O improves the arylation yield.

The phenonium ion intermediate bears some resemblance to the  $\pi$ -complex with alkenes in metal catalysis (Scheme 1a), but in this case the carbon–carbon bond is already formed, with no metal atom in between. In catalysis, the ensuing steps, such as insertion and hydride transfer in the Heck reaction, still take place with the intermediates complexed at the metal center,<sup>1–3</sup> whereas in the reaction of Scheme 7 the subsequent evolution of the phenonium ion depends only on its structure and on the medium. These aspects are discussed in the next sections.

## Arylation of Alkenes and Alkynes

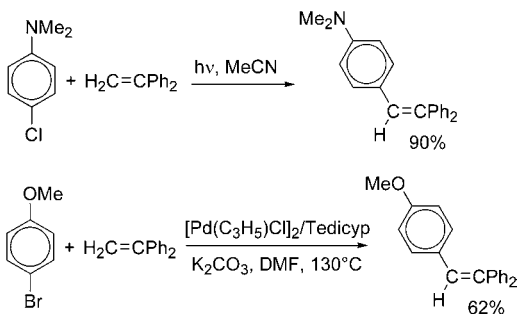
Addition of alkenes has been observed in a large number of cases and can be consistently rationalized through the formation of a phenonium ion, thus arriving through an unusual path to an intermediate otherwise invoked in substitution reactions of phenethyl derivatives.<sup>29</sup> The reaction pathways of this cation are shown in Scheme 8.

The presence of a good electrofugal group makes elimination the predominant path. As an example, a benzylic proton is lost after addition of the cation to diphenylethylene (Scheme 8, path a) and a styrene is formed, resulting in a photochemical analogue of the Heck reaction.<sup>20,27</sup> This is shown in Scheme 9, where the photochemical reaction is compared with a thermally catalyzed process.<sup>30</sup>

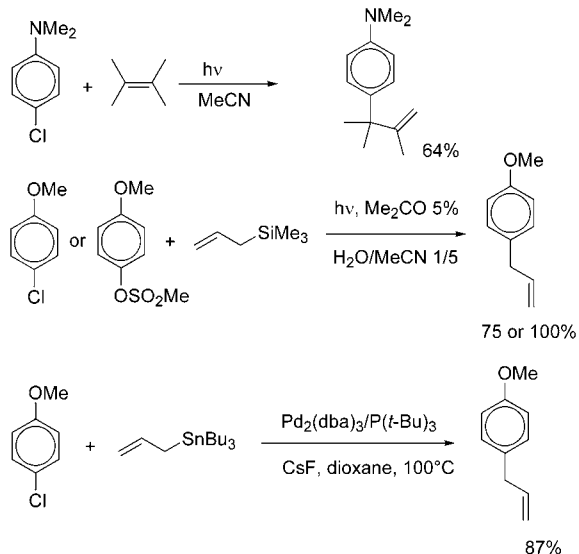
With allyltrimethylsilane or alkylated alkenes, the leaving group  $\text{L}^+$  ( $\text{H}^+$ ,  $\text{Me}_3\text{Si}^+$ ) is lost and an allylbenzene is efficiently formed (Scheme 8, path b). Typical examples are reported in Scheme 10,<sup>19,27</sup> where they are compared with a Stille coupling;<sup>31</sup> the method has been applied to the synthesis of naturally occurring (in plants of the genus *Piper*) phenols with medicinal activity.<sup>32</sup>

In the absence of a good electrofugal group, the following course of the reaction may be directed by

