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Approaches towards photochemical reactivity using organoiodanes and organo(trifluoro)borates.

Estudios hacía la reactividad fotoquímica con el uso de reactivos de organoyodo hipervalente y organo(trifluoro)boratos.

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A mi familia y mis amigos por apoyarme siempre.

A mis compañeros de laboratorio Wei Chen y Marta Díaz por tener paciencia y ayudarme en todo momento.

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REPORT

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1. SUMMARY

Controlled photochemical generation of reactive radical species has become a powerful bond-forming tool in organic synthesis. In this project, we have performed initial and preliminary studies towards photochemical radical generation using the C-O bond of hypervalent iodine reagents. We also initiated a project (for the first time in the group) to carry out dual nickel/photoredox coupling of α-substituted C(sp^3) trifluoroborates.

Studies towards hypervalent iodine compounds have been successfully realized. Focusing on the first goal, the generation and the controlled transfer of $\cdot CF_2H$ and $\cdot CFH_2$ radicals to C-H positions of activated heterocyclic substrates *via* homolytic I-O cleavage followed by decarboxylation process has been successfully carried out. Specifically, new hypervalent reagents have been designed and prepared in order to help prevent harmful radical side reactions.

In another iodane-based approach, the synthesis of 1,8-diiodonaphthalene by homolytic bond cleavage and later decarboxylation process was assayed. For comparison, the target compound was also obtained by the diazonium salt intermediate. The adaptation of the photochemical (diradical) route to a small-scale photoreactor has proven challenging and will be continued in the group.

The last goal which is the synthesis of two different Iridium photocatalyst to be applied in cross-coupling photo-redox reactions has been achieved. The photocatalyst synthesis has been successful realized in all steps, obtaining the desired pure catalysts as a crystalline yellow powder. On the other hand, the cross-coupling photo-redox products have not been obtained due to the air sensitivity of the other photocatalyst used in this process, $Ni(COD)_2$. However, with the use of a more robust Ni complex (e.g. [glyme]$NiCl_2$), we anticipate that this final objective could be successfully achieved in the host research group.

Keywords: hypervalent iodine, radicals, homolytic I-O cleavage, decarboxylation process, dual photocatalyst, cross-coupling, photo-redox reaction.

2. RESUM

La generación fotoquímica controlada de especies reactivas de radicales se ha convertido en una potente herramienta creadora de enlaces en síntesis orgánica. En este proyecto, hemos realizado estudios preliminares acerca de generación fotoquímica de radicales usando el enlace C-O de compuestos de yodo hipervalente. También hemos iniciado un proyecto (por primera vez en el grupo) para llevar a cabo acoplamiento dual niquel/fotoredox en α-substituidos C(sp^3) trifluoroboratos.

Los estudios acerca de compuestos de yodo hipervalente han sido realizados con éxito. Centrándonos en el primer objetivo, la generación y la transferencia controlada de los radicales $\cdot CF_2H$ y $\cdot CFH_2$ hacia posiciones de C-H activadas en substratos heterocíclicos *via* ruptura homolítica del enlace I-O seguido de un proceso de descarboxilación han sido llevados a cabo exitosamente. Específicamente, se han diseñado y preparado nuevos compuestos de yodo hipervalente para ayudar a prevenir reacciones radicalarias no deseadas.

En otro acercamiento hacia la química de yodo hipervalente, se intentó la síntesis del 1,8-diyodonaftaleno por la ruptura homolítica del enlace y el posterior proceso de descarboxilación. Por comparación, el compuesto deseado se obtuvo también pasando por la sal de diazonio como intermedio. La adaptación de la ruta fotoquímica (diradical) a pequeña escala en el fotoreactor ha demostrado ser desafiante y será continuada por el grupo.

El último objetivo, el cual es la síntesis de dos fotocatalizadores de Iridio diferentes para llevar a cabo reacciones fotoredox de acoplamiento cruzado se ha conseguido. La síntesis de los fotocatalizadores se ha realizado correctamente en todos sus pasos, obteniendo al final los catalizadores puros en forma de polvo amarillo cristalino. Por otra parte, los productos de acoplamiento cruzado por reacciones fotoredox no se han podido obtener debido a la sensibilidad al aire del otro fotocatalizador usado en este proceso, el $Ni(COD)_2$. Sin embargo, en un futuro, usando un catalizador de Ni más robusto (por ejemplo [glyme]$NiCl_2$), anticipamos que el objetivo final será alcanzado por el grupo de investigación.

Paraules clau: yodo hipervalente, radicales, ruptura homolítica del enlace I-O, proceso de descaboxilación, fotocatalizador dual, reacciones fotoredox de acoplamiento cruzado.

3. INTRODUCTION

Iodine is the heaviest of the halogen elements. Iodine derivatives are known to have this halogen center in the range of oxidation states covering -1, 0, +1, +3, +5, +7. Of these, the -1 oxidation state is the most common, covering both the inorganic metal iodides, and the common organoiodine species, e.g. iodomethane or iodobenzene. The first trivalent organoidine compound was synthesized in 1886 by Conrad Willgerodt, a German chemist who reported this pioneering research in the Journal für Praktische Chemie.[1] Willderogt's experiment consisted in bubbling chlorine gas into a chloroform solution of iodobenzene. The reaction resulted in the precipitation of a yellow solid which was identified as the (dichloroiodo)benzene. While this species proved somewhat unstable, just a few years later, Willgerodt also reported the formation of an analogous diacetate species $PhI(OAc)_2$,[2]a stable white solid which has since been used in a wide variety of synthetic applications, and which is nowadays readily available from commercial sources. These types of compounds are commonly referred to as "hypervalent" in reference to the halogen center bound to more than one atom. This research served as the starting point to develop in the posterior decades various types of hypervalent iodine reagents, of which the most common are the bis(acyloxy)iodoarenes, $ArI(O_2CCR)_2$, the diaryliodonium salts, Ar_2IX (X=weak anion),[3] the pentavalent iodine reagents,[4] including the popular Dess-Martin periodinate (DMP) and the iodoxybenzoic acid (IBX). This work will be focused mainly on the trivalent iodine reagents such as (diacetoxyiodo)benzene, commonly known as ***P***henyl***I***odine ***D***i***A***cetate and abbreviated as PIDA[2].

3.1. CLASSIFICATION OF TRIVALENT IODINE REAGENTS

The trivalent organoiodine compounds are generally classified by the nature of their three substituents. Hence, based on the substitution pattern, three fundamental groups can be identified: (1) compounds with an iodine center bonded to two heteroatom ligands and one carbon ligand; (2) compounds in which the iodine center is bound to one heteroatom and two carbon ligands; (3) an iodine center bonded to three carbon ligands (figure 1). These three

groups can be further subdivided. In particular, the first group represents a very wide range of derivatives, which can be also grouped into cyclic and acyclic.

It is also important to know that in most trivalent iodine compounds; at least one of the carbon ligand is of a C-sp^2-carbon atom, normally from an aryl group. Nevertheless, some derivatives of trivalent iodine reagents have been prepared with sp^3-carbon substituents, although these tend to be very unstable. An exception to this trend, are, for example, R_f-I(X)$_2$ compounds, where R_f represents a fluorinated alkylic chain.

The second group, where the iodine center is bound to one heteroatom and two carbon ligands, can also be subdivided again into cyclic an acyclic (figure 1). The iodine reagents of this group (Ar$_2$IX) have a strong ionic character because of the facile dissociation of the X bound anion, being that anion character the key to name these compounds as salts.

In the third group, which includes the trivalent iodine compounds with three carbon ligands, the ArI(CN)$_2$ is one of the few stable structures (figure 1).[5]

Other trivalent compounds that have to be mentioned are the iodonium imides (ArI$^+$N$^-$R) and the iodonium ylides (ArI$^+$C$^-$HR$_2$), which are formally written with as I=N or I=C, but are better described as charge-separated ylides (figure 1). These two types of compounds have been used as nitrene[6] and carbene[7] group transfer agents; recently, aryliodonium ylides have also become popular as precursor for efficient and selective radiofluorination reactions in Positron Emission Tomography (PET) imaging [8]

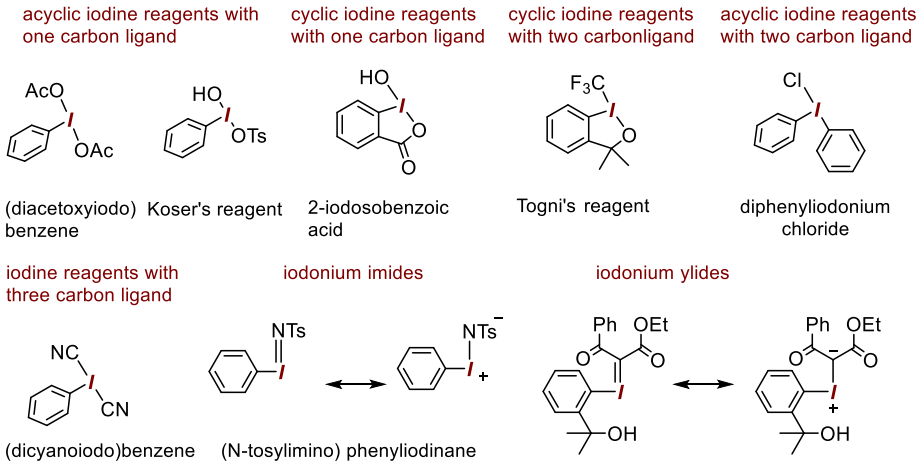


Figure 1. Different types of trivalent iodine compounds.

3.2. STRUCTURE AND GEOMETRY OF TRIVALENT IODINE REAGENTS

Generally, organic trivalent iodine compounds are written as organic λ³-iodanes. This is a standard IUPAC nomenclature where λⁿ refers to the non-standard valence state of the atom (n = 3 in this case). These compounds have a very specific and characteristic configuration. This geometry has been studied and discussed in books and reviews in this field,[6,9,10] and has been confirmed numerous times by the solid-state single crystal X-ray determination, which provides the special arrangement of the three ligands around the iodine center in the space. So what the X-ray determination reveals is that in a λ³-iodane which contains a carbon ligand and two heteroatoms (Het), the C-I-O angle in the cyclic and acyclic hypervalent iodanes is almost 90°,[11] which gives this special configuration commonly known as T-shaped geometry (figure 2). This angle and the overall geometry are easily rationalized by including the two lone electron pairs. In this scenario, iodine, apart from its three ligands, would have two stereoactive lone electron pairs leading to an overall trigonal bipyramid where the most electronegative ligands (the two Het) are situated in the apical positions and the less electronegative group (the aryl) and the two lonely electron pairs occupying the equatorial positions. The X-ray determination of λ³-iodane also sheds light on the nature of the I-C and the I-O bond. In reference to the carbon-iodine bond, the length between the two atoms is in the (diacetoxyiodo)benzene, 2.08 Å which is nearly equal to the distance of the covalent radio between carbon and iodine (2.09 Å) (figure 2), suggesting a regular C-I σ-bond. On the other hand, referring to the C-O bond of PIDA, the length is 2.09 Å which is now higher than the sum of the covalent radius of C and O (1.99 Å),but shorter than an ionic radius What this different length suggests is that we are in front of an intermediate position which is called the “hypervalent bond”.

