Rafael Alves Rippel

Licenciado em Bioquímica

Exploring the Benziodoxole Chemistry: New Routes for Arylation and Amidation Reactions

Dissertação para obtenção do Grau de Mestre em Química Bioorgânica

Orientador: Doutora Maria Manuel B. Marques, Investigadora Auxiliar, FCT-UNL

FACULDADE DE CIÊNCIAS E TECNOLOGIA
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Agradecimentos

Em primeiro lugar, gostaria de agradecer à Doutora Maria Manuel Marques. É uma satisfação enorme poder trabalhar com alguém que é tão apaixonada por aquilo que faz e que consegue transmitir essa mesma paixão e entusiasmo aos que estão ao seu redor. Gostava também de agradecer todo apoio que me foi prestado durante a mudança do tema da tese e de toda a dedicação e entusiasmo que à Professora mostrou durante esse processo. Este projeto, com certeza, teve momentos "menos bons" nos quais a Professora tinha sempre uma palavra de motivação e uma alternativa para seguirmos em frente e por isso, mais uma vez, obrigado. Obrigado por tudo!

À Catia Santos por me receber de braços abertos durante os meses em que estive inserido, naquele que foi, o meu tema inicial de tese, pelos conhecimentos prestados e pela paciência e por vezes falta dela.

A todos os meus colegas de grupo: Fausto Queda, Carlos Rafael, João Macara, Sofia Santos, Ana Mortinho, Diogo Poeira e Marina Pires, um grande obrigado pelos momentos que passamos ao longo destes meses.

À Sara Purificação que afinal descobriu que eu não sou antipático, mas que na realidade sou um fixe. Obrigado pelos bons momentos "Sara maléfica". Espero que para onde quer que vás, possas continuar a ser fit e concretizar os teus objetivos. Não te esqueças do gangue das papas!

A todas as pessoas dos laboratórios 202 e 205. Só quem por lá passou sabe o ambiente fantástico que, por lá, se vive todos os dias. Obrigado a todos pelos concelhos e conhecimentos prestados, pelos momentos menos didáticos, por vezes necessários, pelas gargalhadas e por toda a simpatia. Obrigado malta!

À rede de Ressonância Magnética Nuclear do Departamento de Química FCT-UNL, apoiado pela Fundação para a Ciência e a Tecnologia (RECI/BBB-BQB/0230/2012), em particular à Dra. Ana Teresa Lopes pela rapidez com que realizava o processamento dos espectros e pela simpatia.

Aos meus amigos, que iniciaram esta jornada comigo: João Ramos, Diogo Gonçalves, Luis Silva e Bruno Guerreiro, um enorme obrigado pelas palavras de encorajamento, pelas conversas parvas e por partilharem, por vezes, o stress associado à escrita da tese. Um enorme obrigado à team rijo!

Gostaria de agradecer à minha namorada, Joana Magalhães, que foi o meu o pilar durante os bons e maus momentos pelos quais passei para aqui chegar. Obrigado por estares sempre ao meu lado a apoiar-me e a incentivar-me.

À minha mãe, Sandra Garcia Alves, que passou por muito para me proporcionar tudo o que tenho e que é, sem dúvida alguma, a responsável por eu estar aqui hoje. Um enorme obrigado, mãe!

Resumo

O aparecimento de novas reações e novos reagentes permitem que estruturas conhecidas possam ser sintetizadas com maior eficiência. Neste aspeto, compostos hipervalentes de iodo permitem o desenvolvimento de sintões eletrofílicos através da inversão de polaridade e constituem uma excelente alternativa para emular metais de transição tóxicos e dispendiosos.

A comunidade científica apercebeu-se do potencial destes compostos após a descoberta do reagente de Dess-Martin (DMP), em 1983. Estruturalmente, o DMP pode ser classificado como um derivado de benziodoxole, que são caracterizados pela presença de iodo num anel de cinco membros. A estrutura cíclica dos derivados de benziodoxole confere uma maior estabilidade face aos reagentes hipervalentes acíclicos.

Tendo em consideração o potencial destes reagentes na transferência de grupos funcionais, foi proposto explorar o 1-fenilbenziodoxole na arilação de vários nucleófilos.

Com os núcleos de indole e 1-metilindole, sob condições catalisadas por paládio, obtiveram-se misturas complexas. Nos ensaios seguintes com *p*-toluidina, catalisados por cobre, isolou-se a 4-metil-N-fenilamina com 5% de rendimento, enquanto que nos ensaios com *t*-BuONa e na ausência de catalisadores metálicos o mesmo produto foi obtido com 44 % de rendimento, condições nas quais foi, também, possível isolar a difenilamina com 22% de rendimento. As experiências com benzenosulfinato de sódio revelaram que, na presença de paládio, ocorre decomposição do 1-fenilbenziodoxole, não sendo possível isolar o produto pretendido.

Em paralelo com o trabalho desenvolvido com 1-fenilbenziodoxole, foi desenvolvida uma nova metodologia para a preparação de 1,2-diarilazaindoles através de uma reação de etapa única.

Numa segunda aproximação o potencial da ligação hipervalente para diferentes grupos, nomeadamente aminas, foi explorado. Um novo derivado de benziodoxole, com uma amina ligada ao átomo de iodo foi sintetizado e caracterizado, correspondendo à primeira vez que um benziodoxole contendo um grupo amina é observado.

Para averiguar a sua utilidade sintética e perceber a reatividade, deste novo reagente, realizaram-se estudos preliminares, que visaram a preparação de sulfonamidas e amidas.

Na reação com sais de sulfinato, observaram-se traços do produto, à temperatura ambiente, na ausência de catalisadores metálicos. Em relação à síntese de amidas, a partir de aldeídos, foi possível obter a N-benzil-4-metoxibenzamida com um rendimento de 5%, tendo sido proposto um mecanismo radicalar para a reação.

Palavras-chave: amidação, arilação, derivados de benziodoxole, iodo hipervalente

Abstract

New reactions and new reagents allow known structures to be made more efficiently. In this aspect, hypervalent iodine compounds allowed the development of electrophilic synthons by the umpolung of normally nucleophilic species and have emerged as a great alternative to emulate more toxic and expensive late transition metals.

The scientific community became more aware of the potential of those compounds after the discovery of the Dess-Martin periodianane (DMP), in 1983. Structurally, the DMP reagent can be classified as a benziodoxole derivative, which are characterized by the presence of the iodine inside a five-membered ring. The cyclic structure of benziodoxole-derived reagents allows them to have an enhanced stability when compared to their acyclic counterpart's.

Considering the potential of these reagents in the transfer of functional groups, our first approach was to explore the potential of 1-phenylbenziodoxolone in the arylation of several nucleophiles.

With the indole and 1-methyl indole nucleus we observe that, under Pd-catalyzed conditions, there may have been formation of one or more of the desired products, due the complex mixture observed in the TLC plate. In the trials with *p*-toluidine, under Cu-catalyzed conditions, 4-methyl-N-phenylaniline was obtained with 5% yield and under meta-free conditions with *t*-BuONa, the product was attained with 44 % yield. Regarding the trials with aniline, diphenylamine was isolate with 22% yield under the same conditions.

The trials with sodium benzenesulfinate show that, under Pd-catalyzed conditions, 1-phenylbenzidoxole decomposes and no product could be isolate.

In parallel to the work carried out with 1-phenylbenziodoxolone, a new methodology for the constructions of 1,2-disubstituted azaindoles via one-pot reaction was developed.

In our second approach, the potential of the hypervalent bond for different compounds, namely amines, was explored. A novel benziodoxole derivative was synthetized, being the first time that a benziodoxole carrying an amine group was observed.

To showcase the synthetic utility and understand the reactivity, of this novel benziodoxole derivative, we carried out some preliminary studies envisaging the preparation of sulfonamides and amides.

In the first approach to construct sulfonamides, traces of the desired product, at room temperature, under metal-free catalyzed conditions were observed. Regarding the synthesis of amides from aldehydes, N-benzyl-4-methoxyamide was attained with 5% yield and a radicalar mechanism was proposed.

Key words: amide synthesis, arylation, benzidoxole derivatives, hypervalent iodine

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Abbreviations and nomenclature

ABX	Azidobenziodoxolone
Ac	Acetyl
ACN	Acetonitrile
ACS	American Chemical Society
Ar	Aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
CBX	Cyanobenziodoxolone
CMD	Concerted Methalation Deprotonation
CR	Coupling Reagent
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide)
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	*N*,*N* -Diisopropylethylamine
DMEDA	*N,N′*-Dimethylethylenediamine
DMF	Dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide
equiv.	Equivalents
EBX	Ethynylbenziodoxolone
Et	Ethyl
EWG	Electron withdrawing group
HMDS	bis(trimethylsilyl)amide
IBX	2-iodoxybenzoic acid
iPr	Isopropyl
IR	Infrared spectroscopy
m	*meta*
Me	Methyl
mp	Melting point
n-Bu	*n-Butyl*
NMR	Nuclear Magnetic Resonance spectroscopy
o	ortho
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	para
Ph	Phenyl
PTLC	Preparative thin-layer chromatography

Rf	Retardation factor
rt	Room temperature
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TES	Triethylsilane
Tf	Triflyl
TGF	Transforming growth factor
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
VBX	Vinylbenziodoxolone

IR chart

w	Weak
m	Medium
s	Strong
br	Broad
vmax	Wavelenght of absorption peaks

NMR chart

s	Singlet
d	Doublet
t	Triplet
m	Multiplet
δ	Chemical shift

I.Introduction

I.1 - Hypervalent Iodine

The development of new chemical transformations and greener approaches for the current methodologies is one of the main goals of modern organic chemistry. New reactions and new reagents allow known structures to be made more efficiently. In this aspect compounds of iodine in higher oxidation states, which are known as “hypervalent iodine compounds” allowed the development of electrophilic synthons by the umpolung of normally nucleophilic species and have emerged as a great alternative to emulate more toxic and expensive late transition metals[1-3]. The ability, of these reagents, to emulate transition metal derivatives arise from the linear three-center-four-electron (3c-4e) bond (weaker than a covalent bond and highly polarized). This 3c-4e bond is commonly named as a “hypervalent bond” and explain the reactivity pattern of those compounds[1-4].

The scientific community became more aware of the potential of those compounds after the discovery of the Dess-Martin periodianane (DMP), in 1983, as a mild and non-toxic oxidant[2, 5]. The known hypervalent reagents can be represented according to their structures in the following general classes (**Figure I-1**): Trivalent iodine, named as λ^3-iodanes and pentavalent iodine, known as λ^5-iodanes[3].