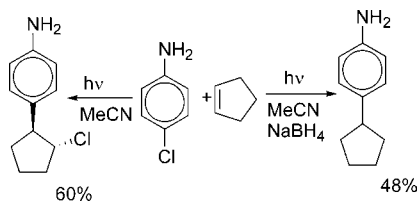
Scheme 9



Scheme 10



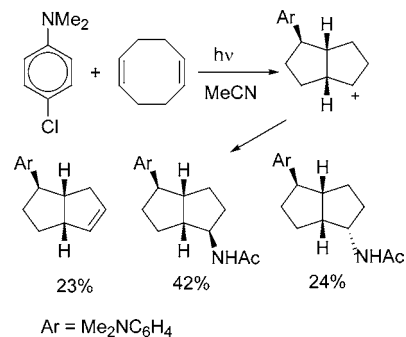
Scheme 11



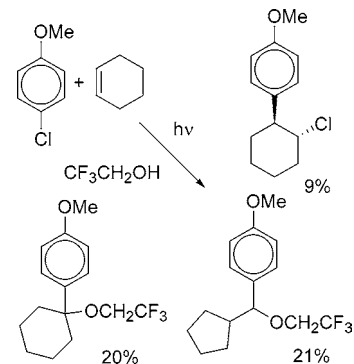
choosing suitable conditions. When using a polar, non-nucleophilic medium, the phenyl cation reacts when still paired to the counterion, and this is incorporated into the adduct. Thus,  $\beta$ -chloroalkylarenes are obtained (Scheme 8, path c; see an example in Scheme 11).<sup>19,27</sup> This process can be envisaged as an ionic complement of the Meerwein arylation of alkenes. Both reactions introduce a  $\beta$ -chloroalkyl group, but the present one involves a cationic attack on nucleophilic olefins, whereas the radical Meerwein reaction is limited to electrophilic olefins.

The conditions can be changed in two ways, viz., (i) by using a more charge stabilizing solvent (e.g., trifluoroethanol, water–acetonitrile) that favors reaction via the free ions rather than the ion pair and (ii) by using a nucleophilic solvent or an added nucleophile that overcomes competition with the counterion generated in the photoheterolysis (Scheme 8, path d). As expected, the phenonium ion reacts easily with  $n$ -nucleophiles. Thus, the selective reaction of phenyl cations with  $\pi$ -nucleo-

Scheme 12



Scheme 13



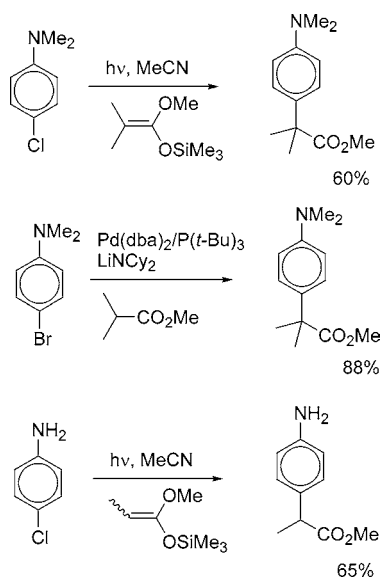
philes can be exploited for C–C bond formation and the ensuing reaction of the phenonium ion with a heteroatom-centered nucleophile for further functionalization. Indeed,  $\beta$ -alkoxyalkyl aromatics are obtained in alcohols<sup>16,23</sup> and  $\beta$ -aminoalkyl derivatives in the presence of amines.<sup>33</sup> Addition of sodium boron hydride leads to reduction of the adduct cation and gives alkyl derivatives. As an example, 4-alkylanilines are obtained from the 4-chloroanilines (Scheme 11),<sup>34</sup> through a path that is simpler with respect to other syntheses, such as nitration and reduction of an alkylbenzene or cross-coupling reactions.

Intramolecular trapping may also be efficient, as demonstrated in the case of pentenoic acid, which gives a benzyl  $\gamma$ -lactone,<sup>27</sup> and with bicyclic dienes, as shown in Scheme 12 for the case of 1,5-cyclooctadiene.<sup>35</sup>