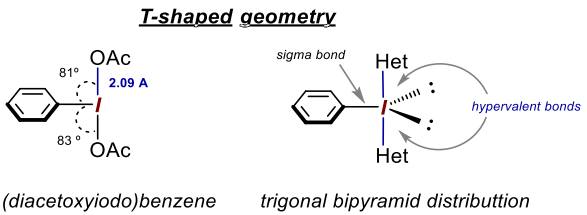


Figure 2. Geometry of λ³-iodanes.

The “hypervalent bond” term was defined in 1969 by J. I. Muscher to explain the molecules and ions with elements in Groups 15-18 of the periodic table having, in their valence shell, more than eight electrons.[12] The fact that some main-group elements can surpass the famous octet

rule, was explained with the molecular orbital theory by the formation of a new ionic arrangement, named a “three center four electron” (3c-4e) bond. The molecular orbital theory describes a combination of three atomic orbitals, the bonding, the nonbonding and the antibonding. In the specific case of λ3-iodanes, these three atomic orbitals are formed by the two half-occupied atomic orbitals from each one of the apical ligands and the full p orbital of the iodine atom. The four electrons fill the molecular orbitals (MO) starting by the bonding which is the lowest energy MO. The result: two filled MO and one empty orbital. The latter corresponds to the Lowest Occupied Molecular Orbital (LUMO) in most hypervalent iodine reagents and is largely responsible for most of the reactivity patterns (figure 3).

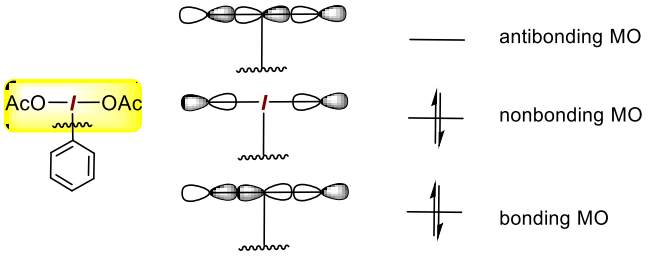


Figure 3. Molecular orbitals of the hypervalent bond in (diacetoxyiododo)benzene.

This distribution has a significant importance on the characteristics and the reactivity of the iodine atom. In particular, due to the central node that the highest occupied molecular orbital (HOMO) has at the iodine atom, these hypervalent bonds become very polarized, acquiring so a positive density charge at the iodine atom and a negative density charges at both of the diacetoxy ligands. (figure 4)

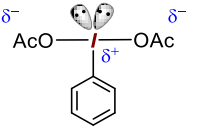


Figure 4. Density charge in (diacetoxyiodo)benzene.

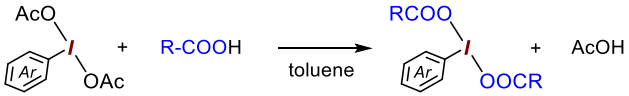
3.3. GENERAL REACTIVITY PATTERNS OF λ3 IODANES

The λ3-iodanes have a wide and varied reactivity, with the facility to return to the monovalent iodine oxidation state, i.e. to conventional organoiodine Ar-I derivatives constituting the cornerstone of their reactivity and being the responsible of the oxidant character of these

compounds. Another important point is the electrophilic character of the iodine atom (see in figure 4), which also plays a crucial role in a variety of common reactivity patterns. These general reactivity patterns can be grouped in ligand exchange, reductive eliminations, single electron transfer (SET) reactions and the homolytic bond cleavage.

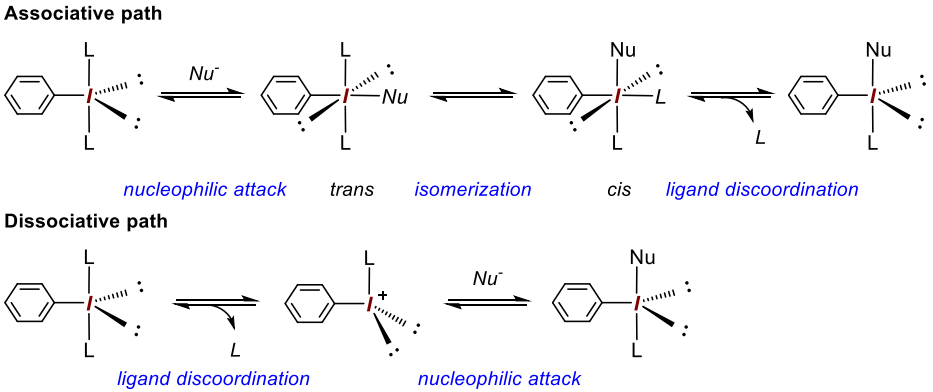
3.3.1. Ligand exchange

This kind of reaction is normally used in the formation of non-containing acetates or trifluoroacetates λ³-iodanes. These compounds are synthetized by ligand exchange from (diacetoxyiodo)arenes with the addition of an organic acid (scheme 1).[13] This reaction is an equilibrium, but can be displaced to the product formation by the elimination of the acetic acid.



Scheme 1. Synthesis of (dicarboxyliodo)arene by ligand exchange reaction

There are two different possible mechanisms for the ligand exchange in the hypervalent iodine reagents: the dissociative and the associative (scheme 2).[9] The dissociative path is initiated by a ligand dissociation from the iodine center followed by a nucleophilic attack to obtain the corresponding (dicarboxyliodo)arene. The associative path starts with a nucleophilic attack to form a *trans* tetra-coordinated intermediate, followed by a reordering to get a *cis* isomer. The *trans* ligand dissociates and finally there is a nucleophilic attack to obtain the corresponding (dicarboxyliodo)arene.

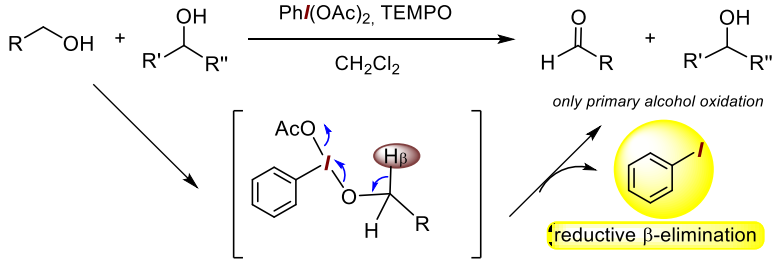


Scheme 2. Different mechanisms for the ligand exchange reaction

3.3.2. Reductive elimination

The leitmotiv of this reactivity pattern is the leaving facility of the Ar-I group. The reductive elimination can be divided into two subgroups: the reductive α-elimination and the reductive β-elimination.

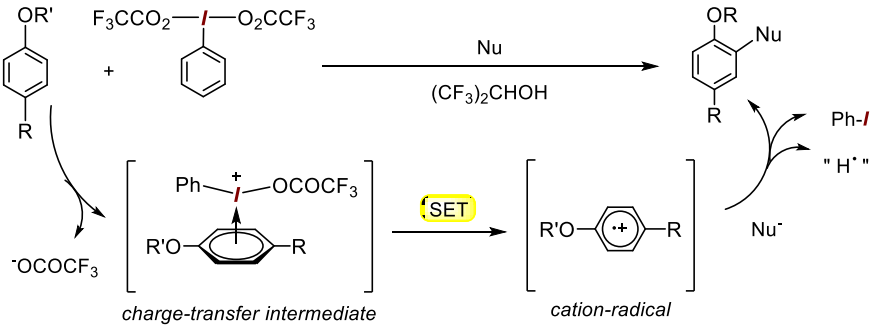
Reductive α-elimination consists on the elimination of a H in α position from iodine atom. Further more important is the reductive β-elimination, so focusing on this field, this type of reaction is involved in the popular alcohols oxidation into the corresponding carbonyl compounds by iodine (III) reagents. This kind of reaction has the advantage of being able to oxidize selectively primary alcohol in presence of secondary alcohols. Specifically, combining a mixture of a primary and a secondary alcohols with (diacetoxyiodo)benzene (PIDA) and TEMPO, the primary alcohol can react with the PIDA undergoing a ligand exchange reaction, evolving to the corresponding carbonyl compound and releasing iodobenzene as the product of the reductive β-elimination (scheme 3).[14] This reactivity has also been used in the conversion of amines into imines.[15]



Scheme 3. Reductive β-elimination to oxidize a primary alcohol in presence of a secondary alcohol

3.3.3. Single electron transfer (SET)

In most cases, the reactivity of hypervalent iodine reagents start with a two electron transfer process and finishes in a reductive elimination and a consequent Ar-I release. On the other hand, there are some hypervalent iodine compounds such as: PIDA, [bis(trifluoroacetoxy)iodo] benzene (PIFA), the Koeser's reagent (see in section 3.1) capable of acting as selective single-electron-transfer (SET) oxidizing reagents under specific conditions. For example, PIFA can react with phenyl ethers producing the charge-transfer intermediate which evolves to a radical cation. Finally in the presence of a nucleophile the substitution gets completed (scheme 4).[14]



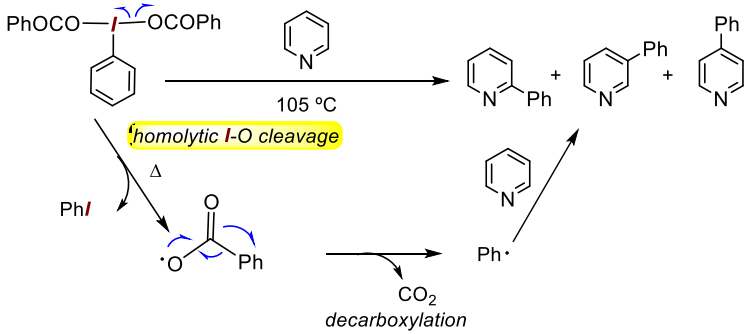
Scheme 4. Nucleophilic substitution by SET process.

3.3.4. Homolytic bond cleavage

Studies towards homolytic bond cleavage reactions in hypervalent iodine compounds have evolved a great deal in the last decades. There are two types of homolytic bond cleavage: *via* thermal decomposition and *via* photocatalytic decomposition.

3.3.4.1. Homolytic bond cleavage via thermal decomposition

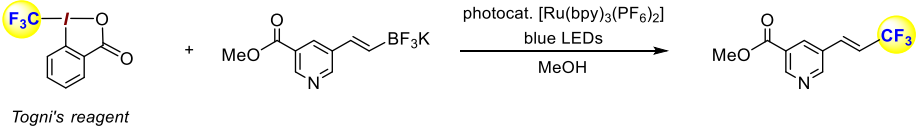
The thermal decomposition of (dibenzoyloxyiodo)benzene in pyridine was first reported in 1950 by Williams to produce three isomers of the phenylpyridine. The reaction is based on the simple idea that the thermal decomposition of (dibenzoyloxyiodo)benzene would generated the benzoyloxy radical which would undergo a decarboxylation process to evolve to phenyl radical. The resulting highly reactive phenyl radical would be attacked the pyridine to give the three possible isomers (scheme 5).[16]



Scheme 5. Thermal decomposition of (dibenzoylozyiodo)benzene in pyridine by homolytic cleavage.