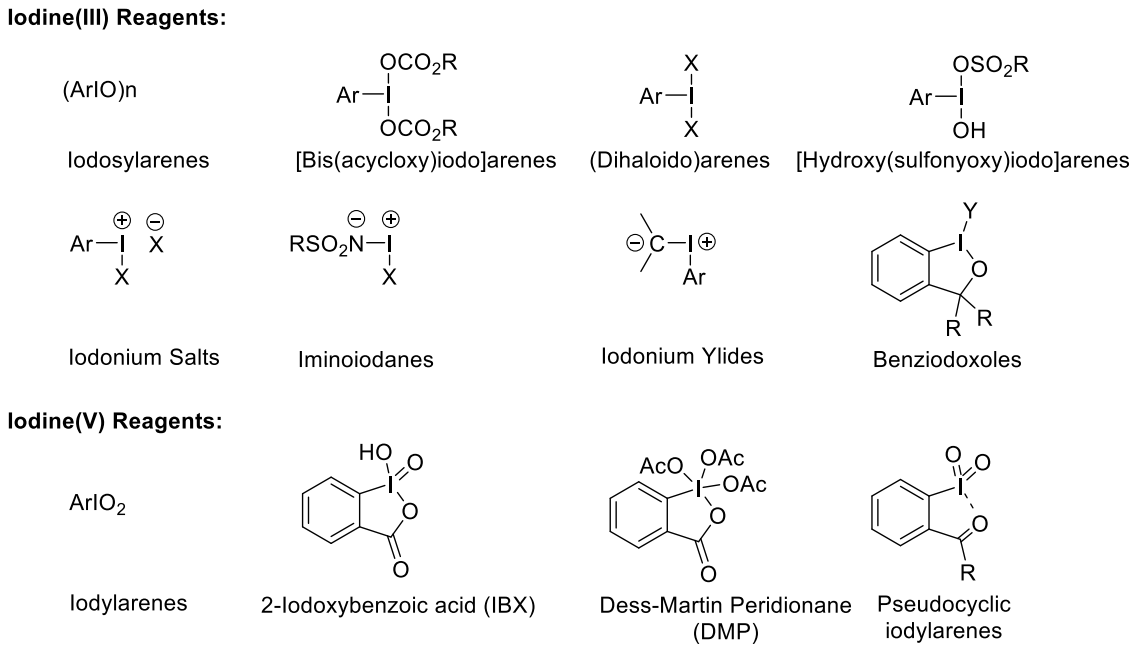


***Figure I-1**: Main classes of hypervalent iodine reagents[3].*

Structurally the DMP reagent can be classified as a benziodoxole derivative, which is characterized by the presence of the iodine inside a five-membered ring[5]. The cyclic structure of benziodoxole-derived reagents allows them to have an enhanced stability when compared to their acyclic counterpart’s due to a higher overlap of the nonbonding electrons on the iodine atom with the π-orbitals of the benzene[2, 3, 5]. For instance, the ability of the benziodoxole ring to

stabilize the functional groups, hypervalently bonded to the iodine, has allowed the synthesis of reagents, such as, trifluoromethylbenziodoxolone (Togni`s reagent) and azidobenziodoxolone (ABX) which are too unstable to be isolated as acyclic structures[6, 7](**Figure I-2**).

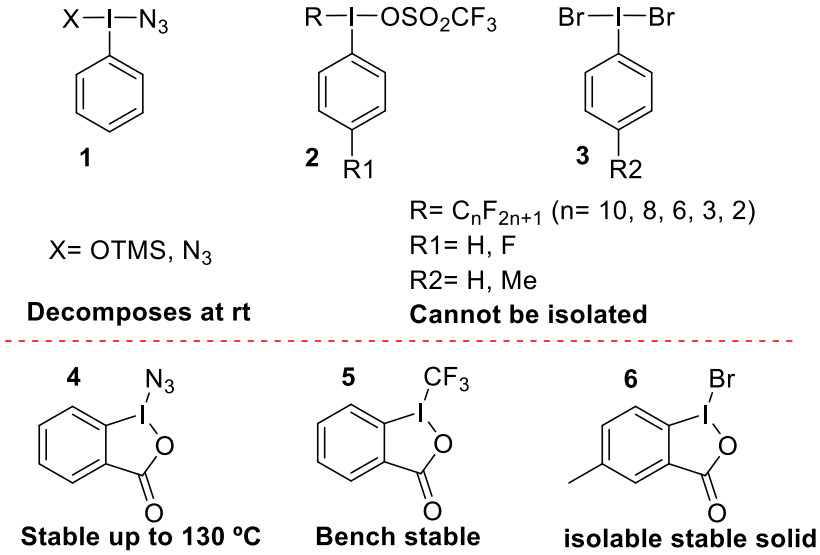
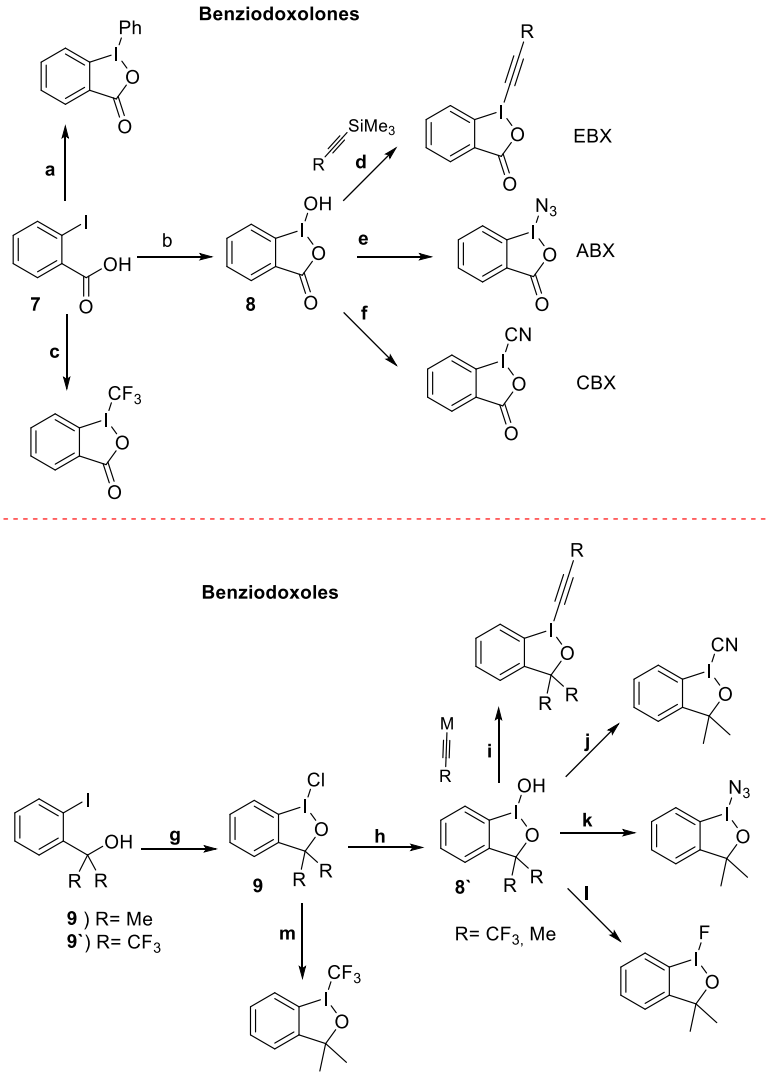


***Figure I-2**: Comparison of the stability between acyclic derivatives (**1**, **2** and **3**) and benziodoxole derivatives (**4**, **5** and **6**).*

This superior stability of these type of hypervalent iodine compounds could be an advantage in the case of highly unstable structures, where decomposition of the reagent is an issue.

Concerning the synthesis of benxiodoxole derivatives, they can be readily prepared from the commercially available 2-iodo-benzoic acid (**7**), normally by one-pot procedures that proceeds through the formation of hydroxy **8** and acetoxy **8`** derivatives, that act as key intermediates for the synthesis of most of the reagents (**Scheme I-1**)[1, 6].



***Scheme I-1**: Synthesis of benziodoxole derivatives: a) oxone, H_2SO_4, 5 °C then PhH, CH_2Cl_2, 5 °C to rt, then aq. $NaHCO_3$, 88%; b) NaIO4, H20, CH_3CO_2H, reflux, 81%; c) TCICA, ACN, reflux, then KOAc, 75 °C, then $TMSCF_3$, rt, 72%; d) TMSOTf, ACN, then pyridine or $NaHCO_3$ 30-85%; e) $TMSN_3$, ACN, 94%; f) TMSCN, ACN, 94%; g) trichlorocyanuric acid, ACN, 89%; h) KOH, H_2O/CH_2Cl_2, 89%; i1) R= Me, M= Li, TMSOTf, YHF, -78 °C to rt, 86%; i2) R= CF_3, M= $SiMe_3$, TMSOTf, ACN, then pyridine, 50-95%; j) TMSCN, CH_3CN, 74%; K) $TMSN_3$, CH_3CN, 87%; l) $Et_3N.3HF$, CH_2Cl_2, 94%; m) KF, rt, then $TMSCF_3$, -10 °C to rt, 85-91%.*

The alcohol **9** be prepared by the addition of Grignard to methyl 2-iodobenzoate and (**9`**) from phenylhexafluoro-2-propanol by iodination[1] (**Scheme I-2**).

I.1.1 - Hypervalent Iodine Compounds for Functional Group Transfer Reactions

The use of benziodoxole derivatives reagents has been focused for many years in the oxidation of primary and secondary alcohols to ketones while the formation of new C-C and C-X bonds was made exclusively by non-cyclic iodonium reagents with remarkable success[8, 9]. However, the common hypervalent iodine reagents such as ylides ($PhICX_2$) and 2-iodoxybenzoic acid (IBX) have some drawbacks associated with their low thermal stability and low reactivity, due the presence of extensive networks of I---O or I---N intermolecular secondary bonds, forming a

polymeric structure[4, 10] that limits the utilization of these compounds only to heterogeneous conditions [3, 11].

Only in 2006 Togni and co-workers reported the first group transfer reaction using the benziodoxole derivative (**5** and **5`**) by transferring a $CF_3$ group[6]. Soon Togni was followed by Waser and co-workers that in 2009 presented the ethynylbenziodoxole derivatives (EBX– **11** and **11`**) for acetylene transfer reactions[12]. After the promising results obtained by Waser and Togni a wide variety of benziodoxole derivatives emerged for different group transfer reactions (**Figure I-3**)[1].