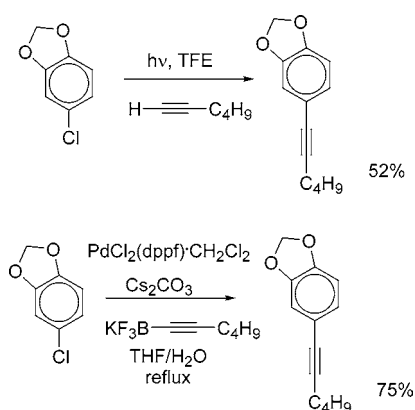
On the other hand, carrying out the reaction under free ion conditions favors Meerwein rearrangements (hydride or alkyl shift) of the intermediate phenonium ion. As an example, using an alcohol with a better ionizing power, e.g., trifluoroethanol rather than methanol, rearranged ethers are obtained, as shown for the case of cyclohexene in Scheme 13.<sup>19</sup>

Another instance of rearrangement is the reaction with norbornene, where a phenylnorbornene and various acetamido (in MeCN) or alkoxy (in alcohols) phenylnorbornanes are obtained, with a regioisomeric distribution closely matching that observed by solvolysis of 2-norbornyl derivatives.<sup>36</sup> This demonstrated a novel entry to the nonclassical 2-norbornyl cation<sup>37</sup> under unconventional and mild conditions, which offers the possibility of some control over the outcome (e.g., the competition between elimination to give a tricyclic and addition to

Scheme 14



Scheme 15



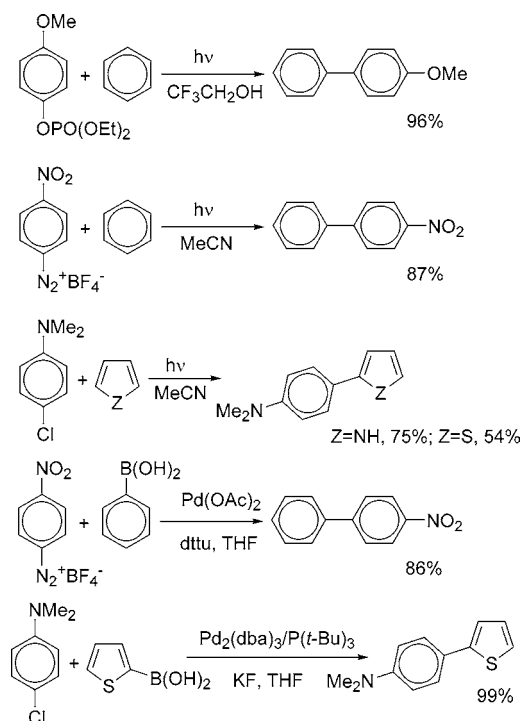
give isomeric norbornanes is governed by the basicity/nucleophilicity of the solvent).

Apart from these more mechanistic aspects, a preparatively interesting application is the reaction with a particular class of alkenes, viz., silyl enol ethers or silyl ketene acetals. These afford a smooth synthesis of  $\alpha$ -aryl ketones and aldehydes, or, respectively, of arylacetic esters.<sup>38</sup> An example is shown in Scheme 14, once again in comparison with a palladium-catalyzed coupling.<sup>39</sup> Noteworthy, the photochemical method can be applied to nonmethylated aniline to give methyl 2-(4-aminophenyl)propionate (Scheme 14, bottom),<sup>38</sup> the direct precursor for the drugs alminoprofen and indoprofen, which has *not* been obtained by thermal catalysis, but only via alkylation of the nitro compound and reduction.<sup>40</sup>

Arylation of alkynes is likewise successful,<sup>32</sup> offering an entry to arylalkynes alternative to the Sonogashira reaction (see Scheme 15).

Summing up, smooth arylation reactions exploiting the high, but selective, reactivity of phenyl cations with neutral  $\pi$ -nucleophiles such as alkenes, alkynes, or enol ethers are possible and complement catalyzed processes usually requiring anions or organometallic nucleophiles.