3.3.4.2. Homolytic bond cleavage via photocatalytic decomposition

There have been great advances in the last years in this field,[17] given that this reactivity could constitute a very useful chemical tool to generate the desired radicals under mild conditions. These reactions are carried out under UV or visible light. Togni's reagent with the corresponding Ruthenium photocatalyst generates ·CF_3 radical (scheme 6).[18]

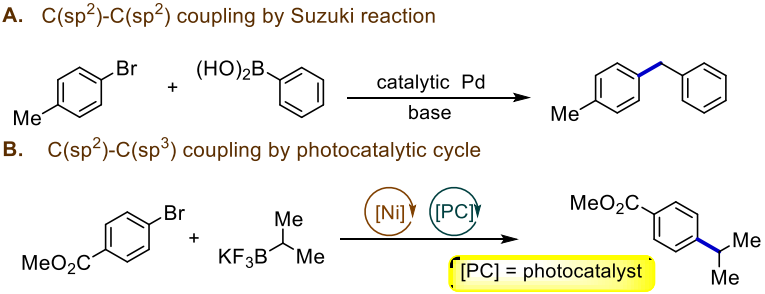


Togni's reagent

Scheme 6. Trifluoromethilation *via* photocatalytic decomposition

3.4. DUAL Ni –PHOTOCATALYSIS: A NEW TOOL FOR CARBON-CARBON BOND-FORMING REACTIONS

Reactions towards catalytic coupling of C-C bonds have been very important for the organic chemistries in the last years. One of the most common reactions in this field is the Suzuki reaction, which has now become a standard tool for C(sp^2)-C(sp^2) coupling (scheme 7-A). As was stressed in a recent review by prof. Gary Molander, "among such transformations, the formation of C-C bonds at sp^3-hybridized centers is a particularly desirable construct because of its potential to provide rapid access to 3D-rich architectures".[19] In the same review, the authors also note the scarcity of cross-coupling approaches to engage the C(sp^3) centers using mild conditions. In a seminal recent discovery (2014), Molander and co-workers[20] reported a dual Ni/photoredox catalysis approach to obtain sp^2-sp^3 coupling products (scheme 7-B).



Scheme 7. Examples of a canonical (A) and dual Ni-photocatalytic to C-C coupling.

Photoredox catalysis transforms light into chemical energy under mild conditions, using a photoexcitable catalyst. Once these catalysts get excited, they can induce SET reactions to finally return to the lowest energy state by reductive or oxidative quenching cycle (figure 5).

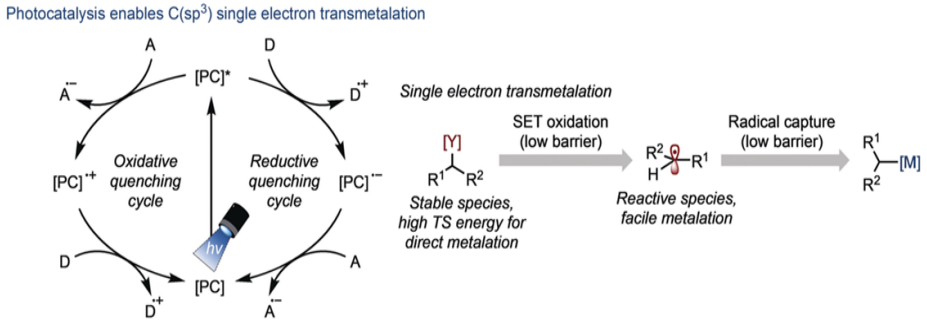


Figure 5: Photocatalyst excitation and quenching cycles. *Reproduced with permission from John Wiley and sons. License number: 4603071448509.*

Here photoredox catalysis allows a new approach to the controlled formation of alkylic C(sp^3) radicals where this radicals, which can then engage in the target C(sp^2)-C(sp^3) couplings using a Ni-based cross-coupling cycle (figure 6).

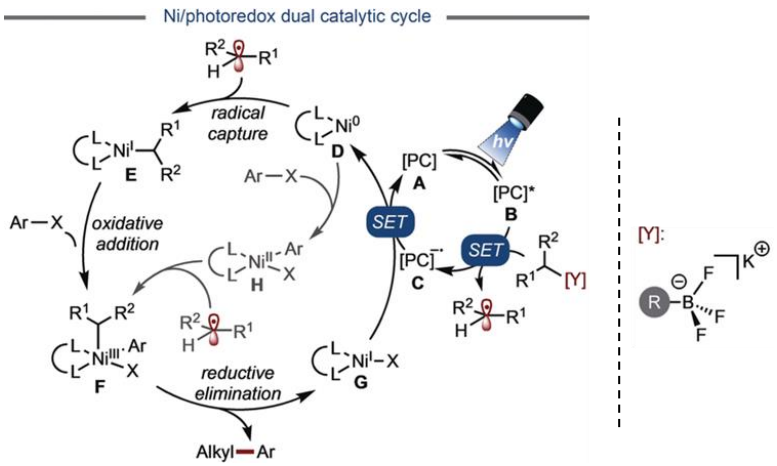


Figure 6. Net reductive Ni/photoredox cross-coupling cycle. *Reproduced with permission from John Wiley and sons. License number: 4603071448509.*

This approach enabled very mild Suzuki type coupling of alkyl trifluoroborate salts which is one of the wished objectives of this project.

4. OBJECTIVES

The main objective of this work is to keep improving and learning; but focusing on this specific project, the main objectives are:

Carry out studies towards photochemical radical generation using the C-O bond of hypervalent iodine reagents using a photoreactor.

Generate and control the radical transfer process of $\cdot CH_2F$ and $\cdot CHF_2$ to nitrogen containing heterocyclic substrates.

Get a new approach for the synthesis of 1,8-diiodonaphthalene using hypervalent iodine and the photoreactor.

Test the dual nickel/photoredox coupling reactions for the future interests of the group.

Synthetize two different Iridium photocatalysts, starting by the formation of the ligands.

Carry out dual nickel/photoredox coupling of α-substituted C(sp^3) trifluoroborates using the photocatalyst prepared.

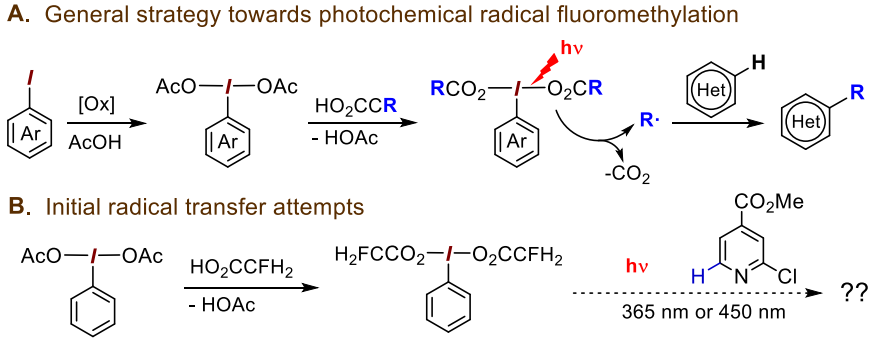
5. STUDIES TOWARDS SYNTHETIC METHODOLOGY *VIA* PHOTO-HOMOLYTIC I-O CLEAVAGE

As discussed in section 3.3.4.1, hypervalent iodine reagents can undergo facile photolytic decomposition, in this specific case of the I-O bond, homolytic bond cleavage

In this part of the project we wished to explore the homolytic I-O cleavage of compounds type $ArI(O_2CR)_2$ to give the radical R· via subsequent loss of CO_2.

In order to have a general view of this project we are going to introduce a global reaction scheme. The process starts with the oxidation of the iodoarene to give the corresponding λ^3-iodane. The oxidation can be realised by different methods that will be seen in more detail later. Once we have the diacetate derivative of the λ^3-iodane, the next step consists in installing the desired carboxylate group by ligand exchange (see section 3.3.1) to obtain the corresponding ($ArI(O_2C\mathbf{R})_2$). The final step is the generation of the **R·** radical by photolytic decomposition (see

section 3.3.4.1), and the subsequent addition of this reactive species to the desired substrate (scheme 8-A).



Scheme 8. Global view of the project

With the general vision of the project in mind, we can now take a look at the initial process of the formation of the λ³-iodane. As mentioned earlier, three different types of oxidants have been commonly used in the group, with the exact choice of procedure depending on the characteristics of the iodoarene employed, in this case the 1-[Bis(diacetoxy)iodo]-4-chlorobenzene or 1-[Bis(diacetoxy)iodo]-4-tert-butylbenzene.

Indeed, in the literature the most common oxidants employed for this purpose have been the *meta*-chloroperbenzoic acid, m-CPBA, the sodium periodate, $NaIO_4$, and sodium perborate $NaBO_3$. More recently, there have been important advances in this area, with one of the newest methods for the synthesis of compounds of the type $ArI(OAc)_2$ consisting of the rather mild oxidation of iodoarenes with Selectfluor. The conversion of an iodoarene into the corresponding aryliodine diacetates easily assessed by NMR thanks to the substantial chemical shifts changes that occur in going to the iodine (III) oxidation state. This change is illustrated in Figure 7 for the oxidation of iodobenzene. As can be observed, all three aromatic resonances undergo a downfield displacement upon the formation of $PhI(OAc)_2$, including the change of the *ortho* C-H resonance from 7.7 ppm to 8.1 ppm. A particularly impressive change, however, is observed in the ^{13}C-NMR spectrum, where the iodine-bound ^{13}C nucleus is shifted from ~95 ppm (abnormally low due to the heavy atom effect) all the way to 128 ppm upon the formation of the $–I(OAc)_2$ group.

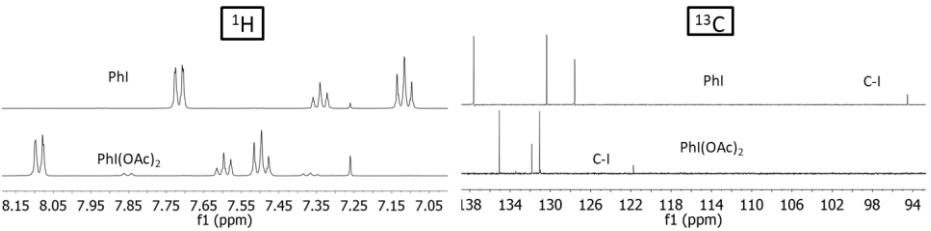
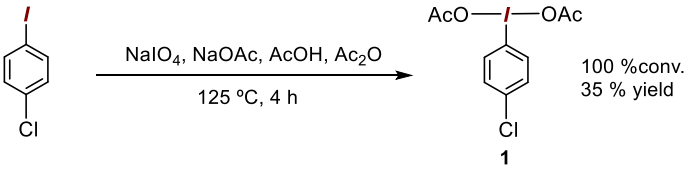


Figure 7. NMR spectra from iodobenzene and (diacetoxyiodo)benzene.

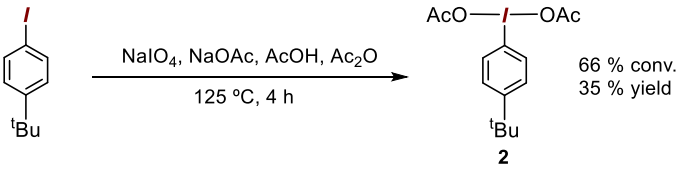
First, we did all the steps, starting from PIDA, to try to obtain the fluoromethyl radical transfer product using nicotinic acid derivative as seen in scheme 8-B. We began by performing ligand exchange in PIDA with fluoroacetic acid obtaining the [Bis(fluoroacetoxy)iodo]benzene with 98 % yield. The last step consisted on the mixture of this product with a nicotinate derivative using $CDCl_3$ as solvent. After putting the solution into the photoreactor a GC-mass analysis was done and instead of obtaining the desired product we observed the *para*-iodobenzene radical addition.