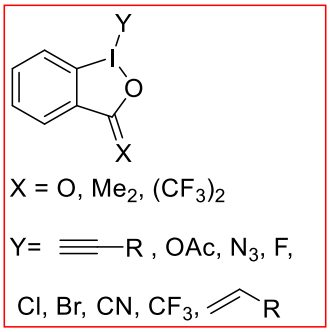
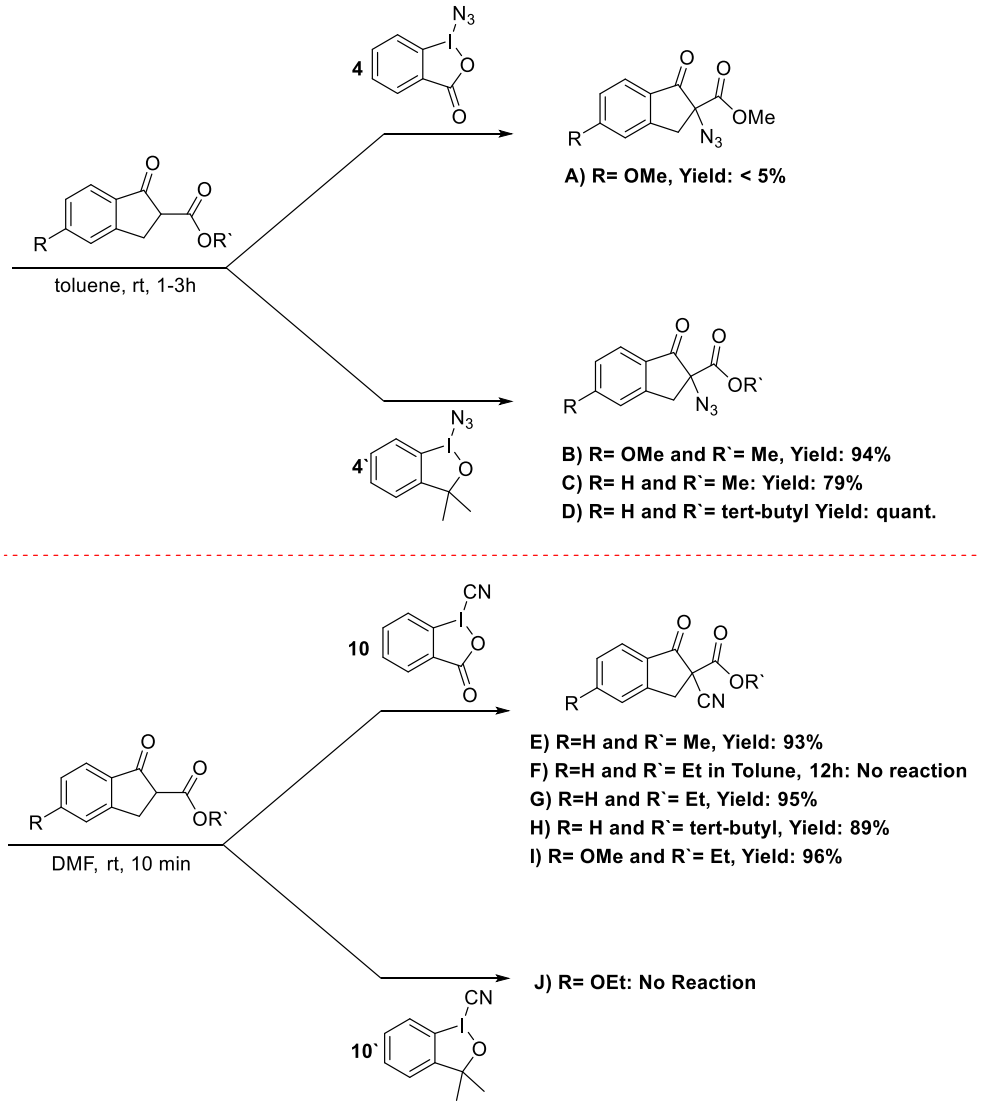


***Figure I-3**: Benziodoxole derivatives, for functional group transfer, reported until the date[1, 3, 7].*

I.1.2 - The Influence of the Substituents in the Benziodoxole Ring for the Reactivity of Benziodoxole Derivatives

It is still unclear what is the influence of the substituents in the benziodoxole ring for the reactivity of benziodoxole derivatives, but is certain that this is a key factor for some of the group transfer reactions reported (**Scheme I-2**).



***Scheme I-2**: Electrophilic azidation and cyanation with benziodoxole derivatives*[13, 14]

As can be observed in **Scheme I-2**, for the azidobenziodoxolone derivatives (**4** and **4`**), the yield obtained in the presence of a carbonyl group in **4** stands in contrast with the result achieved with **4`**. Regarding the cyanobenziodoxolone (**10** and **10`**), the outcome is the opposite from the results attained with ABX. While the presence of the carbonyl seems to be fundamental for the cyanation reaction, it completely fails for the azide transfer, where the reaction occurs when the reagent possesses methyl groups instead of the carbonyl group, blocking this position to possible nucleophilic attacks.

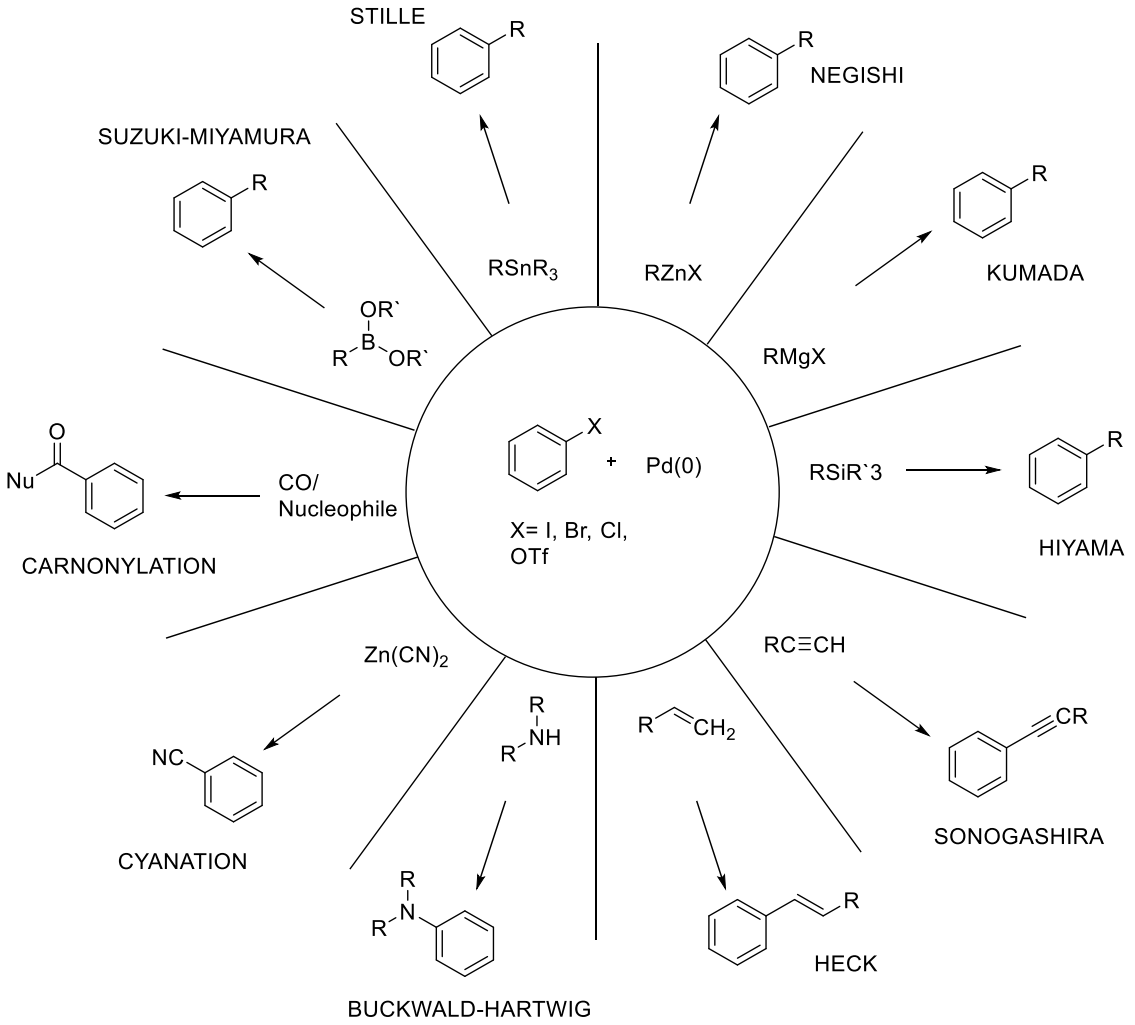
Curiously, comparing the results **B** and **C** for the reagent **4`**, it can be conceived that the effect of the methoxy group in the benzene ring is much more extensive than in **G** and **I**, where the effect of the methoxy group seems trivial for the result of the reaction. Another interesting point, is that CBX-**10** is much more tolerable with different esters (**E**, **G**, **H**), while the benziodoxole derivative **4`** suggests a higher reactivity toward more hindered esters such as **D**.

Although, previous reports concerning the ABX[15, 16] point out a radical pathway for the reaction mechanism, in the case of the azidation of β-keto esters there is no evidence for a similar

mechanism, which might indicate that the mechanism is substrate-dependent. Other examples in the literature, concerning other benziodoxole derivatives such as Togni`s reagent[17], demonstrate that the substitution pattern of the benziodoxole ring is crucial for the reactivity of these compounds. Until recently there were few studies, regarding the reactivity of benziodoxole derivatives[18] and they are limited to Togni`s reagent and EBX, standing in contrast with the number of applications reported for these reagents. It was only in 2017[19] that Waser *et al.* studied, for the first time, the mechanism of CBX in the cyanation of carboxylic acids compared to alkynylation, where the authors proposed that the cyanation reaction proceeds via a radical mechanism.

I.2 - Palladium-Catalyzed C–C and C–Heteroatom Bond Formation

Currently, the palladium catalysis is used worldwide in industry and in academic research as a powerful tool for the formation of C-C and C-Heteroatom bond and several coupling reactions have been developed, allowing transformations that previously were no possible, required harsh methods or resulted in low yields (**Scheme I-3**)[20, 21].



***Scheme I-3**: Palladium-catalyzed coupling reactions.*

Despite the versatility and efficiency of palladium catalysis, the future for a more sustainable chemical synthesis lies in the use of first row, earth abundant transition metals, as a more inexpensive and more environmentally friendly option[22, 23]. When looking at the reported chemical transformations with benziodoxole derivatives it can be observed that they can be employed under both metal catalyzed (Cu, Fe, Zn and Co) and metal-free conditions[1, 3, 24].Therefore, it is plausible to assume that benziodoxole derivatives may be, in a near future, a potential less expensive and greener alternative for C-C and C-Heteroatom bonding forming reactions.

I.2.1 - Synthesis and Functionalization of Heterocycles Using Benziodoxoles Reagents and Metal–Catalyzed Reactions

Since 2016, our group has been developing new strategies based on palladium catalyzed coupling reactions starting from commercially available amino-halogenated pyridines for the synthesis of functionalized azaindoles[25] and recently we report an one-pot synthesis for 1,2-disubstituted azaindoles[26].

Azaindoles are bioisosters of indoles and the replacement of a benzene ring in the indole by a pyridine ring in the azaindole, provide unique proprieties for the azaindole nucleus (**Figure I-4**)[27, 28]. Regarding the azaindole synthesis, they are normally prepared from aminopyridines followed by building up of the pyrrole ring[27].