Scheme 16



## Arylation of Aromatics and Heteroaromatics

Generation of aryl cations in the presence of benzene leads to biphenyls.<sup>19,27</sup> Analogously to the reaction with alkenes, this is an ionic variation of a known radical process, the Gomberg–Bachmann biphenyl synthesis. Two examples are reported in Scheme 16 and compared with a thermal process.<sup>41</sup> An intramolecular variation, an ionic analogue of the Pschorr synthesis, was demonstrated by the photosensitized decomposition of the *o*-benzyl-oxidiazonium fluoroborate.<sup>32</sup> Using substituted benzenes of course may lead to mixtures, but preliminary experiments suggest a remarkable regioselectivity in some cases.<sup>32</sup>

The selectivity of phenyl cation is demonstrated in the arylation of five-membered heterocycles.<sup>42</sup> Virtually exclusive arylation in position 2 is obtained with pyrrole and thiophene (Scheme 16), though 2,5-dimethyl derivatives were smoothly arylated in position 3. This is analogous to the heteroaryl Heck reaction and compares well with the analogous Pd-catalyzed reaction<sup>43</sup> and with cross-coupling reactions (Scheme 16).<sup>44</sup> The selectivity for attack in position 2 (>50:1) is much greater than in other electrophilic substitutions, another indication that triplet phenyl cations are not localized cations and therefore are not unselective electrophiles. With furan, as one might expect, 2,5-addition occurred in place of electrophilic substitution.<sup>42</sup> Thus, this phenylation method is an alternative to the Suzuki catalyzed procedure.

## Conclusion and Outlook: Synthetic Significance of the Photo-S<sub>N</sub>1 Arylation

The discussion above shows that an S<sub>N</sub>1 process is a viable path for arylation reactions, provided that the phenyl

cations are generated in the triplet state. These thermally inaccessible intermediates are smoothly obtained by (sensitized) irradiation of benzenediazonium salts, used also for thermally catalyzed arylation reactions.<sup>41,45</sup> Perhaps more importantly, with electron-donating-group-substituted derivatives, the cations are efficiently obtained also by photolysis of phenyl halides (both chlorides and fluorides, the latter substrates being only rarely reactive under catalyzed conditions)<sup>46</sup> and of inorganic phenyl esters (mesylates, triflates, phosphates). The phenyl cations attack selectively  $\pi$ -nucleophiles, through a process that mimics, to a degree, the course of Pd-catalyzed arylation reactions via the same classes of Ar–X reagents (see Scheme 1), though the reaction sequence is significantly simplified. Additional studies are needed for demonstrating the scope of the method, but some advantages are apparent in terms of the choice of the starting materials (e.g., the reactivity of fluorides and phosphates, unusual in thermal catalysis, adds versatility; chlorides are usually less expensive and more easily available than bromides and iodides) and mild conditions [room temperature, no anhydrous condition (indeed, water may be a convenient cosolvent), small effect of oxygen (except with sensitized reactions), no expensive catalyst (thus also avoiding the time-consuming ligand synthesis and the concern about metal contaminants in the products)]. These characteristics make photoarylation an attractive “green” synthetic method as well as make it highly versatile, since a large choice of reagents able to direct the chemistry of the adduct cation can be present without affecting the generation of the phenyl cation and the primary addition step, as shown in several example above. A number of appealing synthetic applications have already been demonstrated (e.g., for products with pharmaceutical activity; see above), and it is hoped that the method will be adopted in synthetic planning.

Palladium-catalyzed coupling reactions of aryl halides have rapidly progressed in the past few years, greatly enlarging the scope of the method that was initially rather limited. The photo-S<sub>N</sub>1 reaction is still in its infancy, though already noticeable for the large range of reactive precursors. Clearly, photoactivation cannot cope with the multiform possible variation of the catalyst, the activity of which can be extensively modulated by the ligands. Furthermore, the catalyst also directs the following course of the reaction, while in the photochemical method the “naked” cations can be influenced only by the bulk properties of the medium (unless the reaction is carried out in an organized medium). However, the peculiar reactivity of triplet phenyl cation allows a series of straightforward syntheses that in some cases may complement thermal catalysis. As an example, the alkene may interfere with the oxidative addition of the aryl derivative onto Pd<sup>0</sup>, leading to unreactive, or more slowly reacting, Pd complexes<sup>47</sup> and thus to a less efficient Heck reaction. Obviously, there is no such interference in the photochemical process via phenyl cation (however, the alkene may, e.g., quench the triplet of the sensitizer). Considering the differences of each method, e.g., the different reac-

tivities of various aryl derivatives, such as bromides and fluorides, it is possible that both catalysis and photoactivation can be used for different arylations in subsequent steps of a synthetic plan.