We decided to try with *para* substituted iodoarenes to avoid this unwished radical insertion. The first iodoarene tested was the 1-chloro-4-iodobenzene and we decided to start with a medium power oxidant agent, the $NaIO_4$. So mixing the 1-chloro-4-iodobenzene with 1 equivalent of sodium periodate, sodium acetate, acetic acid and anhydride acetic, allowed for total oxidation of the iodoarene, with ^{1}H-NMR analysis showing a total conversion to the oxidized λ^3-iodane with 35% of final yield (scheme 9).[21]



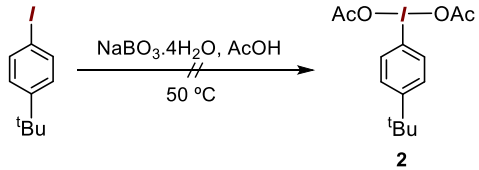
Scheme 9. Oxidation of 1-chloro-4-iodobenzene with sodium periodate.

The second iodoarene attempted was the 4-*tert*-butyliodobenzene. We followed the same procedure with sodium periodate to finally obtain the 1-[Bis(diacetoxy)iodo]-4-tert-butylbenzene showing a 3:1 conversion with 35 % of final yield (scheme 10).[21]



Scheme 10. Oxidation of 4-*tert*-butyliodobenzene with sodium periodate.

In view of the electronic nature of the iodoarene core, we considered that the efficiency of the oxidation step could be improved using $NaBO_3 \cdot 4H_2O$, which is generally considered to be a milder oxidant than sodium periodate. So mixing sodium perborate with acetic acid, 4-*tert*-butyliodobenzene and heating at 50 ºC for 4 hours is expected to give the λ³-iodane. Unfortunately, no new product could be observed, with the starting iodoarene recovered unaltered (scheme 11).[21]



Scheme 11. Oxidation of 4-*tert*-butyliodobenzene with sodium perborate.

Undeterred, seeking to develop a more practical synthesis of the target λ³-iodane, we decided to try to achieve the iodine(I) to iodine(III) oxidation using Selectfluor (figure 8), an organic salt which had been developed to act as a F^+ electrophile donor.[22]

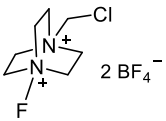
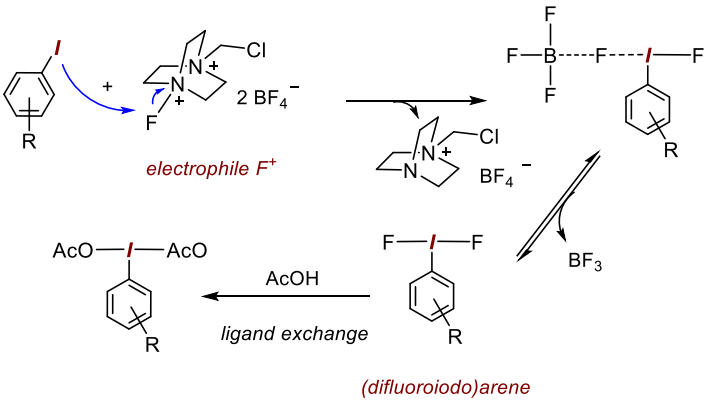


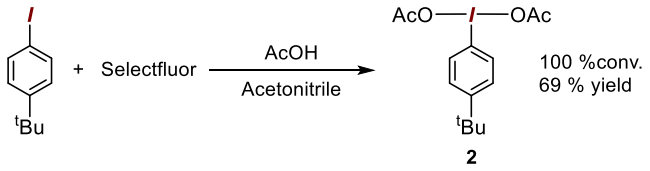
Figure 8. Molecular structure of Selectfluor

Selectfluor with its capacity to be a F^+ electrophile donor, is attacked by the iodine atom of the iodoarene leading to the formation of an intermediate where the iodine atom is attached to a fluorine atom and formally shares another fluorine atom with the BF_3. This intermediate evolves to the formation of the (difluoroiodo)arene which undergoes a ligand exchange reaction with acetic acid to give the corresponding (diacetoxyiodo)arene (scheme 12).



Scheme 12. Selectfluor oxidation mechanism.

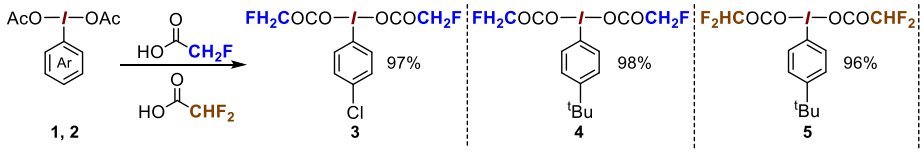
So as discussed before, in order to look for a more efficient alternative in the oxidation of the *para*-^{t}Bu iodobenzene, the Selectfluor-based approach was tested. Gratifyingly, unlike the two earlier methods, the use of Selectfluor led to a full a conversion of the iodoarene, leading, upon work-up, to the final yield of 69% of the target ArI(OAc)$_2$ (scheme 13).[22]



Scheme 13. Oxidation of 4-tert-butyliodobenzene with selectfluor.

Once we have the ArI(OAc)$_2$ prepared, we are going to focus on the second step, the ligand exchange reaction to generate the desired hypervalent iodine reagents. As mentioned earlier (including in the Objectives), a part of this effort has been directed to the generation of ·CH_2F and ·CHF_2 radicals using the different λ^3-iodanes prepared. As a way to prepare the corresponding λ^3 precursors, a mixture of the mono-fluoroacetic acid with **1** using toluene as solvent, after solvent evaporation, yields a white solid **3** with a 97% yield. Following the same procedure, **4** was obtained as a white solid with 98 % yield from the exchange between **2** and fluoroacetic acid. The **5** was obtained also as a white solid with 96 % yield form the exchange between **2** and difluoroacetic acid (scheme 14).[23]

These reactions were easy to carry out in the laboratory, were very rapid (10 min), and afforded high yields of clean products, given only acetic acid as byproducts which is easily eliminated by rotatory evaporation



Scheme 14. Obtention of the desired λ³-iodanes.

With the new hypervalent iodine reagents in hand, the final goal is to generate and control the insertion of ·R radicals in different substrates by decarboxylation process. The substrates tried were nitrogen-containing heterocycles such as nicotine derivatives and caffeine, as inspired by the work of Maruoka and co-workers. [24]

The model reaction consisted of preparing a mixture of the trivalent iodine compound with the heterocyclic substrate using $CDCl_3$ or CCl_4 as the solvent, followed by a purge with argon and, finally, placing the vial in the photoreactor with defined settings. We tried with three different substrates (methyl 2-chloroisonicotinate, methyl 2-chloronicotinate and caffeine), with the range of the trivalent iodine compounds at two different wavelengths (365 nm and 450 nm). Initial tests were conducted, as mentioned earlier, by using two nicotinate derivatives and PIDA, but GC-mass analyses allowed for the observation of rather complex reactions mixtures, which included peaks consistent with the insertion of the fluoroalkyl radicals in the *para* position of the iodobenzene ring. After a series of attempts we were able to observe by ^{1}H-NMR the desired radical transfer as we can see in this specific case (figure 9).

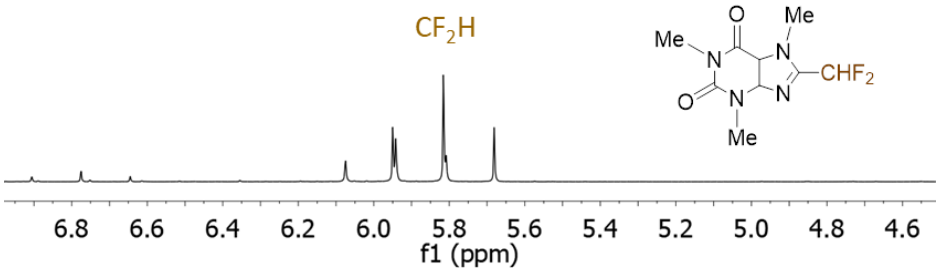
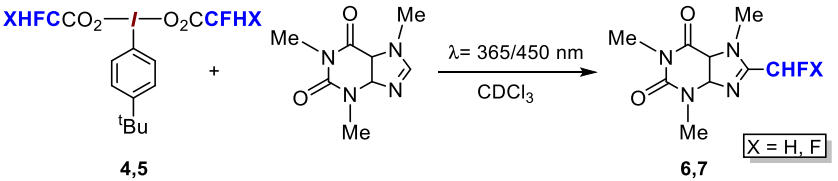


Figure 9. ^{1}H-NMR of 8-(Difluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione.

Specifically, this results were obtained using caffeine as the substrate, $CDCl_3$ as the solvent and 1-[Bis(difluoroacetoxy)iodo]-4-tert-butylbenzene or 1-[Bis(fluoroacetoxy)iodo]-4-tert-butylbenzene as the hypervalent iodine compounds (scheme 15). It's important to know that we could observe the desired products at both wavelengths tested, although ^{1}H and ^{19}F analyses of reaction mixtures suggested that the process appears to be more efficient when using the 365 nm LED source.



Scheme 15. Radical transfer obtaining using caffeine as substrate.

6. ALTERNATIVE PHOTO-CHEMICAL WAY FOR THE SYNTHESIS OF 1,8-DIIODONAPHTHALENE.

The alternative photo-chemical synthesis of 1,8-diiodonaphthalene has special interest for our work due to the use of hypervalent iodine and the radical's generation by CO_2 release to get the final product. It is also interesting because it is a useful compound for the research group.

The new goal was to obtain the 1,8-diiodonaphthalene by an alternative approach using hypervalent iodine compounds because of its difficulty to be prepared by the traditional way, starting by the 1,8-diaminonaphthalene and going through the diazonium salt (figure 10).

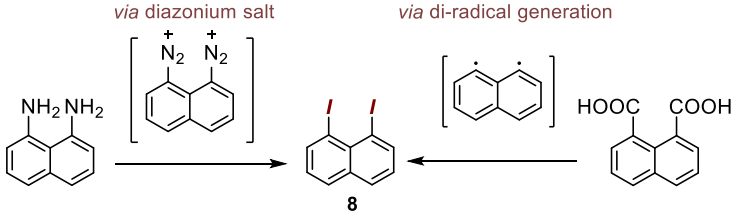
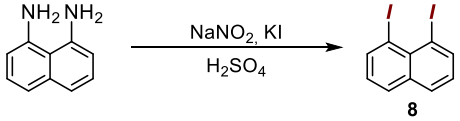


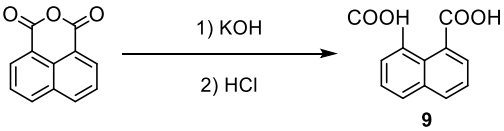
Figure 10: Two diferent ways to afford 1,8-diiodonaphthalene.

In order to compare the two methods, we began by the synthesis of the 1,8-diiodonaphtalene by the traditional way by mixing naphthalic acid with a $NaNO_2/H_2SO_4$ solution under a -15 ºC bath to afford the bis-diazonium intermediate. After adding KI, with a series of washing steps and purifying the product, **8** is obtained with 20-30 % yield (scheme 16). The problem of this reaction is the formation of an undesired black and sticky subproduct which makes the overall work-up extremely difficult.