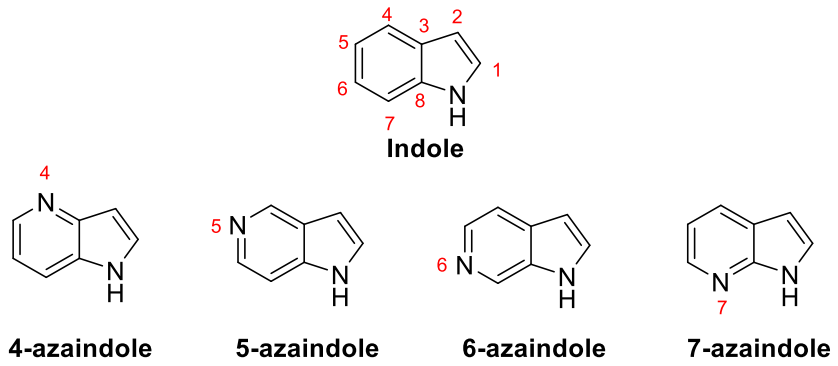
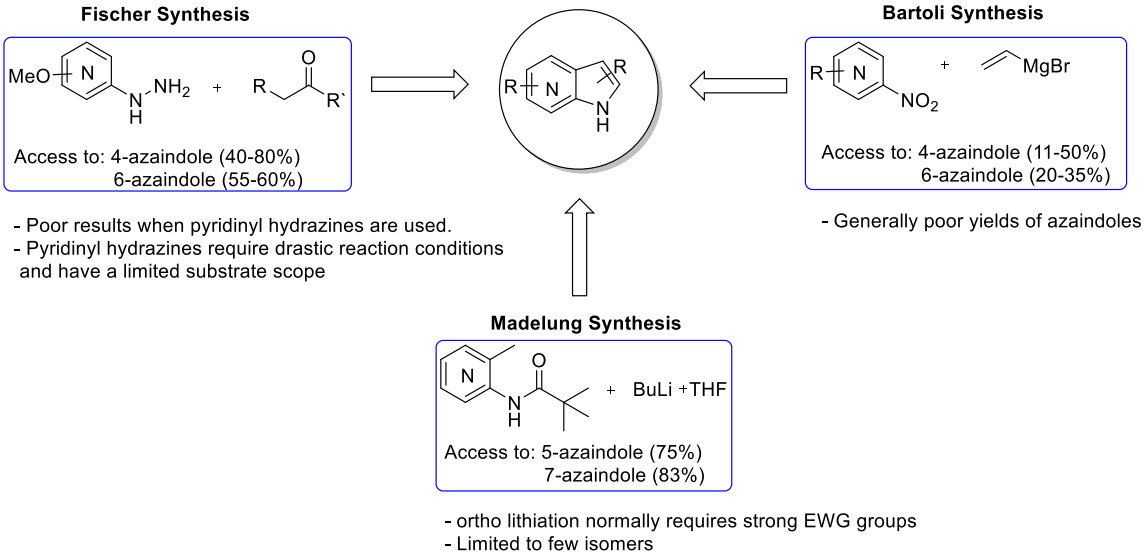


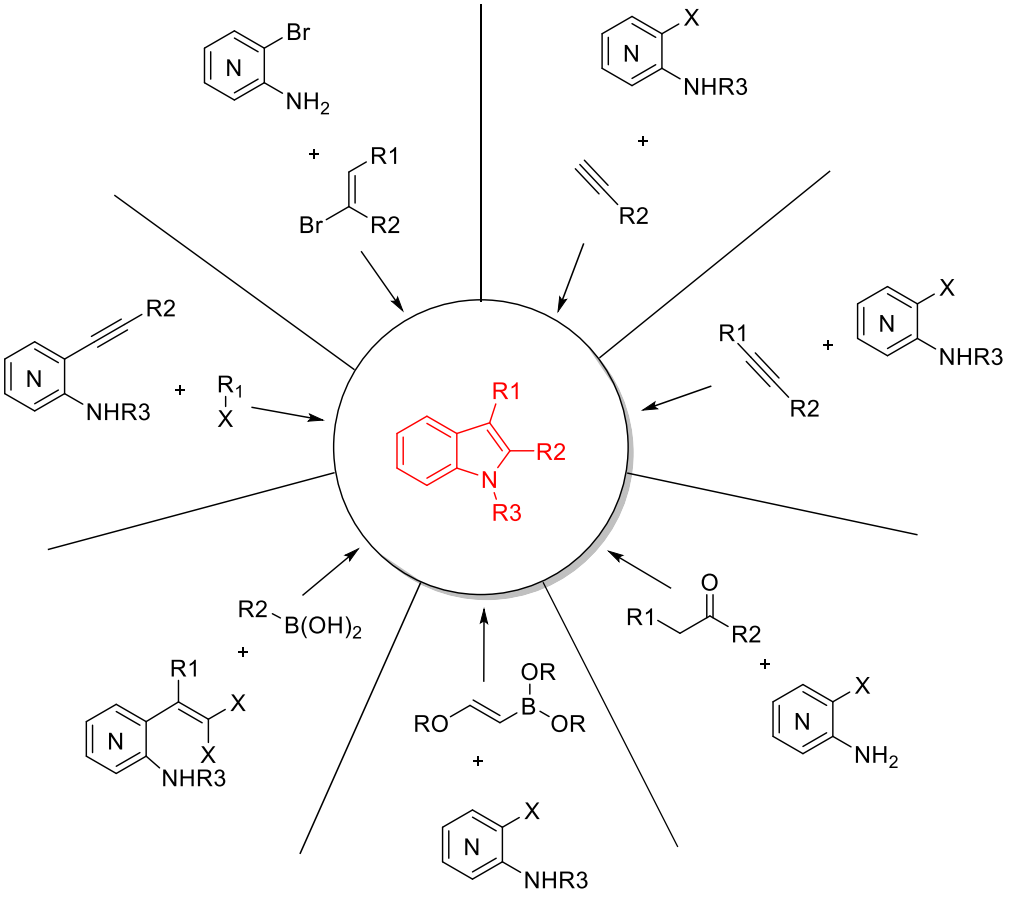
***Figure I-4**: Numbering of the indole nucleus and structure of 4-, 5-, 6-, 7-azaindoles*

Azaindoles containing compounds have been show to possess several biological activities, such as kinase inhibitors[28-30], treatment of influenza[31, 32], HIV-1 reverse transcriptase inhibitors[33], among many others. In addition to being an important therapeutic scaffold, our interest in the development of new methods for the synthesis and functionalization of azaindoles relies on the fact that the methods for the synthesis of indoles are normally not efficient or simply do not work when applied in the synthesis of azaindoles. Indeed, procedures such as the Bartoli synthesis, Fischer indolization, Madelung synthesis, among others are not efficient methods to prepare azaindoles due to the electron-deficient nature of pyridine ring that alters the electronic properties of the conjugate system[27] (**Scheme I-4**)



***Scheme I-4**: Classical methods for the synthesis of indoles applied to the preparation azaindoles.[34-36]*

Given the limitations of the classical methods for the synthesis of indoles in the synthesis of azaindoles, the use of transition metal catalyzed cross-coupling reactions have emerged as the most efficient approach to obtain azaindoles from pyridine derivatives (**Scheme I-5**)[25, 27].



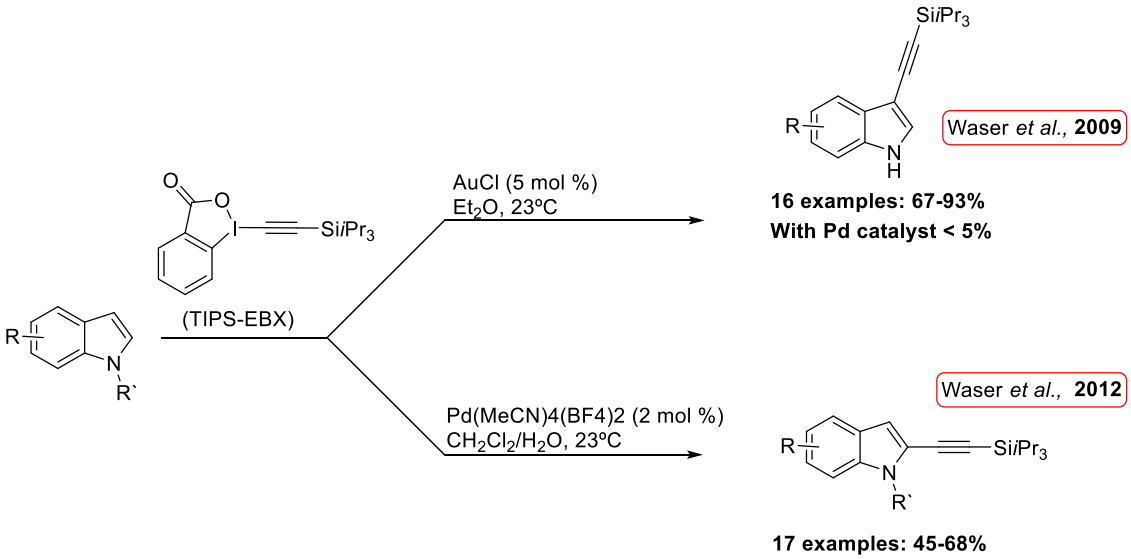
***Scheme I-5**: Synthetic routes for the preparation of azaindoles from aminopyridines[25].*

However, these methods were shown to have some drawbacks such as not being fully regioselective, having a limited substrate scope or requiring the preparation of a specific molecular template. Additionally, most methods are restricted to the preparation of only one or two azaindoles isomers[37, 38].

The applicability of benziodoxole derivatives in palladium catalyzed reaction is limited, to best of our knowledge, to alkynylation reactions with EBX[12, 39]and alkoxylation reactions with cetoxy- and methoxybenziodoxolones[40].