Despite the many possibilities it offers,<sup>48</sup> photochemistry is not often regarded as a valuable preparative method. However, particularly when used for the mild generation of a highly activated intermediate, as is the case here for the phenyl cation, it gives two opportunities. First, it allows a direct appreciation (e.g., by flash photolysis) of the reactivity of such an intermediate, often difficult for related thermal reactions. In the present case, the results with isolated phenyl cation may give some indication about the complexed phenyl cation involved in the palladium-catalyzed reaction. Second, in cases where it applies, the photochemical method is extremely simple. Schemes 9, 10, and 14–16 show that comparable results are obtained by catalysis and by irradiation, though the experimental setup is much simpler in the latter case. Indeed, the solution is usually argon purged for several minutes (a step that may be omitted for nonsensitized reactions) and irradiated for a few hours. Evaporation and bulb-to-bulb distillation often give the product with reasonable purity. Thus, this is a cheap and fast procedure, even if neither the generality nor the fine-tuning of catalytic methods can be reached in this way.

*Note Added after ASAP Publication:* A change was made to one of the citations of ref 21 from the version published ASAP on June 22, 2005; the revised version was published ASAP on July 21, 2005.

## References

- (1) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: Chichester, U.K., 2004. Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.
- (2) Litke, A. F.; Fu, G. C. Palladium-catalyzed coupling reaction of aryl chlorides. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
- (3) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. Probing the mechanism of the Heck reaction with arene diazonium salts by electrospray mass and tandem mass spectrometry. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514–2518.
- (4) Swain, C. G.; Sheats, J. E.; Harbison, K. G. Evidence for phenyl cation as an intermediate in the reaction of benzenediazonium salts in solution. *J. Am. Chem. Soc.* **1975**, *97*, 783–790.
- (5) Waters, W. A. Mechanism of the Sandmeyer reaction. *J. Chem. Soc.* **1942**, 266–270. Cain, J. C. On the decomposition rate of diazonium salts. *Ber. Dtsch. Chem. Ges.* **1905**, *28*, 2511–2518.
- (6) Stang, P. J. Alkynyl and aryl cations. In *Dicoordinated Carbocations*; Rappoport, Z., Stang, P. J., Eds.; Wiley: New York, 1997; pp 451–460.
- (7) Himeshima, Y.; Kobayashi, H.; Sonoda, T. A first example of generating aryl cations in the solvolysis of aryl triflates in trifluoroethanol. *J. Am. Chem. Soc.* **1985**, *107*, 5286–5288. Apeloig, Y.; Arad, D. Stabilization of the phenyl cation by hyperconjugation. *J. Am. Chem. Soc.* **1985**, *107*, 5285–5286.
- (8) Holweger, W.; Hanack, M. Phenyl cation as a reactive intermediate in the solvolysis of dienyl triflates. *Chem. Ber.* **1984**, *117*, 3004–3020.
- (9) Galli, C. Radical reactions of arenediazonium ions: an easy entry into the chemistry of the phenyl radical. *Chem. Rev.* **1988**, *88*, 765–792.
- (10) Aschi, M.; Harvey, J. N. Spin isomerization of *para* substituted phenyl cations. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1059–1062. Lali, K. K.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. DFT study of substituted and benzoannulated aryl cations: substituent dependency of singlet/triplet ratio. *J. Org. Chem.* **2002**, *63*, 2913–2918.