Scheme 16. Synthesis of 1,8-diiodonaphthalene *via* diazonium salt.

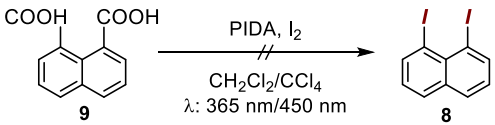
Once we had synthetized and characterized the product, the next step was to try the new way. We started by preparing the naphthalic acid which is the starting reagent to get the 1,8-diiodonaphthalene in this method. Naphthalic acid was prepared by mixing the naphthalic anhydride with KOH and after a reflux process, the precipitation of the diacid by the addition of HCl to yield **9** with 86 % yield (scheme 17).[25]



Scheme 17. Synthesis of the naphthalic acid.

With the naphthalic acid prepared we could start this reaction which was previously done in the literature[26] but under other conditions. The reaction has to be carried out under reflux and what we attempt was to do the reaction with our photoreactor. The problem is that we cannot heat the vial inside the photoreactor so we cannot carry out the reaction under reflux.

We start by mixing naphthalic acid, PIDA, I_2 and an organic solvent. This vial was then put in the photoreactor and we tried the four possibilities with two different solvents: CCl_4 and CH_2Cl_2 and two different wavelengths: 365 nm and 450 nm (scheme 18).[26]



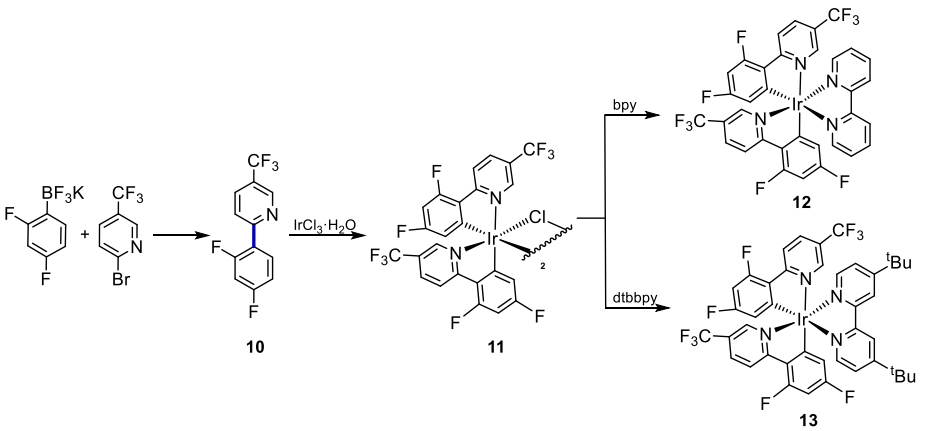
Scheme 18. 1,8-diiodonaphthalene synthesis attempt *via* homolytic decarboxylation.

In all the cases the result was the same, no product could be observed. We think that the problem is due to the impossibility to get the reaction to reflux inside the photoreactor so the systemdoes not overcome the energy barrier needed for the reaction.

7. APPROACHES TOWARDS DUAL PHOTOCATALYTIC C-C COUPLING REACTION

In this section we are going explore the use and the potential of the photoredox catalyst and, obviously, the photoredox reactions.

The initial idea of this project was the preparation of an Iridium photoredox catalyst in order to carry out dual photocatalytic/catalytic cross-coupling reactions. First of all a general view of the synthesis of the photocatalyst bearing two slightly different ancillary ligands will be introduced (scheme 19).

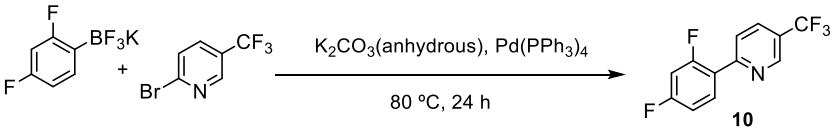


Scheme 19. General view of the photocatalyst synthesis.

The Iridium catalyst needs specific ligands, one is the 2-2'-bypiridine or 4,4'-di-tert-butyl-2,2'-bipyridine and the other ligand comes from a Suzuki reaction between potassium trifluoro(2,4-difluorophenyl)borate and 2-Bromo-5-(trifluoromethyl)pyridine. In the second step, newly prepared arylpyridine ligand is introduced into the coordination sphere of the Iridium atom. The synthesis is completed by the addition of a 2,2'-bipyridine ligand. Two different

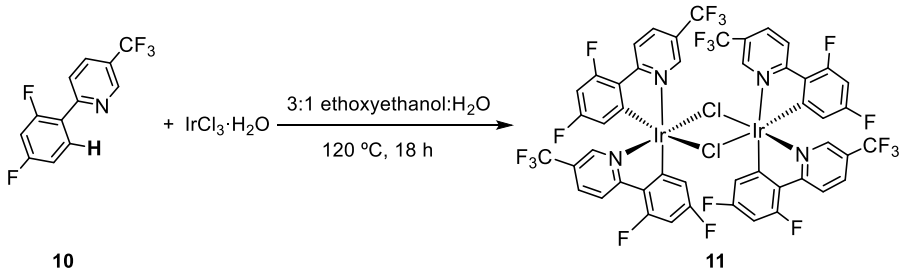
bipyridine have been used in this work. The final cationic Ir(III) photocatalyst is precipitated as a hexafluorophosphate salts by the the addition of a NH_4PF_6 solution.[20]

With these precedents, the first step consists of the palladium-catalyzed carbon-carbon coupling between potassium trifluoro(2,4-difluorophenyl)borate and 2-bromo-5-(trifluoromethyl)pyridine in presence of anhydrous K_2CO_3 and catalytic $Pd(PPh_3)_4$. The reaction reached completion upon heating at 80 ºC for 24 h. Product column chromatography afforded the desired **10** with yields between 80-90 % (scheme 20).[20] It should be noted that the column chromatography failed to fully eliminate the PPh_3 present in the reaction mixture, as observed by ^{1}H-NMR analysis. Nevertheless, this impurity, present at levels ranging from 2 - 12 % was found not to interfere in the subsequent complexation reactions.



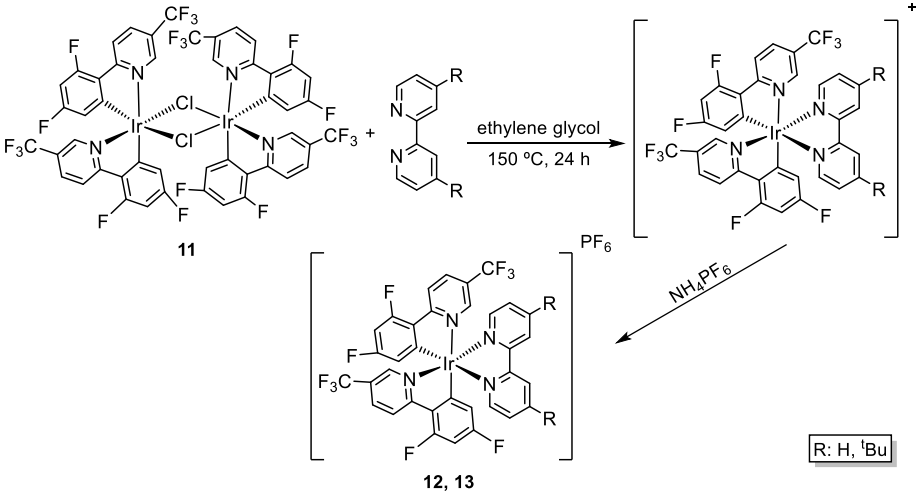
Scheme 20. Synthesis of 2-(2,4-Difluorophenyl)-5-(trifluoromethyl)pyridine.

The second step is a reaction between the $IrCl_3{\cdot}H_2O$ and the new ligand. Mixing the $IrCl_3{\cdot}H_2O$ and **10** using a 3:1 mixture of 2-ethoxyethanol with H_2O as solvent and heating the solution to 120 ºC for 18 h. This cyclometallation reaction affords the dimeric iridium complex in which the chloride atoms serve as bridges connecting the two Iridium atoms. By following this procedure, the dimer $[(dF(CF_3)ppy)_2\text{-}Ir\text{-}\mu\text{-}Cl]_2$ was obtained in 25% yield as a bright yellow solid (scheme 21).[20] This synthesis was repeated several times, with better results for higher scale runs. For example, while on 0.166 mmol scale (for the $IrCl_3.H_2O$) a 25 % yield was obtained, the 0.91 mmol scale reaction afforded the products in a 62 % yield. This difference could be related to the common work up losses in low scale runs.



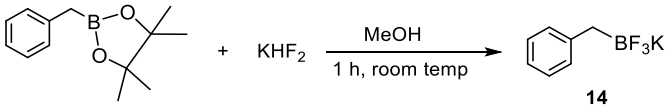
Scheme 21. Formation of of the dimeric μ-Cl iridium species **11**.

The last step involves the breaking of the dimer with a bipyridine ligand, to give two equivalents of the target monomeric Ir catalyst. As explained before, this last step could be performed with either 2,2'-bipyridine or its substituted derivative 4,4'-di-tert-butyl-2,2'-dipyridyl. The reaction starts with the mixture of the **11** with the corresponding bipyridine ligand using ethylene-glycol as the solvent. After heating up to 150 ºC for 24 hours and carry out the corresponding work up, we obtain the anion of the catalyst. The cationic Ir(III) photocatalyst is precipitated as a hexafluorophosphate salts by the addition of a NH_4PF_6 solution. After that, we purified the products by vapour diffusion crystallization, using acetone as the solvent and pentane as the counter solvent, to give the pure crystalline structures: $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ or $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ depending on the ligand used (scheme 22).[20] The yields of these reactions are 27 % in **13** (R = ^{t}Bu) and 45 % in **12** (R = H).



Scheme 22. Synthesis of the Iridium photocatalyst

Once the photocatalyst is prepared, the next target is the synthesis of the substrate that will be the subject of the coupling, in our case is a BF_3^- salt, the potassium benzyl(trifluoro)borate. The BF_3^- salt was easily prepared from benzylboronic acid pinacol ester by mixing it with KHF_2 using MeOH as the solvent. After removing the impurities with a series of washing step, **14** was obtained with a 65 % yield (scheme 23).[27] The difficulty of improving this yield is due to the different washing that we have done to remove the remaining part of the starting reagents, due to the similar solubilities of the product and the KHF_2.



Scheme 23. Synthesis of potassium benzyl(trifluoro)borate

The final objective is the carbon-carbon coupling between **14** and a bromoaryl using the iridium photocatalyst.

The idea was to try first with the potassium benzyl(trifluoro)borate, because it's a known reaction, to check if the photocatalyst and everything work out properly and then try the coupling with α-substituted benzyl(trifluoro)borate compounds (figure 10) that the group has prepared.

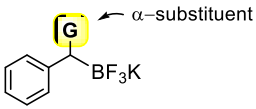
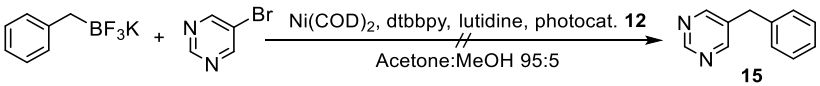


Figure 10. α-substituted benzyl(trifluoro)borate compounds

Due to the lack of time and a problem with one catalyst, that will be explained later, these other cross-coupling photo-redox reactions could not be realized so we are going to focus with the only attempt that we were able to try in the period of time that we had.