In 2009[12], Waser and co-workers reported the first gold-catalyzed direct alkynylation of indole by using a benziodoxole derivative (**Scheme I-6**). During the optimization of the reaction conditions, the authors reported that no product could be isolated when palladium and copper catalysts were examined. Later, in 2009, Waser *et al.* reported an Pd-catalyzed intramolecular oxyalkynylation [41] of alkenes and in 2011 demonstrated the efficiency of EBX in acetylene transfer with Pd catalyst in aminoalkynylation reactions[42]. Driven by the results obtained in the

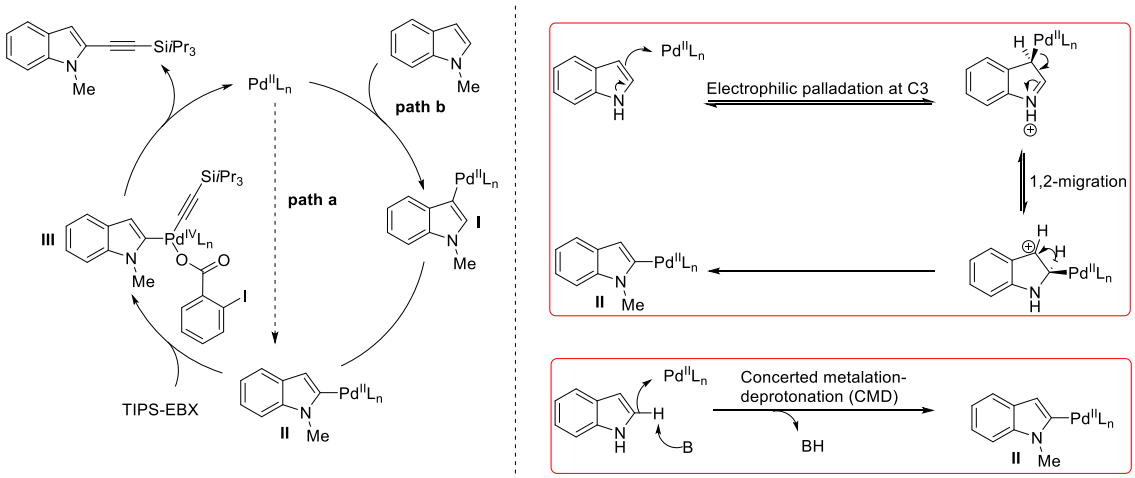
previous approaches, the same group described, in 2013, the first Pd-catalyzed C-2 selective alkynylation of N-substituted indoles[39].



***Scheme I-6**: Palladium and gold-catalyzed conditions for the alkynylation of indoles.*

In the Au-catalyzed alkynylation of indoles the author reported that the reaction could be carried out in the absence of inert conditions and dry solvents. Notably, only a slight excess of TIPS-EBX was required to obtain good yields. The reagent also exhibits good tolerance with both electron-donating (R=OMe (80%); R=OH (76%)) and electron-withdrawing groups (R= CN (80%); R= CO_2H (67%); R=NO_2 (85%); R= Br (93%); R=I (91%)). The results attained for R=I and R= Br represented a breakthrough in palladium catalyzed cross-coupling reactions, since that at room temperature it would expected that an oxidative addition step might occur in the C-halogen bond of the benzene ring in the indole, thus making this approach orthogonal to classical palladium reactions and differing from the previously[43] palladium(0) catalyzed methods for direct alkynylation.

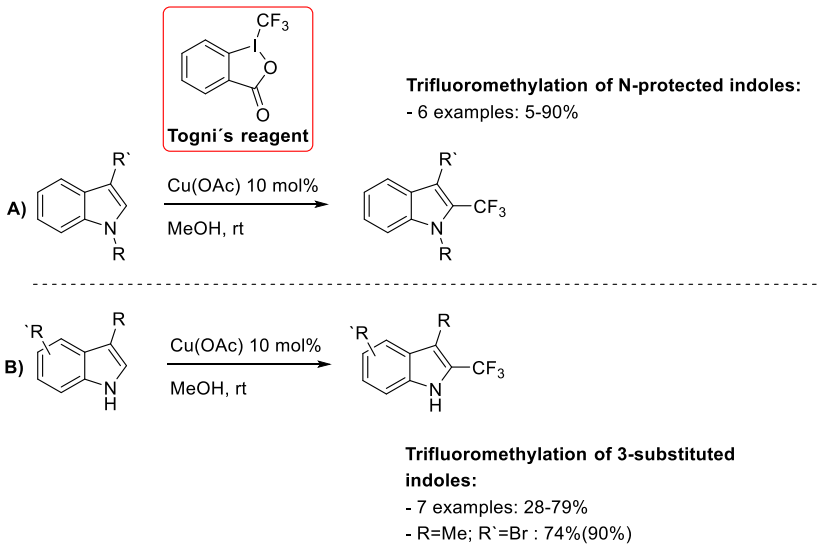
Concerning the palladium catalyzed alkynylation, in 2012 Waser and co-workers reported the first Pd-catalyzed C2-selective alkynylation of indoles using TIPS-EBX. The reaction proceeds at room temperature under air and tolerate several functional groups. Interestingly, a similar result to that obtained in the Au-catalyzed conditions was observed and the best yields were obtained in the presence of R=I (68%) and R=Br (72%). The authors reported that these results might indicate that the reaction did not proceed via a Pd(0) intermediate, since no oxidative addition was observed in the carbon-halogen bond, which is a significant advantage over previously reported methods containing Pd(0) catalysis as cross-coupling reactions can be used for further modifications. Based on these results the authors made a mechanistic proposal where a Pd(II)/Pd(IV) cycle could be involved (**Scheme I-7**).



***Scheme I-7**: Proposed mechanism for the alkynylation reaction.*

That reaction could follow two paths, where in path **a** the intermediate **II** can be formed by direct concerted metalation-deprotonation (CMD) or via electrophilic palladation at the C3 position to form **I** followed by palladium 1,2-migration.

As far as the indole nucleus is concerned, Hamashima and co-workers reported, in 2010, the use of Togni`s regent for the direct C-2 trifluoromethylation of indoles derivatives catalyzed by copper(I), proving the enormous potential of these reagents in direct C-H functionalization[44](**Scheme I-8**). It is worth to mention, that despite the narrow scope of the reaction, the only example with a halogen substituent (R=Me; R`= Br) had the highest yield (condition **B**). This might indicate a reaction pattern in the direct C-H functionalization with benziodoxole derivatives.

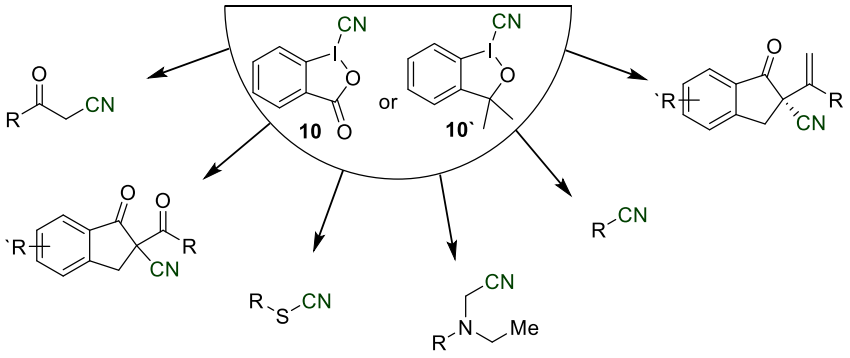


***Scheme I-8**: Trifluoromethylation of indole derivatives catalyzed by copper acetate. The numbers in parentheses are yields based on recovered starting material.*

Undoubtedly, benziodoxole derivatives can grow into an elegant and appealing reagent for C-H functionalization, but despite the encouraging results presented by Waser the potential of other benziodoxole derivatives in Pd-catalyzed reactions remains unexplored.

I.3 - Benziodoxole-derivates for C–C and C–Heteroatom Bond formation

The utilization of benziodoxole derivates for C-C bond formation contrast with the remarkable results achieved with non-cyclic iodonium salts[8]. Regarding the cyanobenziodoxolone (CBX-**10** and **10`**) there are very few examples of CN-transfer and only in 2014, almost twenty years after its discovery by Zhdankin *et al.,* its potential, previously neglected, was explored (**Figure I-5**).



FigureI-5: *C-C and C-X bond forming reactions with cyanobenziodoxolone[19, 45-47]*

Contrary to the reagents for CN-transfer, the use of CF_3-transfer reactions and alkynylation have been widely explored and a variety of examples have already been reported using the transfer agents containing both the cyclic hypervalent iodine and CF_3 or an alkynyl moiety (**Figure I-6**).

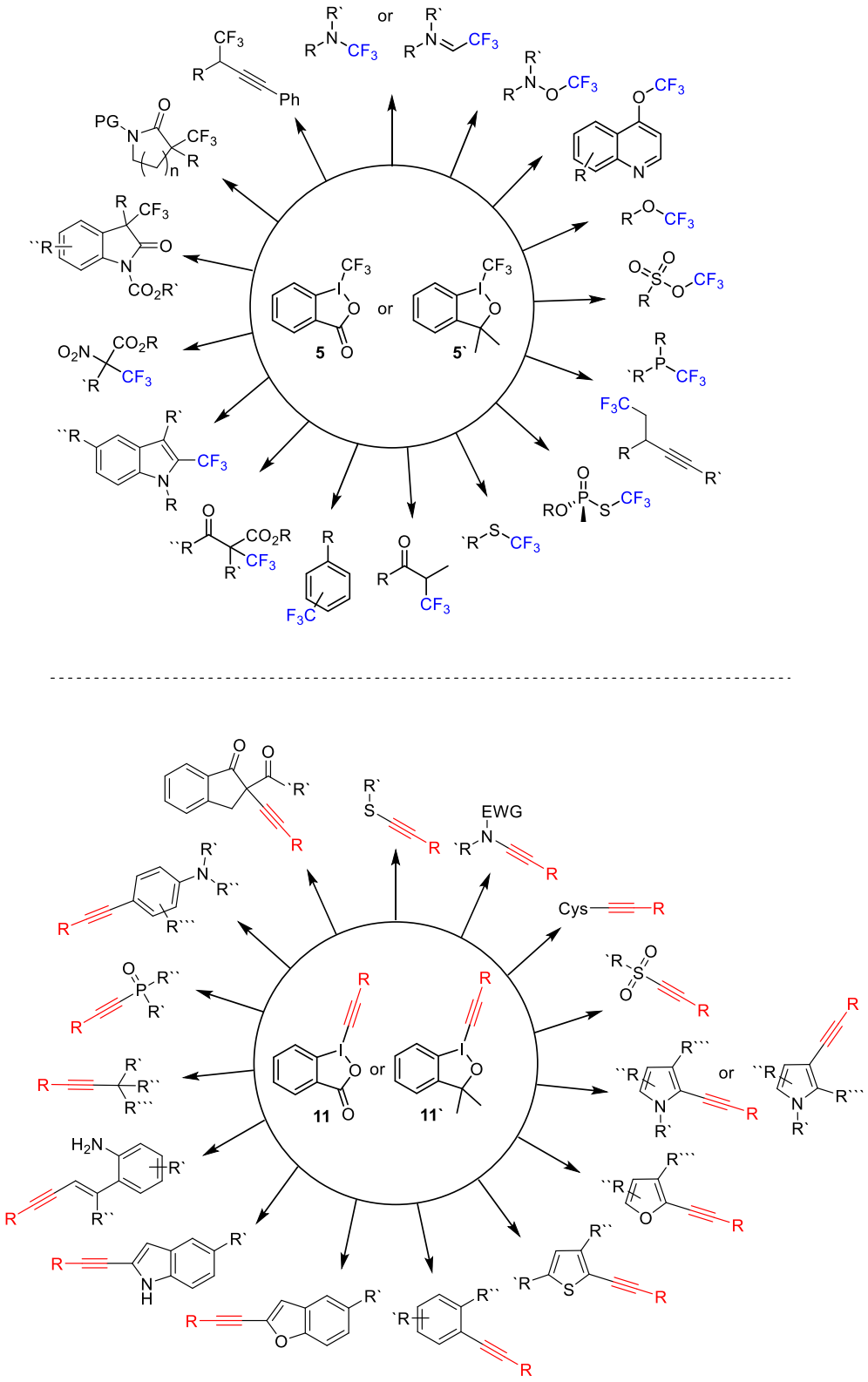
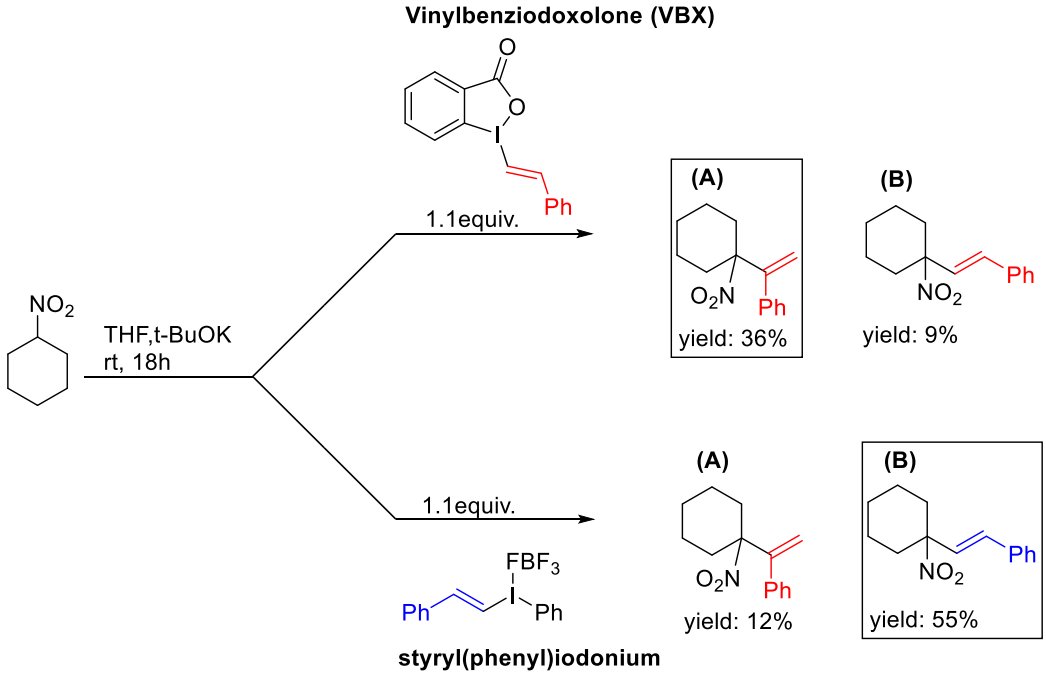