- (11) Fasani, E.; Mella, M.; Caccia, D.; Tassi, S.; Fagnoni, M.; Albini, A. The photochemistry of lomefloxacin. An aromatic carbene as the key intermediate in photodecomposition. *Chem. Commun.* **1997**, 1329–1330. Albini, A.; Monti, S. Photophysics and photochemistry of fluoroquinolones. *Chem. Soc. Rev.* **2003**, *32*, 238–250.
- (12) Gasper, S. M.; Devadoss, S.; Schuster, G. B. Photolysis of substituted benzenediazonium salts: spin-selective reactivity of aryl cations. *J. Am. Chem. Soc.* **1995**, *117*, 5206–5211.
- (13) Fagnoni, M.; Mella, M.; Albini, A. Smooth synthesis of aryl and alkylanilines by photoheterolysis of haloanilines in the presence of aromatics and alkenes. *Org. Lett.* **1999**, *1*, 1299–1301. Precedent for cationic arylation reactions are the phenylation of mesitylene upon photodecomposition of diazonium salts (Steenken, S.; Askokkuna, M.; Maruthamuthu, P.; McClelland, R. A. Making photochemically generated phenyl cations visible by addition to aromatics: production of phenylcyclohexadienyl cations and their reactions with bases/nucleophiles. *J. Am. Chem. Soc.* **1998**, *120*, 11925–11931) and possibly the formation of 2,4'-dihydroxy-5-chlorobiphenyl from 4-chlorophenol in water, though differently rationalized by the authors (Grabner, G.; Richard, C.; Köhler, G. Formation and reactivity of 4-oxocyclohexa-2,5-dienylidene in the photolysis of 4-chlorophenol in aqueous solution at ambient temperature. *J. Am. Chem. Soc.* **1994**, *116*, 11470–11480).
- (14) Karapire, C.; Iclii, S. Photochemical aromatic substitution. In *Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; p 37/1-14. Kropp, P. J.; Fryxell, G. E.; Tubergen, M. W.; Hager, M. W.; Harris, G. D., McDermott, T. P.; Tornero-Velez, R. Photochemistry of phenyl thioethers and phenyl selenoethers. Radical vs ionic behavior. *J. Am. Chem. Soc.* **1991**, *113*, 7300–7310.
- (15) Bunnett, J. F. Aromatic substitution by the  $S_{RN}1$  mechanism. *Acc. Chem. Res.* **1978**, *11*, 1983. Rossi, R. A.; Peñeñory, A. B. The photostimulated  $S_{RN}1$  process. In *Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; p 47/1-24.
- (16) Havinga, E.; Cornelisse, J. Aromatic photosubstitution reactions. *Pure Appl. Chem.* **1976**, *47*, 1–10.
- (17) Groen, M. B.; Havinga, E. Nucleophilic photosubstitution of some heteroaromatic nitro compounds. *Mol. Photochem.* **1974**, *6*, 9–21. Zhang, G.; Wan, P. Photogeneration of HF from fluoromethoxybenzenes in aqueous solution. *Chem. Commun.* **1994**, 10–11. Yang, N. C.; Huang, A.; Yang, D. H. Photodehalogenation of 4-haloindoles. *J. Am. Chem. Soc.* **1989**, *111*, 8060–8061. Zhang, B.; Zhang, J.; Yang, D. H.; Yang, N. C. Photoamidation of *N*-acetyl-2-chlorotyrosine methyl ester and 3-chlorophenol. *J. Org. Chem.* **1996**, *61*, 3236–3237.
- (18) Freccero, M.; Fagnoni, M.; Albini, A. Homolytic vs heterolytic paths in the photochemistry of haloanilines. *J. Am. Chem. Soc.* **2003**, *125*, 13182–13190.
- (19) Protti, S.; Fagnoni, M.; Mella, M.; Albini, A. Aryl cations from aromatic halides. Photogeneration and reactivity of 4-hydroxy (methoxy) phenyl cations. *J. Org. Chem.* **2004**, *69*, 3465–3473.
- (20) The wealth of evidence obtained clearly differentiates the present  $S_{N}1$  reaction via the phenyl cation from both the  $S_{RN}1$  process via the phenyl radical<sup>15</sup> and other fragmentations induced by photoelectron transfer (see: Mangion, D.; Arnold, D. R. The photochemistry of 4-halobenzonitriles and 4-haloanisoles with 1,1-diphenylethylene in methanol. Homolytic cleavage versus electron-transfer pathway. *Can. J. Chem.* **1999**, *77*, 1655–1670).