The reaction consists on a photocatalytic cycle between the Iridium catalyst prepared and the $Ni(COD)_2$ (see section 3.4).

The bromo-aryl compound chosen was the 5-bromopyrimidine and the BF_3^- salt was the prepared potassium benzyl(trifluoro)borate, so mixing them with 4,4'-Di-tert-butyl-2,2'-dipyridyl, lutidine and the two photocatalyst, the $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ and $Ni(COD)_2$, using a 95:5 mixture of Acetone:MeOH as the solvent, we were supposed to obtain 4-Benzyl-2-methylpyridine (scheme 24)[20] but nothing was observed by ^{1}H-NMR.



Scheme 24. Cross-coupling photo-redox reaction attempt.

The catalyst $Ni(COD)_2$ that was commercially obtained, is sensitive to air and light and has to be manipulated in a glovebox. The group had one glovebox but was not working out properly at the time that we were carrying out the reaction so we had to do the reaction without the

glovebox. Due to this problem, the reaction could not get completed and we could not observe the product. The main problem of $Ni(COD)_2$ is that in presence of air it gets oxidized very quickly, losing its photo-redox catalytic characteristics and changing the colour from orange to black as we could observe (figure 11)

Figure 11. Different colours of $Ni(COD)_2$.

8. EXPERIMENTAL SECTION

8.1. MATERIALS AND METHODS

Reagents. All commercially acquired reagents were used as received.

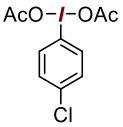
Reaction conditions. Reactions requiring inert atmosphere were conducted under argon using standard Schlenk line techniques. All other reactions were performed employing standard organic synthesis protocols.

Chromatography. Thin layer chromatography (TLC) was performed using Merck aluminium-backed plates of TLC Silica gel 60 F254; the plates were revealed using UV light at 254 nm or by staining using potassium permanganate. Standard Flash Column chromatography was accomplished using silica gel (60 Å pore size, 230-400 μm mesh size).

NMR. Spectra were recorded using a Varian Mercury 400 instrument (400 MHz for 1H and 101 MHz for 13C). Chemical shifts (δH) are quoted in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s).

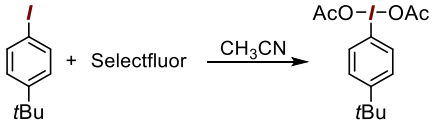
Photoreactor. PennOC m^2.

8.2. PREPARATION OF ALL COMPOUNDS.



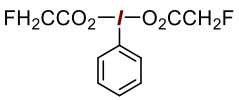
(1) To a stirred mixture of AcOH (3 mL) and Ac_2O (0.3 mL) in a 25 mL round bottom flask, $NaIO_4$ (3.0 mmol, 650 mg) and NaOAc (7.0 mmol, 570mg) were added. The 4-chloroiodobenzene (3.0 mmol, 720 mg), was added and the mixture was heated to 125 ºC. After 3.25 hours, a white solid was observed. The ^{1}H NMR analysis of an aliquot revealed 100% conversion to the desired hypervalent target. The reaction mixture was diluted with H_2O (40 mL) and extracted with 3x15 mL of CH_2Cl_2 The organic fractions were then combined, dried over MgSO4 and concentrated to afford a yellow oil. First a couple of drops of CH_2Cl_2 and then 30 mL of pentane were added leading to the formation of a white precipitate. This solid was isolated by filtration, washed with pentane three times and dried under high vacuum. The 1-[bis(diacetoxy)iodo]-4-chlorobenzene: 405 mg, 35%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2H), 7.46 (d, 2H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 138.5, 136.3, 131.2, 118.8, 20.3.



(2) To a stirred mixture of AcOH (25 mL) and CH_3CN (75 mL) in a 500 mL round bottom flask, Selectfluor (19.2 mmol, 6.8 g) and 4-*tert*-Butyliodobenzene (9.6 mmol, 2.5 g, 1.7 mL) were added. The mixture was allowed to stir for 24 hours. A ^{1}H NMR analysis of an aliquot revealed a 100% conversion to the desired hypervalent target. H_2O (80 mL) was added and the mixture was extracted with 3x50 mL of CH_2Cl_2. The organic fractions were then combined, dried over $MgSO_4$, and concentrated by rotatory evaporation. Precipitation was induced after putting the solution on a -78 ºC bath. This solid was isolated by filtration, washed with pentane three times and dried under vacuum. The 1-[Bis(diacetoxy)iodo]-4-tert-butylbenzene: 2.22 g, 67%.

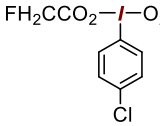
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 2.01 (s, 6H), 1.34 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 155.5, 134.7, 128.3, 118.2, 35.2, 31.1, 20.4.



To a stirred solution of (diacetoxyiodo)benzene (2.0 mmol, 644 mg) in toluene (2 mL), fluoroacetic acid (0.46 mL) was added dropwise. After 20 minutes of stirring the mixture was concentrated by rotatory

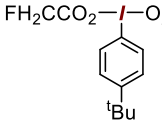
evaporation to yield a white oil. An additional portion of toluene (1 mL) was added, and the volatiles were once again removed with rotatory evaporation. The resulting oil was dried under vacuum for 18h, leading to the formation of The [bis(fluoroacetoxy)iodo]benzene as a white solid: 756 mg, 98%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2H), 7.68 – 7.61 (t, 1H), 7.54(t, 2H), 4.76 (d, J_{H-F} = 47.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (d, *J* = 21.2 Hz), 135.1, 132.6, 131.4, 122.4, 76.6 (d, *J* = 185.5 Hz). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ -224.4 (t, *J* = 47.5 Hz).



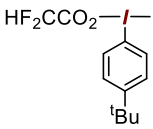
(3) To a stirred solution of (diacetoxyiodo) 4-chlorobenzene (2.0 mmol, 713 mg) with toluene (2 mL), fluoroacetic acid (0.45 mL) was added dropwise. After 20 minutes of stirring the mixture was concentrated by rotatory evaporation to yield an oil. An additional portion of toluene (1 mL) was added, and the volatiles were once again removed with rotatory evaporation. The resulting oil was dried under vacuum for 18h, leading to the formation of the product as a white solid. The [Bis(fluoroacetoxy)iodo]-4-chlorobenzene (2): 762 mg, 97%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 4.76 (d, *J* = 47.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (d, *J* = 21.1 Hz), 139.7, 136.7, 131.9, 119.6, 76.7 (d, *J* = 186.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -224.6 (t).



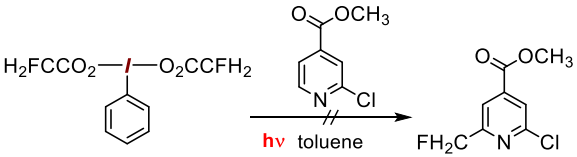
(4) To a stirred solution of 1-[Bis(diacetoxy)iodo]-4-*tert*-butylbenzene (2.9 mmol, 1.1 g) with toluene (3 mL), fluoroacetic acid (0.67 mL) was added dropwise. After 20 minutes of stirring the mixture was concentrated by rotatory evaporation to yield a yellow oil. An additional portion of toluene (1.5 mL) was added, and the volatiles were once again removed with rotatory evaporation. The resulting oil was dried under vacuum for 18h, leading to the formation of the product as a white solid. The 1-[Bis(fluoroacetoxy)iodo]-4-tert-butylbenzene: 1.17 g, 98%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.76 (d, *J* = 47.6 Hz, 4H), 1.34 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (d, *J* = 21.0 Hz), 156.6, 134.9, 128.7, 119.0, 76.6 (d, *J* = 185.5 Hz), 35.3, 31.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -224.3 (t, *J* = 47.5 Hz).



(5) To a stirred solution of 1-[Bis(diacetoxy)iodo]-4-*tert*-butylbenzene (1.0 mmol, 390 mg) with toluene (1 mL), difluoroacetic acid (0.25 mL) was added dropwise. After 15 minutes of stirring the mixture was concentrated by rotatory evaporation to yield a yellow oil. An additional portion of toluene (0.5 mL) was added and the volatiles were once again removed with rotatory evaporation. The resulting yellow oil was dried under vacuum for 18h, leading to the formation of the product as a white solid. The 1-[Bis(difluoroacetoxy)iodo]-4-tert-butylbenzene: 433mg, 96%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 5.82 (t, *J* = 53.7 Hz, 2H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 157.3, 134.9, 129.0, 119.0, 105.6 (t, *J* = 251.8 Hz), 35.4, 31.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.3 (d, *J* = 53.8 Hz).



Attempt to 2-Chloro-6-difluoromethylisonicotinic acid methyl ester by radical transfer from [Bis(fluoroacetoxy)iodo]benzene. [Bis(fluoroacetoxy)iodo]benzene (0.4 mmol, 143 mg) and methyl 2-chloroisonicotinate (0.2 mmol, 34 mg) and $CDCl_3$ (0.5 mL) were placed into a vial and purged with Ar. The mixture was put into the photoreactor with the following parameters: LED intensity: 100%, stir: 100, fan rpm: 3100, **λ: 365 nm**, time: 3 hours. After this time a ^{1}H NMR was made and no product was observed.

This procedure was attempted with different substrates, iodoarenes, wavelengths (365/450 nm) (figure 12), solvent (CH_2Cl_2/CCl_4), getting the same result in all the cases, excepting one case that is going to be detailed later.

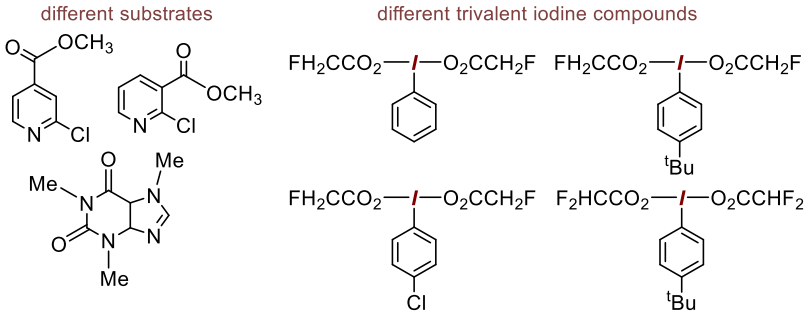


Figure 12. Substrates and iodoarenes attempted.

On the other hand, following also the same procedure, we observe this radical transfer using caffeine as the substrate and the two ^{t}Butil para substituted iodoarenes, obtaining the two final products: 8-(difluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione and 8-(fluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (figure 13) which were detected by ^{1}H-NMR analysis but were not isolated.

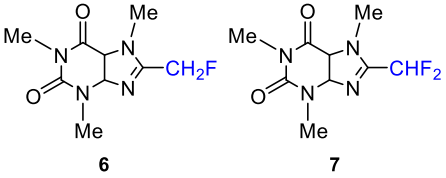
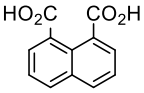


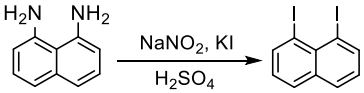
Figure 13. Obtaining of **(6)** 8-(fluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione and **(7)** 8-(difluoromethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione.



