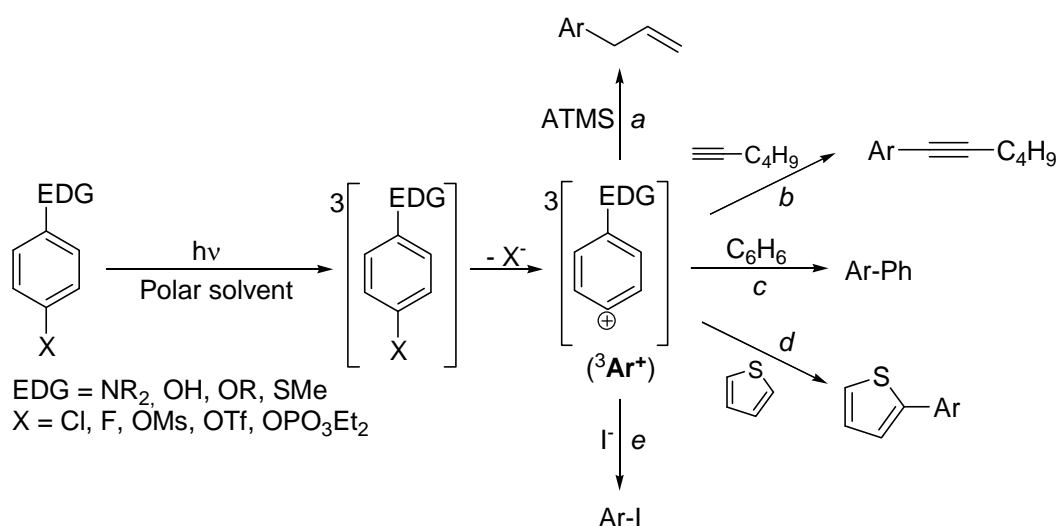


SYNTHETIC APPLICATIONS OF PHOTOARYLATION REACTIONS

PhD thesis by Dr. Valentina Dichiarante – Abstract

The formation of aryl-carbon bonds is one of the most important, as well as difficult, targets of organic synthesis. Modern arylation methods are based on organometallic chemistry; the photochemical approach, however, offers an alternative that is in accord with the green chemistry principles (actually light is *the* clean reagent) and has a large synthetic potential not fully exploited as yet. This method is based on the electronic excitation of the starting compounds that leads to the generation of high-energy intermediates (such as aryl radicals Ar^\cdot or cations Ar^+), under mild conditions.

The heterolytic fragmentation of substituted aromatics to give a phenyl cation has been initially deemed as a rare occurrence, because of the high instability of the latter species, but recently our research group has demonstrated that heterolytic cleavage is the main photochemical process from the triplet excited state of phenyl fluorides, chlorides, mesylates, triflates and phosphates bearing an amino, alkoxy, hydroxy or alkylthio group in the *para* position (Scheme 1).

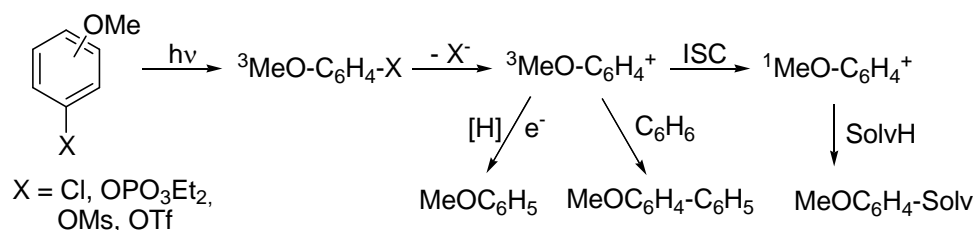


Scheme 1

Irradiation of these substrates in polar media (e.g. water/acetonitrile mixtures, methanol or 2,2,2-trifluoroethanol) leads to the corresponding *triplet* aryl cations ($^3\text{Ar}^+$), which exhibit a high reactivity towards π nucleophiles, such as alkenes, alkynes and arenes (differently from the unselective singlet). With allyltrimethylsilane (ATMS), for example, the leaving group Me_3Si^+ is lost from the adduct cation and an allylbenzene is efficiently formed

(Scheme 1, path *a*). Arylation of alkynes is likewise successful and offers an alternative to the Sonogashira reaction for the preparation of arylalkynes (path *b*), while the generation of phenyl cations in the presence of benzene leads to biphenyls (path *c*). Even more interesting is the selective arylation in position 2 of five-membered heterocycles, such as pyrrole and thiophene (path *d*). Phenyl cations can also react with inorganic anions (e.g. iodide, path *e*), giving the corresponding aryl iodides.