***Figure I-6**: C-C and C-X bond formation reactions with trifluoromethyl benziodoxolone (**5** and **5`**) and ethynyl benziodoxolone (**11** and **11`**)[1-3, 17, 48-50].*

Until very recently, except for Togni`s reagent, the available benziodoxole derivatives, for functional group transfer were limited to the transfer of sp carbons. It was just in 2016 that Olofsson and co-workers developed a one-pot synthesis and investigated the potential of

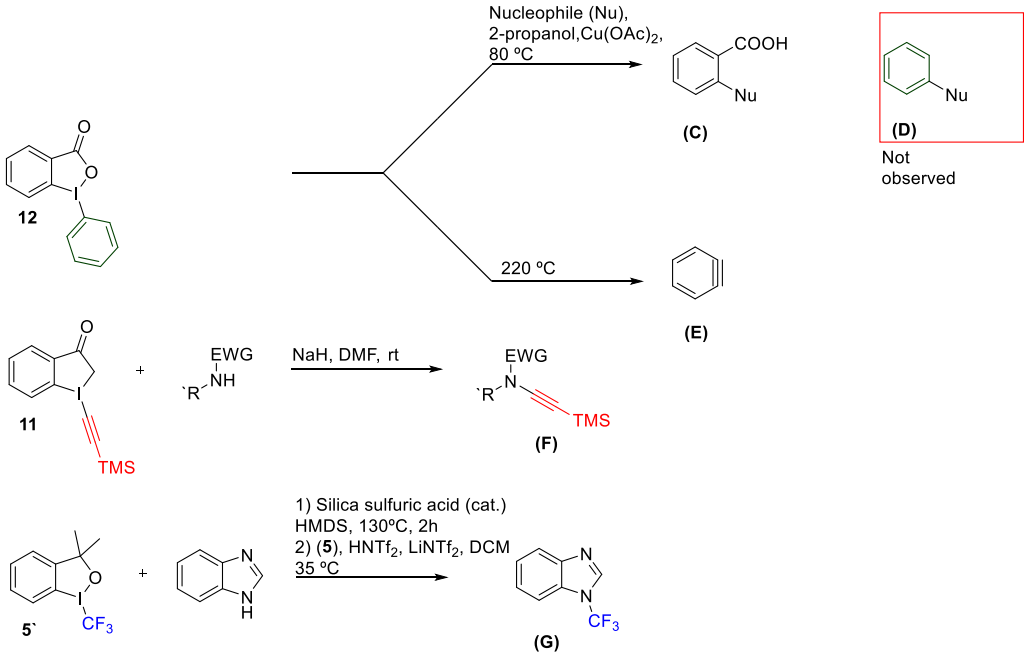
vinylbenziodoxolone (VBX) as a reagent. Being the first time that a sp^2 carbon was transferred by a benziodoxole derivative[7]. Curiously, when the reactivity of VBX with nitrocyclohexane was compared to the known reactivity of acyclic vinyliodonium salts, it was found that the regioselectivity of the reaction was opposite to the regioselectivity observed with acyclic vinyliodonium salts (**Scheme I-9**). The distribution of products between VBX and acyclic vinyliodonium salts could be related to the existence of different reaction pathways, which are still being investigated[7].



***Scheme I-9**: Difference in reactivity of VBX and styryl(phenyl)iodonium[7].*

Zhdankin and co-workers reported, in 2009, an optimized synthesis for the one-pot preparation of various 1-arylbenziodoxolones[51], that could be valuable for transfer of sp^2 carbons. Although the reagent can be obtained in a simple and elegant manner, the potential of these reagents for electrophilic arylation remains unexplored.

The 1-phenylbenziodoxolone **12** was primarily used as a precursor to benzyne (**E**) and in the presence of nucleophiles, such as amines, reacted to form the correspondent anthranilic acid derivative under the presence of a copper catalyst (Cu(II))[51-54]. It becomes clear that the reactivity, of the most stable reagent from the benziodoxole class, differs greatly from the reactivity of EBX (**11**) and Togni`s reagent (**5`**), where the transfer occurs on the group hypervalently bonded to the iodine leading to the formation of (**F**) and (**G**), in mild conditions, whereas in the case of 1-phenylbenziodoxolone the reaction occurs exclusively in the benziodoxolone ring, resulting in the formation of *o*-substituted benzoic acids[1, 49] (**Scheme I-10**)

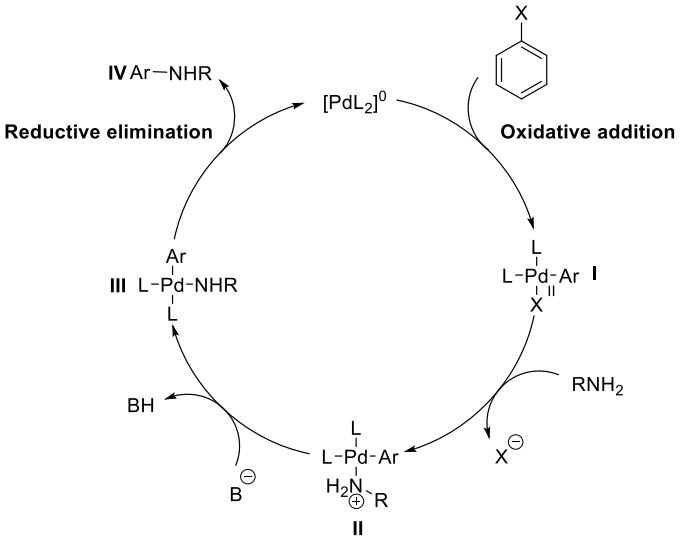


***Scheme I-10**: Reactivity of 1-phenylbenziodoxolone (**12**), EBX (**11**) and togni`s reagent (**5**`) in the presence of nitrogen nucleophiles[1, 49, 54].*

As we can observe, in **Scheme I-10**, each benziodoxole derivative has its own reactivity and there are few mechanistic studies in this matter[18].

I.4 - Palladium-Catalyzed C–N Coupling: Buchwald-Hartwig Amination

Currently, the reaction of choice for the formation of C-N bonds is undoubtedly the Buchwald-Hartwig's amination. The palladium catalyzed reaction is currently applied in several areas such as synthesis of heterocycles, synthesis of natural products and medicinal chemistry due to the wide presence of arylated amines in pharmaceuticals and natural products, becoming an appealing alternative to more traditional methods for the synthesis of arylamines such as the Cu-catalyzed Ullmann and Golberg couplings[20, 21]. Since the 1990s, when Buchwald and Hartwig developed the Pd- and Cu-catalyzed N-arylation, using suitable diamine or phosphine ligands, the identification of several families of phosphine ligands of broad utility and the development of pre-catalysts for the rapid formation of active catalyst in the reaction mixture upon exposure to base, have contributed to the versatility and widespread use of this reaction[55, 56]. Most of the Pd-catalyzed reactions follow a similar catalytic cycle (**Scheme I-11**).



***Scheme I-11**: Generic catalytic cycle for Buckwald-Hartwig amination.*

The cycle starts with the oxidative addition of the Pd(0)- ligand complex in wich the Pd(0) center is incorporated between the R–X bond in the haloarene and is oxidized to Pd(II), forming the complex **I**. In the next step, the amine nucleophile coordinates with the complex **I**, forming **II** and is deprotonated by the base resulting in the complex **III** that undergoes reductive elimination, closing the catalytic cycle and affording the arylated amine **IV**[57].

The presence of a base is essential for the formation of **III**, but is still uncertain the order of coordination and deprotonation steps. By the relative pKa values of amines it seems evident that when activated by coordination with the metal, the amine can be deprotonated by bases such as alkoxides. However, it is unclear whether the base can deprotonate the amine directly from the complex **II** or if have to dislodge the leaving group X after the coordination with the complex **I**, with this information being relevant in the choice of base for the reaction[57].

In general, anilines and slightly acidic groups like amides are arylated with easiness by bases, such as hydroxide and phenolates, contrasting with dialkyl amines that are less prone to deprotonation, thus requiring *tert*-butoxide or other alkoxide base of similar basicity[57].