(9) A 100 mL round-bottom flask equipped with a magnetic stirbar was charged with an aqueous KOH solution (1 g in 30 mL H_2O) followed by 1-8-naphthalic anhydride (1.0 g, 5.0 mmol). The reaction flask then equipped with a reflux condenser and the mixture was stirred at refluxed for 1.5h, and then cooled to room temperature. The resulting solution was transferred to a separatory funnel and washed with CH_2Cl_2 (3 x 25 mL). The aqueous phase was treated with hydrochloric acid (aqueous, 12M, 5 mL) at 0 ºC leading to the precipitation of a white solid, which was isolated by filtration, washed with H_2O and dried to air. Finally, the

resulting powder was dried under reduced pressure to afford naphthalene-1,8-dicarboxylic acid (0.969 g, 86%).

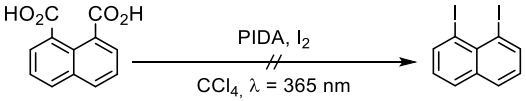
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (br s, 2H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.93 (dd, *J* = 7.1, 1.3 Hz, 2H), 7.61 (t, *J* = 8.2, 7.1 Hz, 2H).^{1}H NMR matched with the literature spectrum.[25]



(8) A 250 mL round-bottom-flask equipped with a magnetic stirbar was charged with 1,8-diaminonaphthalene (1.58 g, 10 mmol) and H_2SO_4 (6.9M, 20 mL) and the resulting solution was cooled to -20 ºC with vigorous stirring. $NaNO_2$ (aqueous, 2.03 g, 30 mmol in 8 mL of H_2O) and KI (9.96 g, 60 mmol, 8.4 mL H_2O) solutions were subsequently added dropwise. Once the addition was complete, the flask was equipped with a reflux condenser and allowed to stir at 80 ºC for 20 minutes. The solution was neutralized with NaOH and large amounts of a black rubbery substance appeared, being extremely difficult to work with it. $Na_2S_2O_3$ was added and the solution was extracted with CH_2Cl_2 (4 x 15 mL). This procedure was made extremely difficult by the formation of this black rubbery substance. The combined organic phases were subsequently washed with HCl (9M 50 mL), $Na_2S_2O_3$ and NaOH (1M 50 mL). The solution was dried with $MgSO_4$, filtrated and the solvent was removed by rotatory. The corresponding solid was purified by silica gel column chromatography eluting with a 40:1 hexanes:AcOEt mixture to obtain 1-8-diiodonaphtalene as a shiny yellow solid.

This procedure was repeated several times, with yields ranging in the 15-25% range. This low yields appears to stem not from the reaction itself, but from losses incurred during the inconvenient work-up procedure. Nevertheless, even the modest quantities obtained in these runs provided valuable starting materials for the group projects.

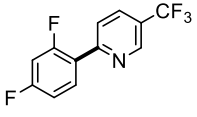
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 7.3, 1.3 Hz, 2H), 7.85 (dd, J = 8.2, 1.3 Hz, 2H), 7.08 (dd, J = 8.1, 7.3 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 135.8, 131.0, 126.9, 96.0.



(8) *Attempt to 1,8-diiodonaphtalene by photochemical decarboxylation of naphthalic anhydride*. A large vial equipped with a magnetic stirbar was charged with naphthalic anhydride (32 mg, 0.148 mmol), (diacetoxyiodo)benzene

(43 mg, 0.13 mmol), I_2 (32 mg, 0.126 mmol) and CH_2Cl_2 (2 mL). The solution was purged under Ar., and the vial was placed into the photoreactor to carry out the irradiation under the following parameters: LED intensity: 100%, stir: 100, fan rpm: 2800, **λ: 365 nm**, time: 4 hours. After this time a ^{1}H-NMR was done and no product was observed.

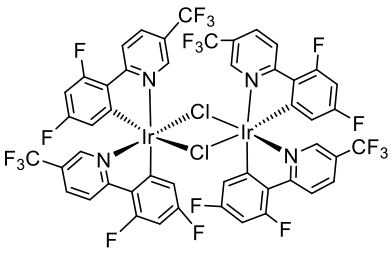
Further experiments were carried under four possible parameter combination: $CDCl_3$ or CCl_4 as the solvent and using: λ= 365 nm or λ= 450 nm following. No product was observed by ^{1}H NMR.



(10) A Schlenk tube was charged with potassium trifluoro(2,4-difluorophenyl)borate (3.18 mmol, 700 mg), 2-bromo-5-(trifluoromethyl)pyridine (2.12 mmol, 479 mg), K_2CO_3 (anhydrous, 10.6 mmol, 1.476 g) and $Pd(PPh_3)_4$ (0.21 mmol, 245 mg) and was subsequently purged under Ar three times. The contents were dissolved in a mixture of the previously degassed H_2O (3.37 mL) and THF (6.75 mL). The tube was sealed with a teflon stopper and the solution was allowed to stir at 80 ºC for 24h. The mixture was cooled to room temp, diluted with H_2O and extracted with CH_2Cl_2 (5x15 mL). The combined organic layers were dried with $MgSO_4$, filtered under vacuum and the solvent was removed by rotatory evaporation. The corresponding solid was purified by silica gel column chromatography, eluting with a 27:1 hexanes:AcOEt mixture to obtain 2-(2,4-Difluorophenyl)-5-(trifluoromethyl)pyridine as a white solid (464 mg, 84%).

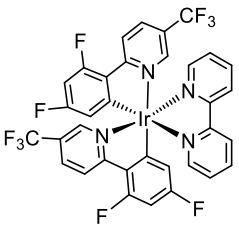
Column chromatography in this and smaller scale runs consistently afforded the product contaminated with ~2-10% of PPh_3. This impurity did not affect the subsequent complex formation and then yield is given with this impurity subtracted.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (m, 1H), 8.10 (td, *J* = 8.8, 6.6 Hz, 1H), 7.99 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.91 (m, 1H), 7.04 (tdd, *J* = 8.6, 2.5, 0.9 Hz, 1H), 6.95 (ddd, *J* = 11.3, 8.7, 2.5 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.43, -107.25 (ddd, *J* = 16.1, 8.9, 6.9 Hz), -112.08 (q, *J* = 10.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 – 162.6 (m), 161.1 (dd, *J* = 253.7, 12.1 Hz), 155.9, 133.9 (d, *J* = 3.5 Hz), 132.6 (dd, *J* = 9.9, 4.1 Hz), 128.6 (d, *J* = 7.4 Hz), 125.3 (q, J = 33.0 Hz) 123.8 (d, *J* = 10.9 Hz), 123.7 (q, J = 271.0 Hz) 122.6 (dd, *J* = 10.8, 3.9 Hz), 112.4 (dd, *J* = 21.3, 3.7 Hz), 104.8 (dd, *J* = 27.0, 25.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4, -107.3 (ddd, *J* = 16.1, 8.9, 6.9 Hz), -112.1 (q, *J* = 10.0 Hz).



(11) A Schlenk tube was charged with 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine (632 mg, 2.44 mmol), $IrCl_3 \cdot H_2O$ (355 mg, 1.12 mmol) and was subsequently purged 4 times with argon. Degassed 2-ethoxyethanol (13.3 mL) and degassed H_2O (4.4 mL) were added and the tube was sealed with a teflon stopper. The solution was heated to 120 ºC with stirring for 20 hours, which lead to the precipitation of a yellow solid, which was filtered and washed with H_2O (110 mL) and hexanes (45 mL). The solid was dried under reduced pressure and checked by ^{1}H-NMR showing multiple aromatic systems. The solid was again dissolved in degassed 2-ethoxyethanol (9 mL) and also degassed H_2O (3 mL) and heated up to 120 ºC for 18 hours. The yellow solid formed was collected by filtration, washed with a solution of H_2O (75 mL) and hexanes (30 mL) and dried under reduced pressure to yield $[(dF(CF_3)ppy)_2\text{-Ir-}\mu\text{-Cl}]_2$ (387 mg, 43 %).

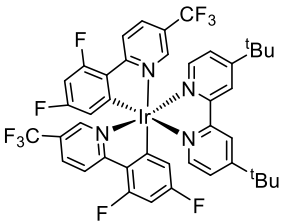
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 2.1 Hz, 4H), 8.46 (dd, *J* = 8.9, 3.0 Hz, 4H), 8.05 (dd, *J* = 8.8, 2.2 Hz, 4H), 6.44 (m, 4H), 5.07 (dd, *J* = 8.8, 2.3 Hz, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1, -103.5 (dt, *J* = 11.8, 8.9 Hz), -107.7 (td, *J* = 12.0, 3.3 Hz). *Due to the low solubility of the product and the extensive ^{13}C-^{19}F coupling, we were only able to identify the five C-H in the ^{13}C with the help of the HSQC:* ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 135.9, 122.6 (d, *J* = 20.5 Hz), 112.5 (d, *J* = 17.6 Hz), 99.0.



(12) A Schlenk tube was charged with $[(dF(CF_3)ppy)_2\text{-Ir-}\mu\text{-Cl}]_2$ (240 mg, 0.16 mmol), 2-2'-bipyridine (60 mg, 0.386 mmol) and was subsequently purged under Ar three times. Degassed ethylene glycol (11 mL) was added and the tube was sealed with a teflon stopper. The mixture was heated up to 150 ºC for 23 hours. After cooling to room temp. the solution was diluted with H_2O, transferred to a separatory funnel and washed with hexane (3 x 30 mL). The aqueous phase was transferred to an Erlenmeyer flask and was heated to 85 ºC for 15 min to remove residual hexanes. After cooling to room temp. NH_4PF_6 (aqueous, 1.8 g in 18 mL) was leading to the formation of a yellow precipitate. This solid was collected by filtration, washed with H_2O (30 mL) and pentane (20 mL) and was dried under reduced pressure. The resulting yellow solid was

dissolved in the minimum amount of acetone and was recrystallized by vapour diffusion with pentane yielding a yellow crystalline solid of [Ir{dFCF$_3$ppy}$_2$(bpy)]PF$_6$ (145 mg, 45 %).

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.89 (dt, *J* = 8.2, 1.0 Hz, 2H), 8.62 (dd, *J* = 8.8, 2.7 Hz, 2H), 8.42 (m, 2H), 8.40 – 8.37 (m, 2H), 8.29 (m, 2H), 7.97 (dt, *J* = 2.0, 1.0 Hz, 2H), 7.80 (ddd, *J* = 7.7, 5.4, 1.2 Hz, 2H), 6.85 (ddd, *J* = 12.8, 9.3, 2.3 Hz, 2H), 5.96 (dd, *J* = 8.5, 2.3 Hz, 2H). ^{19}F NMR (376 MHz, Acetone-d_6) δ -63.6, -72.6 (d, *J* = 707.3 Hz), -104.7 (dt, *J* = 12.0, 8.9 Hz), -108.0 (td, *J* = 12.3, 2.8 Hz). ^{31}P NMR (162 MHz, Acetone-d_6) δ 144.28 (sept, J = 707.5). ^{1}H NMR matched with the literature spectrum [20]



(13) A Schlenk tube was charged with [{dF(CF$_3$)ppy}$_2$-Ir-μ-Cl]$_2$ (240 mg, 0.16 mmol), 4,4'-Di-tert-butyl-2,2'-dipyridyl (104 mg, 0.386 mmol) and was subsequently purged under Ar three times. Degassed ethylene glycol (11 mL) was added and the tube was sealed with a teflon stopper. The mixture was heated up to 150 ºC for 23 hours. After cooling to room temp. the solution was diluted with H_2O, transferred to a separatory funnel and washed with hexane (3 x 30 mL). The aqueous phase was transferred to an Erlenmeyer and it was heated up to 85 ºC for 15 min. to remove residual hexanes. After cooling to room temp. NH_4PF_6 (aqueous, 1.8 g, 18 mL) was added appearing a yellow precipitate. The precipitate was collected by filtration, washed with H_2O (30 mL) and pentane (20 mL) and it was dried under reduced pressure. The resulting yellow solid was dissolved in the minimum amount of acetone and recrystallized by vapour diffusion with pentane yielding a crystalline structure of [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]PF$_6$ (96 mg, 27 %).