- (21) Ambroz, H. B.; Kemp, T. Aryl cations—new light on old intermediates. *Chem. Soc. Rev.* **1979**, *8*, 353–366. The phenyl cation has also been obtained in a matrix from iodobenzene (Winkler, M.; Sander, W. Isolation of phenyl cation in a solid argon matrix. *Angew. Chem., Int. Ed.* **2000**, *39*, 2014–2016) and in the gas phase by decay of tritiated ions (Speranza, M. In *Dicoordinated Carbocations*; Rappoport, Z., Stang, P. J., Eds.; Wiley: New York, 1997, pp 157–187).
- (22) Milanesi, S.; Fagnoni, M.; Albini, A. Cationic arylation through photo(sensitized) decomposition of diazonium salts. Chemoselectivity of triplet phenyl cation. *Chem. Commun.* **2003**, 216–217.
- (23) Miranda, M. A.; Galindo, F. Photo-Fries reaction and related processes. In *Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; p 42/1-11.
- (24) De Carolis, M.; Protti, S.; Fagnoni, M.; Albini, A. Metal-free cross-coupling reactions of aryl sulfonates and phosphates through heterolysis of aryl-oxygen bonds. *Angew. Chem., Int. Ed.* **2005**, *44*, 1232–1236.
- (25) The presence of an  $NR_2$ , OR, or SR group hinders phototransposition of the phenyl ring and makes intersystem crossing efficient besides favoring heterolysis.
- (26) Guizzardi, B.; Mella, M.; Fagnoni, M.; Freccero, M.; Albini, A. Generation and reactivity of the 4-aminophenyl cation by photolysis of 4-chloroaniline. *J. Org. Chem.* **2001**, *66*, 6353–6363.
- (27) Mella, M.; Coppo, P.; Guizzardi, B.; Fagnoni, M.; Freccero, M.; Albini, A. Photoinduced, ionic Meerwein arylation of olefins. *J. Org. Chem.* **2001**, *66*, 6344–6352.
- (28) Manet, I.; Monti, S.; Fagnoni, M.; Protti, S.; Albini, A. Aryl cation and carbene intermediates in the photodehalogenation of chlorophenols. *Chem.—Eur. J.* **2005**, *11*, 140–151.
- (29) Cram, D. J. The stereospecific Wagner-Meerwein rearrangement of the isomers of 3-phenyl-2-butanol. *J. Am. Chem. Soc.* **1949**, *71*, 3863–3870. Olah, G. A.; Head, N. J.; Rasul, G.; Prakash, G. K. S. Protonation of benzocyclobutene with superacid: Cram's phenonium ion (spiro[5.2]octa-5,7-diene-4-yl cation) revisited. *J. Am. Chem. Soc.* **1995**, *117*, 875–872. Del Rio, E.; Menendez, M. L.; Lopez, R.; Sordo, T. L. Rearrangements involving the phenonium ion: a theoretical investigation. *J. Am. Chem. Soc.* **2001**, *123*, 5064–5068.
- (30) Berthiol, F.; Doucet, H.; Santelli, M. Synthesis of polysubstituted alkenes by Heck vinylation or Suzuki cross-coupling reaction in the presence of tetraphosphane-palladium catalyst. *Eur. J. Org. Chem.* **2003**, 1091–1096.
- (31) Littke, A. F.; Schwartz, L.; Fu, G. C. Pd/P(*t*-Bu): a mild and general catalyst for Stille reactions of aryl chlorides and aryl bromides. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6347.
- (32) Unpublished results from our laboratory.
- (33) Guizzardi, B.; Mella, M.; Fagnoni, M.; Albini, A. Phenonium ions from the addition of phenyl cation to alkenes. Photochemical synthesis of (rearranged) aminoalkylanilines from haloanilines in the presence of alkenes and amines. *J. Org. Chem.* **2003**, *68*, 1067–1074.
- (34) Coppo, P.; Fagnoni, M.; Albini, A. Photochemical conversion of 4-chloroaniline into 4-alkylanilines. *Tetrahedron Lett.* **2001**, *42*, 4271–4273.