To the best of our knowledge, regarding the benziodoxole derivatives, there are no examples of Pd-catalyzed C-N bond formation

I.4.1 - Benziodoxole Derivatives for C-N Bond Formation

The chemistry of benziodoxole derivatives for C-C and C-Heteroatom bond formation has a considerable number of examples, due the work of Waser and Togni. However, examples with a nitrogen hypervalently bonded to the iodine are very scarce. The first benziodoxole derivative coupled to a nitrogen atom was reported by Zhdankin in 1994[58], exploring the potential of azidobenziodoxolone (ABX- **4** and **4`**) for electrophilic azidation of cyclic hydrocarbons[59] a year later. Concerning the ABX, Zhdankin reported, in 1996, a novel direct azidation of alkenes,

where he proposed a radical-based mechanism for the reaction[15]. Surprisingly, despite the promising results reported by Zhdankin in 1990`s, it was only from 2013 that further work with ABX were performed (**Figure I-7**)[1, 32, 33].

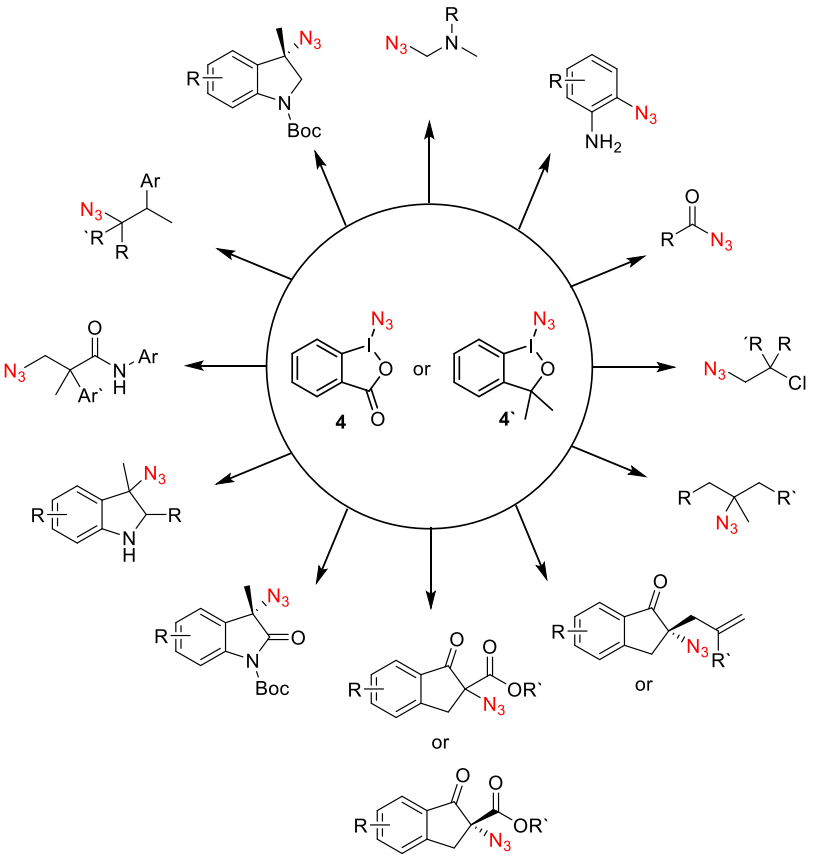


***Figure I-7**: C-N bond formation reactions with azidobenziodoxolone (ABX)[1, 15, 60].*

Zhdankin was also a pioneer in the synthesis of the second and last examples of this type of benziodoxole derivative. Zhdankin presented, in 1997, the amidobenziodoxolones (**13**), which demonstrated a similar reactivity to the previously reported azidobenziodoxolone and was explored for the direct amidation of adamantane and *N, N*-dialkylarylamines[61] (**Figure I-8**).

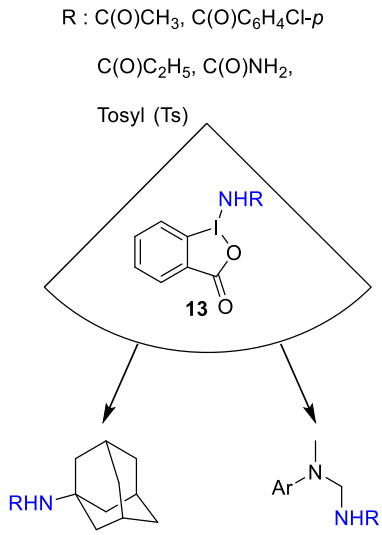


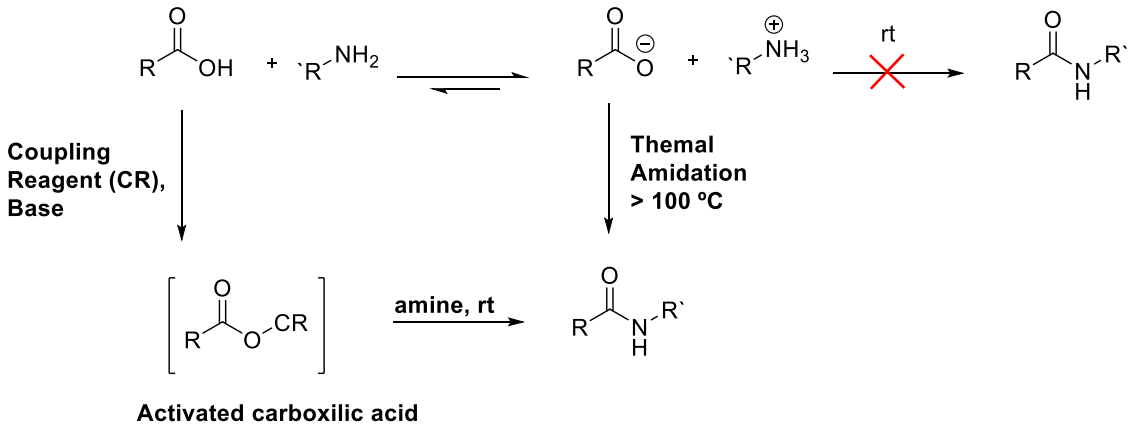
***Figure I-8**: C-C coupling reactions with amidobenziodoxolone.*

Based on the potential of CBX, EBX and Togni´s reagent for C-C bond formation, it seems that the potential of benziodoxole derivatives for C-N bond formation is being neglected and still needs much research regarding its reactivity.

I.5 - The Amide Bond

Amide bond formations is one of the most common transformations carried out in pharmaceutical synthesis and is of major importance in the structure of proteins. It was reported, in 2006, that 25% of all pharmaceuticals currently on the market have an amide bond[62].

In order to overcome the harsh conditions of direct thermal amidation[63], amides are traditionally formed by the reaction of a pre-activated carboxylic acid with stoichiometric amounts of a coupling reagent such as carbodiimides and an amine or alternatively turning the carboxylic acid into the corresponding acid chloride (the Schotten–Baumann reaction)[62, 64, 65]. However, these methods generally present a poor atom economy and are not necessarily green [64, 65] (**Scheme I-12**)



***Scheme I-12**: Thermal amide bond formation and classical activation of carboxylic acids[62].*

To overcome some of the problems related to the use of coupling reagents and minimize the need for protection/deprotection steps, the amide bond formation by enzymatic catalysis proved to be an excellent alternative[65, 66]. Moreover, the excellent stereo- and regioselectivity of enzymes guarantees structural fidelity of the product. Despite the advantages of enzymatic catalysis in amide bond formation, the narrow substrate specificity and the time scale of the reactions of the currently available enzymes severely limits their practical use[65] (**Figure I-9**).

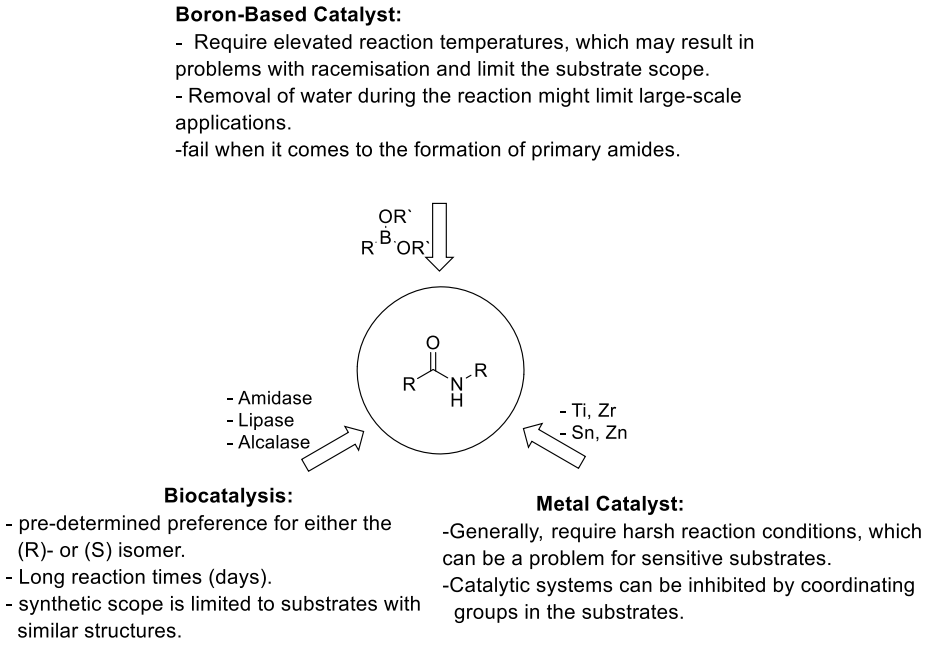


***Figure I-9**: Drawbacks of catalytic amide formation methodologies.*

Given the importance of amide bond and the limitations associated to the previous methodologies, a catalytic and waste-free production of amides was voted, in 2005, as highlighted area by the American Chemical Society's (ACS) Green Chemistry Institute (GCI)

Pharmaceutical Roundtable (PR)[66] and since then, many catalytic methods for the formation of amides have been developed[65].