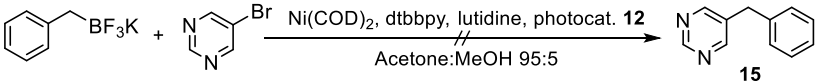
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.9 Hz, 2H), 8.49 (dd, *J* = 8.9, 3.2 Hz, 2H), 8.08 (m, 2H), 7.82 (d, *J* = 5.8 Hz, 2H), 7.57 (dd, *J* = 5.9, 1.9 Hz, 2H), 7.40 (d, *J* = 2.1 Hz, 2H), 6.62 (m, 2H), 5.63 (dd, *J* = 8.0, 2.3 Hz, 2H), 1.58 (s, 18H). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ -62.9, -73.2 (d, *J* = 712.6 Hz), -101.6 (dt, *J* = 12.7, 8.6 Hz), -105.9 (td, *J* = 12.6, 3.4 Hz). ^{31}P NMR (162 MHz, Acetone-d_6) δ -144.3 (sept, J = 707.3). The ^{1}H-NMR matched with the literature spectrum.[20]

(14) A 50 mL round-bottom flask equipped with a magnetic stirbar was charged with benzylboronic acid pinacol ester (1.0 g, 4.6 mmol), followed by MeOH (15 mL). A solution of KHF_2 (aqueous, 3.24 g, 41.4 mmol in 9.2 mL of H_2O) was then added dropwise. The resulting

solution was allowed to stir for 1 hour and then concentrated to dryness by rotatory evaporation. The resulting white solid was washed with hot ether (40 mL), very small amounts of H_2O (2 x 3 mL) and the final solid was collected by filtration. The solid was dried under reduced pressure. The ^{19}F-NMR analysis in acetone-d_6 confirmed the formation of the target salts, it also revealed the presence of residual KHF_2 (peak at -170.17 ppm). Therefore, the solid was again washed with cold H_2O (3 mL), collected by filtration and dried under reduced pressure to afford the pure potassium benzyl(trifluoro)borate (590 mg, 65 %).

^1H NMR (400 MHz, Methanol-d_4) δ 7.11 (m, 2H), 7.06 (m, 2H), 6.91 (br t, J = 6.8, 1.8 Hz, 1H), 1.69 (br m, 2H, CH_2B).^{13}C NMR (101 MHz, Methanol-d_4) δ 146.9, 129.8, 128.3, 123.7, 29.0 (CH_2). ^{19}F NMR (376 MHz, Methanol-d_4) δ -137.6 – -147.9 (m).

The 30-28 peak in ^{13}C-NMR spectrum, corresponding to the CH_2 group, could be detected by HSQC via its cross-peak with the ^1H CH_2 resonance at 1.67 ppm.



(15)

Attempt to 5-Benzylpyrimidine by photo-redox cross-coupling reaction of 5-bromopyrimidine and potassium benzyl(trifluoro)borate. A large vial equipped with a magnetic stirbar was charged with potassium benzyl(trifluoro)borate (59 mg, 0.3 mmol), 5-bromopyrimidine (40 mg, 0.25 mmol), $Ni(COD)_2$ (2.1 mg, 0.0075 mmol), 4,4'-Di-tert-butyl-2,2'-dipyridyl (2 mg, 0.0075 mmol) and Iridium photocatalyst $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (5 mg, 0.005 mmol). Ar was moved on the contents for 10 min and acetone/MeOH previously sieved (2.5 mL, 95:5) and lutidine (0.1 mL) were added. The mixture was put into the photoreactor with the following parameters: LED intensity 100 %, stir: 600, fan rpm: 6800, λ: 450 nm and time reaction: 5 hours. The crude reaction was checked by ^1H-NMR and no product was observed.

9. CONCLUSIONS

The synthesis of the different hypervalent iodine targets has been successful using $NaIO_4$ and Selectfluor as the oxidant agents. Also, the obtaining of the desired λ^3-iodanes by ligand exchange using either fluoroacetic or difluoroacetic acid has been greatly completed.

Despite the initial problems in the radical transfer step, either the no radical generation or the uncontrolled radical generation, we were finally able to observe and control the $\cdot CH_2F$ and $\cdot CHF_2$ radical generation and the final coupling with caffeine, opening a new chemical path for the group interests.

Finally, just as we were able to obtain and characterize the 1,8-diiodonaphtalene by the diazonium salt intermediate, unfortunately we could not get the product by homolytic bond cleavage as we wished due to the impossibility to reach reflux conditions inside the photoreactor.

Good results have been obtained in the synthesis of the photocatalyst, starting from the Suzuki reaction to obtain the first ligands, going through the dimeric species and finally obtaining the desired pure catalysts as crystalline yellow powders. On the other hand we were not able to obtain the cross-coupling redox reaction product due to the sensitivity of $Ni(COD)_2$. However, with the future developments of more robust Ni catalyst, we wish to reach the final coupling products.

10. REFERENCES AND NOTES

[1] C. Willgerodt, *J. für Prakt. Chemie* **1886**, *33*, 154–160.
[2] C. Willgerodt, *Berichte der Dtsch. Chem. Gesellschaft* **1892**, *25*, 3494–3502.
[3] C. Hartmann, V. Meyer, *Berichte der Dtsch. Chem. Gesellschaft* **1894**, *27*, 426–432.
[4] C. Hartmann, V. Meyer, *Berichte der Dtsch. Chem. Gesellschaft* **1893**, *26*, 1727–1732.
[5] P. J. Stang, V. V Zhdankin, R. Tykwinski, N. S. Zefirov, *Tetrahedron Lett.* **1992**, *33*, 1419–1422.
[6] A. Yoshimura, V. V Zhdankin, *Chem. Rev.* **2016**, *116*, 3328–3435.
[7] M. S. Yusubov, A. Yoshimura, V. Zhdankin, *Arkivoc* **2016**, *2016*, 342–374.
[8] A. Yoshimura, Mekhman S. Yusubov, V. V. Zhdankin, *Rev. Accounts* **2016**, 342–374.
[9] V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, **2014**.
[10] T. Wirth, *Hypervalent Iodine Chemistry*, **2016**.
[11] N. W. Alcock, R. M. Countryman, S. Esperås, J. F. Sawyer, *J. Chem. Soc. Dalt. Trans.* **1979**, 854–860.
[12] J. I. Musher, *Angew. Chemie Int. Ed. English* **1969**, *8*, 54–68.
[13] E. B. Merkushev, *Russ. Chem. Rev.* **1987**, *56*, 826–845.
[14] H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111–124.
[15] R. M. Moriarty, R. K. Vaid, M. P. Duncan, M. Ochiai, M. Inenaga, Y. Nagao*, *Tetrahedron Lett.* **1988**, *29*, 6913–6916.
[16] D. H. Hey, C. J. M. Stirling, G. H. Williams, *J. Chem. Soc.* **1955**, 3963–3969.
[17] L. Wang, J. Liu, *European J. Org. Chem.* **2016**, *2016*, 1813–1824.
[18] Y. Yasu, T. Koike, M. Akita, *Chem. Commun.* **2013**, *49*, 2037–2039.
[19] J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chemie Int. Ed.* **2019**, *58*, 6152–6163.
[20] J. C. Tellis, D. N. Primer, G. A. Molander, *Science (80-.).* **2014**, *345*, 433 LP – 436.
[21] Y. Wu, S. Izquierdo, P. Vidossich, A. Lledós, A. Shafir, *Angew. Chemie Int. Ed.* **2016**, *55*, 7152–7156.
[22] C. Ye, B. Twamley, J. M. Shreeve, *Org. Lett.* **2005**, *7*, 3961–3964.
[23] S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós, A. Shafir, *J. Am. Chem. Soc.* **2016**, *138*, 12747–12750.
[24] R. Sakamoto, H. Kashiwagi, K. Maruoka, *Org. Lett.* **2017**, *19*, 5126–5129.
[25] H. Salman, S. Tal, Y. Chuvilov, O. Solovey, Y. Abraham, M. Kapon, K. Suwinska, Y. Eichen, *Inorg. Chem.* **2006**, *45 (14)*, 5315–5320.
[26] R. Singh, G. Just, *Synth. Commun.* **1988**, *18*, 1327–1330.
[27] S. R. Inglis, E. C. Y. Woon, A. L. Thompson, C. J. Schofield, *J. Org. Chem.* **2010**, *75*, 468–471.

11. ACRONYMS

Ac: Acetate.

Ar: Aryl.

Ar.:Argon.

Bpy: bipyridine.

COD: cyclo octadiene.

DMP: Dess Martin periodinate.

Dtbpy: di-tert-butyl bipyridine.

GC: gass-chromatography.

IBX: iodoxybenzoic acid.

LED: light emission díode.

LUMO: lowest unoccupied molecular orbital.

mCPBA: meta-chloroperoxybenzoic acid.

MO: molecular orbital.

PET: possitron emission tomography.

Ph: Phenyl.

PIDA: phenyliodine diacetate.

PIFA: phenyliodine trifluorodiacetate.

ppy: phenylpiridine.

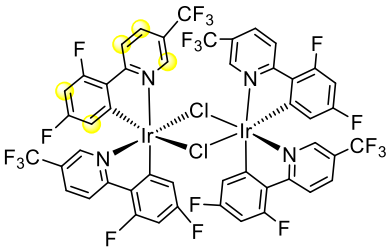
SET: single-electron-transfer.

TEMPO: 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl.

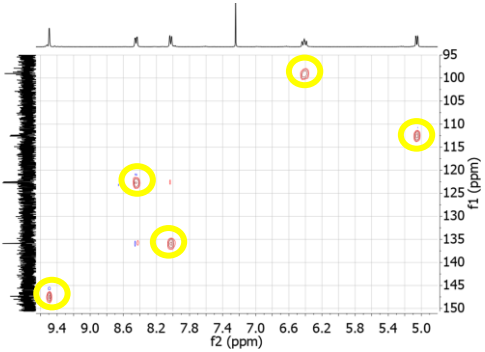
TLC: thin layer chromatography

APPENDICES

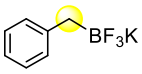
APPENDIX 1: HSQC NMR SPECTRA



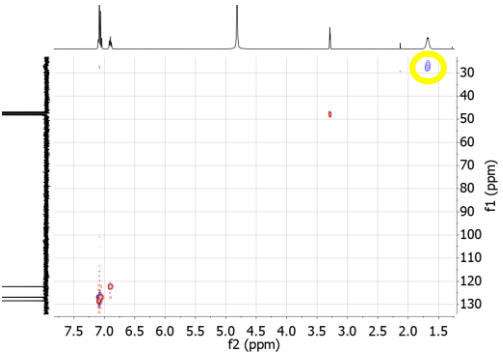
11



HSQC spectrum from **(11)**.



14



HSQC spectrum form **(14)**.