Overall, the reaction can be viewed as a photo-S_N1 reaction of the aromatic derivative and the main purpose of the present thesis has been both to explore further synthetic applications of such process and to better understand the chemistry of aryl cations from a mechanistic point of view. First, I have considered the effect of the position of the substituent by investigating the photoreactivity of the three isomeric chloroanisoles and of the corresponding methoxyphenyl esters (mesylates, triflates and phosphates), in solvents having different polarity, both neat and in the presence of benzene, as a typical π trap for electrophiles (Scheme 2).

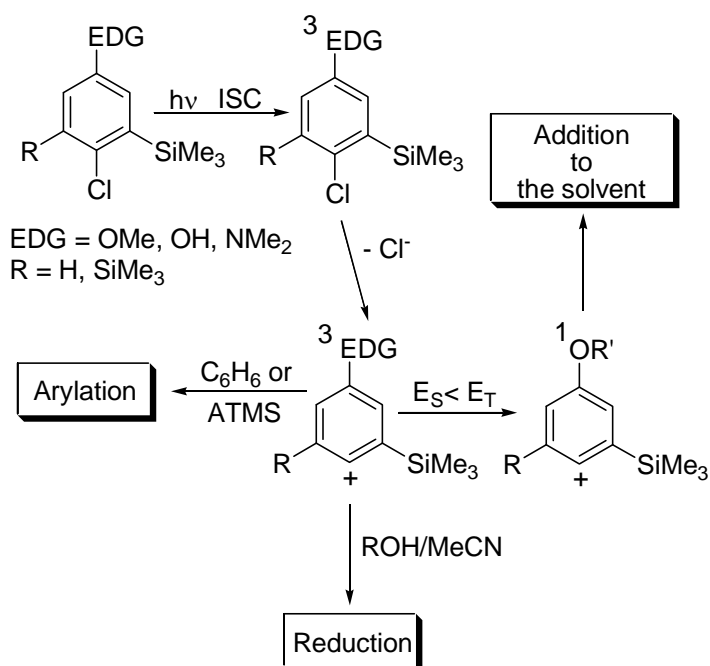


Scheme 2

The triplet methoxyphenyl cations formed by photoheterolysis react with π nucleophiles or, in neat solvent, are reduced to anisole. On the contrary, solvolysis is attributed to the singlet cations (that, as mentioned above, is an unselective electrophile), formed by intersystem crossing (ISC) from the corresponding triplet. The substituent orientation does not influence the efficiency of the photocleavage, but has a marked effect on the key intermediate, the phenyl cation: the *meta* substituted singlet is selectively stabilized, and ISC from the initially formed triplet is favored. This peculiar stabilization is a new, though conceptually different, interesting example of the so called “*meta* effect” in photochemistry.

Another aspect that has been evaluated is the influence of additional substituents in the aromatic ring on the photochemistry of electron-rich aryl halides. In particular, silicon based substituents, such as the trimethylsilyl (TMS) group, are well known to stabilize a positive charge present on a beta position and to facilitate the thermal generation of phenyl cations in solution. In order to assess the β -effect of silicon on the photochemical

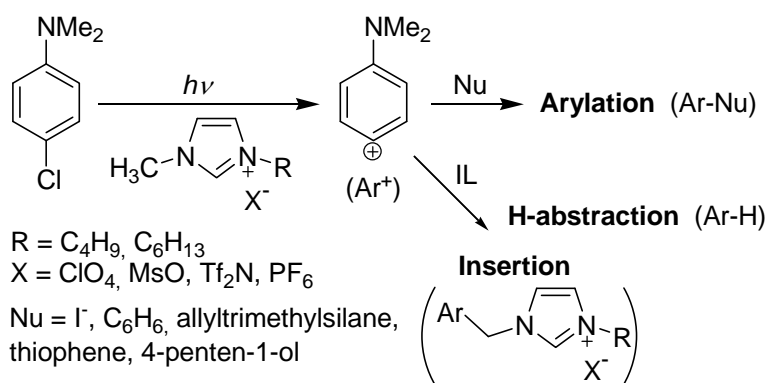
generation of such intermediates, the photoreactivity of some aryl chlorides bearing one or two TMS substituent(s) in *ortho* with respect to the leaving group has been compared with that of silicon-free analogues (Scheme 3).



Scheme 3

Both calculations and steady-state experiments clearly show that the presence of a trimethylsilyl group in *ortho* to the leaving chlorine strongly stabilizes the singlet cation to the extent that it becomes the *reactive* spin state. As a result the chemistry expected from the triplet (reduction or C-arylation) is replaced by that of the singlet (solvolysis, and thus O or N arylation).