- (35) Guizzardi, B.; Mella, M.; Fagnoni, M.; Albini, A. Photochemical reactions of *N,N*-dimethyl-4-chloroaniline with dienes. New synthetic paths via a phenyl cation. *Chem.—Eur. J.* **2003**, *9*, 1549–1555.
- (36) Mella, M.; Esposti, S.; Fagnoni, M.; Albini, A. A novel access to 3-aryl-2-norbornyl cation. *Chem. Commun.* **2003**, 738–739.
- (37) Brown, H. C. *The Nonclassical Ion Problem*; Plenum: New York, 1977. Kirmse, W. Rearrangements of carbocations. *Top. Curr. Chem.* **1979**, *80*, 125–311. Olah, G. A. 100 Years carbocations and their significance in chemistry. *J. Org. Chem.* **2001**, *66*, 5943–5957.
- (38) Fraboni, A.; Fagnoni, M.; Albini, A. A novel  $\alpha$  arylation of ketones, aldehydes and esters via a photoinduced  $S_{N}1$  reaction through 4-aminophenyl cation. *J. Org. Chem.* **2003**, *68*, 4886–4893.
- (39) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. Efficient synthesis of  $\alpha$ -aryl esters by room-temperature palladium-catalyzed coupling of aryl halides with ester enolates. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565.
- (40) Harna, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. Palladium-catalyzed  $\alpha$ -arylation of esters and amides under more neutral conditions. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177.
- (41) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. Synthesis of novel C2-symmetric thiourea and its application in the Pd-catalyzed cross-coupling reactions with arenediazonium salts under aerobic conditions. *Org. Lett.* **2004**, *6*, 221–224. For the use of aryl chlorides, see: Old, D. W.; Wolfe, J. P.; Buchwald, S. L. A highly active catalyst for the palladium-catalyzed cross-coupling reactions: room temperature Suzuki coupling and amination of unactivated aryl chlorides. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
- (42) Guizzardi, B.; Mella, M.; Fagnoni, M.; Albini, A. Easy photochemical preparation of 2-dimethylaminophenylfurans, -pyrroles and -thiophenes. *Tetrahedron* **2000**, *56*, 9383–9390.
- (43) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. Palladium catalyzed arylation of azole compounds with aryl halides in the presence of alkali metal carbonates and the use of copper iodide in the reaction. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.
- (44) Littke, A. F.; Dai, C.; Fu, G. Versatile catalysts for the Suzuki cross coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
- (45) Schmidt, B. Heck arylation of cyclic enol ethers with aryldiazonium salts: regio- and stereoselective synthesis of arylated oxacycles. *Chem. Commun.* **2003**, 1656–1657.
- (46) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskam, T.; Herrmann, W. A. Catalytic C-C bond formation through selective activation of C-F bonds. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387–3389. Kim, Y.



- M.; Yu, S. Palladium (0)-catalyzed amination, Stille coupling, and Suzuki coupling of electron-deficient aryl fluorides. *J. Am. Chem. Soc.* **2003**, *125*, 1696–1697.
- (47) Jutand, A. Dual role of nucleophiles in palladium-catalyzed Heck, Stille, and Sonogashira reactions. *Pure Appl. Chem.* **2004**, *76*, 565–576.
- (48) Griesbeck, A. G.; Mattay, J., Eds. *Synthetic Organic Photochemistry*; Dekker: New York, 2005. Wender, P. A.; Siggel, L.; Nuss, J. M. Arene-alkene photocycloaddition reactions. *Org. Photochem.* **1989**, *10*, 357–473.

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