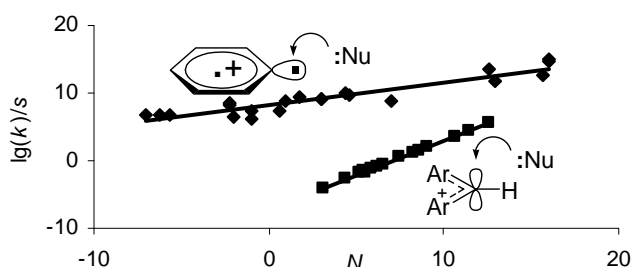
As for the reaction medium, a class of novel and environmental benign solvents, the polarity of which is similar to that of acetonitrile or alcohols, is represented by room temperature ionic liquids (ILs). In order to evaluate the role of the solvent in the reactivity of phenyl cations, the photoreactivity of 4-chloro-*N,N*-dimethylaniline (previously studied in organic solvents of different polarity), has been explored in five *N*-methyl-*N*-alkylimidazolium salts, in the presence of several nucleophiles (Scheme 4).



Scheme 4

The high viscosity of such media and their specific interactions with 4-*N,N*-dimethylaminophenyl cation markedly affect the products distribution, as compared to that obtained in a solvent like acetonitrile. In fact, in the absence of nucleophiles, the triplet 4- $Me_2N-C_6H_4^+$ can abstract a hydrogen from the alkyl chains of imidazolium ring, to afford *N,N*-dimethylaniline (Ar-H, Scheme 4), but can also give insertion into a C-H bond of the imidazolium methyl group. The presence of π traps (e.g. alkenes or arenes) and inorganic anions (such as iodide), however, allows the formation of the corresponding arylation products (Ar-Nu), in yields similar or even higher than those obtained in acetonitrile. As for the above, it emerges that ILs are inert towards highly reactive species such as phenyl cations, provided that the concentration of the nucleophile is high enough to avoid undesired side-reactions. Thus ILs can be convenient media for carrying out syntheses involving highly reactive intermediates.

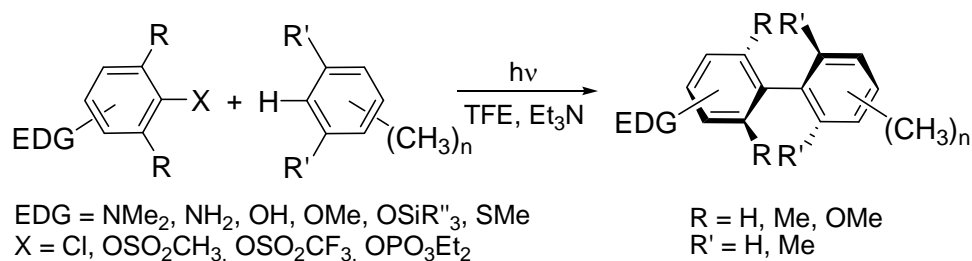
The last issue considered during the mechanistic study is the selectivity of aryl cations towards different classes of nucleophiles (σ , π e n). Singlet 4- $Me_2N-C_6H_4^+$ reacts at diffusion controlled rate with any kind of nucleophiles. The triplet cation, however, shows a certain degree of selectivity and allows to build a nucleophile-electrophile reactivity scale in analogy to that previously reported based on benzhydrylium ions (Scheme 5).



Scheme 5

A synthetic application that has been found viable is trapping with benzenes. This is useful because biaryls actually represent common substructures in many pharmaceutically and

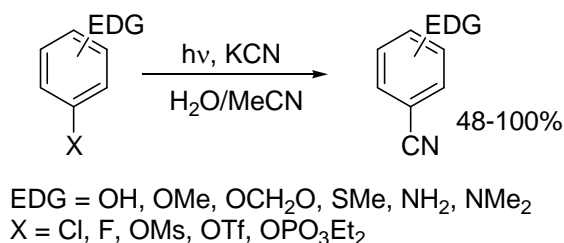
biologically active molecules; their synthesis can be accomplished by the reaction of phenyl cations with arenes. Irradiation of several substrates in trifluoroethanol, in the presence of symmetrical methylbenzenes (*p*-xylene, mesitylene and durene), allowed to prepare a series of biaryl compounds, including sterically congested examples, in high yields (52-84%, Scheme 6).



Scheme 6

Photochemical S_N1 arylation were again strictly chemoselective: neither functionalization at benzylic positions nor multiple arylation were observed and other possible competitive pathways, such as the reduction of the starting halides or sulfonate/phosphate esters, were always negligible. In fact, this novel photochemical synthesis of biaryl compounds represents a convenient and 'green' alternative to organometallic mediated processes.

Further synthetic applications are based on the fact that, as mentioned above, triplet aryl cations smoothly react with charged nucleophiles. Thus, the photoreactivity of several electron-rich aryl halides and esters in the presence of cyanide ion has been explored (Scheme 7), to synthesize different benzonitriles which find large applications as agrochemicals and pharmaceuticals. A mild photoinduced cyanation protocol was finally achieved at room temperature, by using a cheap cyanating agent (KCN) and aqueous acetonitrile as the solvent and benzonitriles are formed in good to excellent yields. In contrast to palladium catalyzed processes, the present photochemical method requires extremely mild conditions and applies to precursors less reactive under thermal conditions, such as phenyl chlorides and fluorides.



Scheme 7