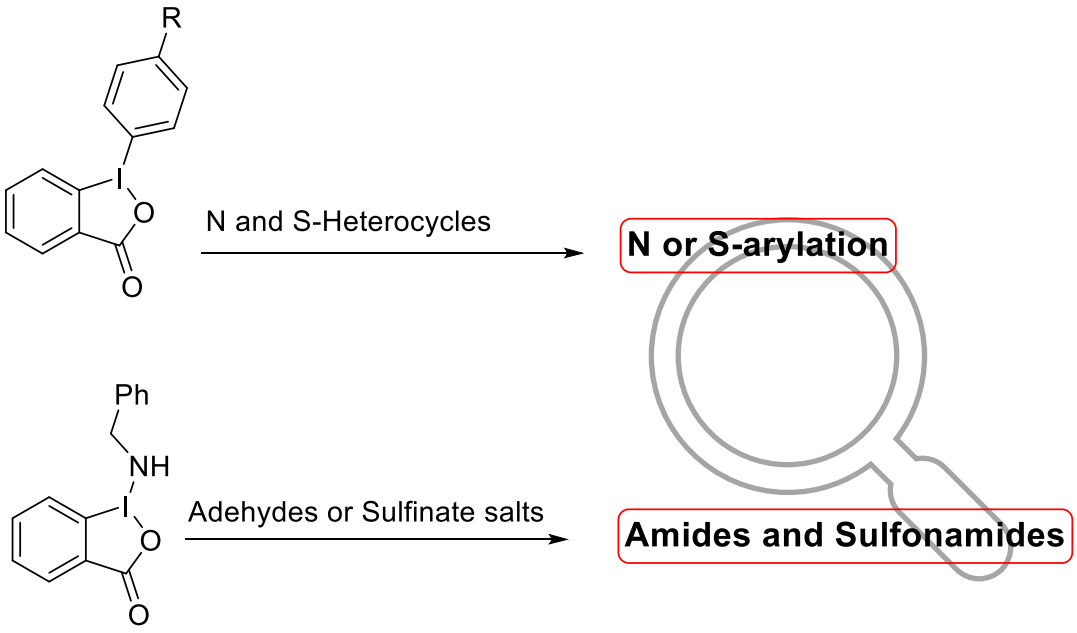
Despite all the results achieved in the transfer of functional groups by benziodoxole derivatives, there is still a long and fascinating journey to explore and discover the potential of these compounds and which groups may be bonded to the hypervalent iodine, giving rise to new synthetic approaches.

II. Results and Discussion

II.1 - Background

Azaindoles, are indole bioisosters and its properties can be easily tuned (lipophilicity, solubility, pKa, among others) constituting attractive scaffolds in drug discovery programs. Our group has been developing new strategies for the preparation of functionalized azaindoles, especially 1,2-diarylated azaindoles by palladium-catalyzed reactions such as, C-N cross-coupling reactions, the Sonogashira and Heck reactions.

Our main objectives for this Master`s thesis was to explore the potential of 1-arylbenziodoxolone in the arylation of heterocycles as an alternative to haloarenes and investigate the efficiency of benziodoxole derivatives for the transfer of amino groups.



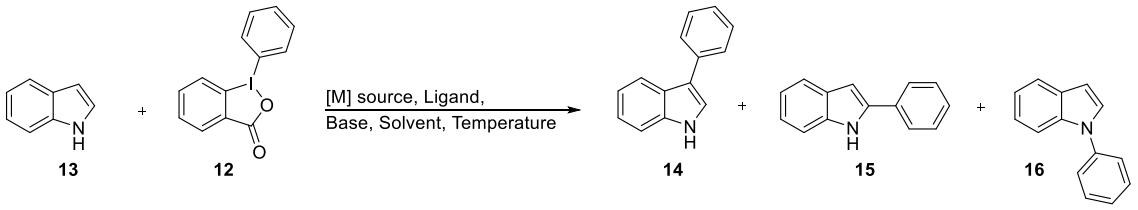
Thus, this thesis aimed to explore the potential of benziodoxoles as functional group transfer agents. The main goals of this study were to:

- Prepares several benziodoxole-derived compounds possessing an aryl moiety;
- Explore the arylated benziodoxole in arylation reactions of heterocyclic compounds such as, indole and pyrrole, aromatic amines (anilines) and also on aliphatic secondary amines;
- Develop a new methodology for the synthesis of 1,2-disubstituted azaindoles
- Explore the arylated benziodoxole in the alpha- arylation reaction of diethyl malonate;
- Investigate the potential of the arylated benziodoxole in the arylation of sulfinic acid salts to prepare diarylsulfones;
- Prepare 2-[(aryl)iodonio]benzenesulfonates (reported in the literature) and explore its application on the arylation of heterocycles.
- Investigate the formation of a benziodoxole derivative possessing an amine group and study the reaction conditions to promote its use in the preparation of sulfonamides and amides.

Our group has been focused on the use of benzidoxole reagents for sulfonyl group transfer and it is the first time that these reagents will be explored for S- and N- arylation reactions and transfer of amino groups, expanding the chemistry of these fascinating reagents.

II.2.2 - First approach: Arylation of heterocycles

II.2.2.1 - Arylation of indole



Scheme II-1*: Conditions for the arylation of indole using the arylbenziodoxole* ***12.***

Since 2016, our group have been developing new methodologies for the synthesis of functionalized azaindoles focusing on the arylation of these compounds.

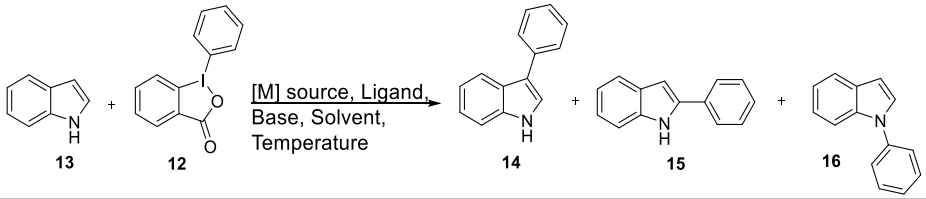
One of the major concerns in the arylation of N-unsubstituted indoles is the control of site selectivity, since the reaction also occur at the C-2 or N-1 position of the indole nucleus. Regarding the arylation at the C-3 position, that is typically achieved by transition-metal catalyzed cross-coupling reactions, it is limited to arylating agents such as aryl iodides and bromides. Additionally, very few examples of reactions with readily available however, less reactive aryl chlorides have been reported. Therefore, the development of efficient and greener site selective methods with a broad scope for the construction of arylated indoles remain highly desirable[67].

Therefore, our first approach in this master´s thesis was the investigation of the potential of 1-arylbenziodoxolone for the arylation of the indole moiety.

As previously mentioned, 1-arylbenziodoxolone are known to react with amines to form the correspondent anthranilic acid under copper catalyzed conditions[54]. To our first approach we follow the conditions reported by Waser and co-workers for alkynylation of indoles with EBX[12, 39].

Envisioning the arylation of the indole nucleus several trials were performed (**Table II-1**).

Table II-1**: Conditions and results of the catalytic trials with indole and 1-phenylbenziodoxolone **12.



Entry	Catalyst (mol%)	Base (equiv)	Solvent	Temperature	Time (h)	Observations
1		-	MeOH	rt	72	Unreacted starting material
2	CuI (10)	-	MeOH	rt	72	Unreacted starting material
3	$Cu(OAc)_2$ (10)	DMEDA (1.3)	Toluene	reflux	76	Unreacted starting material
4[a,b]	$Pd(OAc)_2$ (10)	Cs_2CO_3 (1.3)	Toluene	reflux	72	Complex mixture
5	$Pd(Allyl)Cl_2$ (10)	-	DCM/H_2O (98:2)	rt	48	Complex mixture
6	$InCl_3$ (10)	-	Toluene	reflux	56	Unreacted starting material -
7[a]	$InCl_3$ (10)	-	ACN	reflux	52	Unreacted starting material -

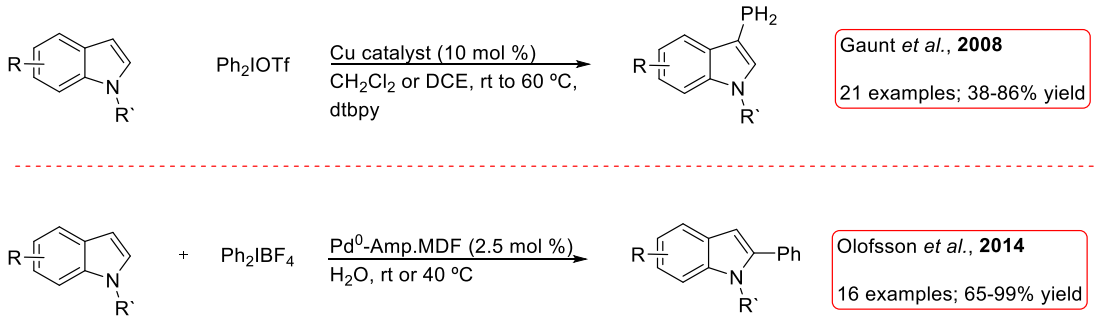
a– Experiment made with 3 equiv. of **12**; **b**– Experiment made in the presence of BINAP (20 mol %).

Unfortunately, the desired product was not obtained which might indicate that the reactivity of 1-arylbenziodoxolone seems to differ greatly from the reactivity of EBX. In our first approach we wanted to investigate if the reaction would occur in the absence of metal catalyst (**Table II-1: Entry 1**), but no product was observed other than the unreacted compounds **12** and **13**. It is worth to mention that MeOH was used due the high solubility of **12** in this solvent. Additionally,

the same result was attained when the conditions adapted from Gaunt and co-workers[68] were used (**Table II-1: Entries 2 and 3**).

Curiously, the result attained with Pd-catalyzed conditions (Entries **4** and **6**) stand in contrast with the outcome reported by Waser and co-workers[39], indicating that **12** is not as compatible with palladium as EBX. By TLC analysis a complex mixture and a considerable consumption of **12** throughout the reaction was observed.

Concerning the functionalization of indoles with benziodoxole derivatives, that was only achieved by Waser[12, 39] and Hamashima[44]. However, regarding the iodonium salts Gaunt *et al.* was the pioneer in the use of diaryliodonium salts in copper-catalyzed arylation of indoles under mild conditions[68] (**Scheme II-2**). The authors proposed that in the presence of diaryl-iodine (III) the Cu(I) catalyst is oxidized to form an extremely electrophilic aryl-Cu(III) specie, that is responsible for the mild conditions required for the indole functionalization. Regarding the selectivity of the reaction, that is regulated by the group attached to the nitrogen atom that control the migration of the Cu(III) specie from C-3 to C-2 position of the indole.



***Scheme II-2**: Cu and Pd-catalyzed arylation of indoles with iodonium salts.*

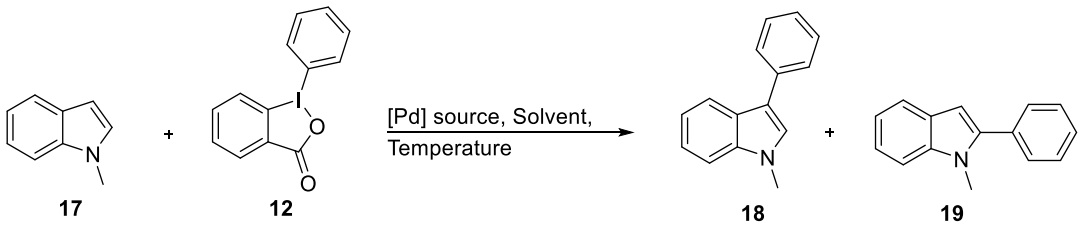
Recently, another breakthrough in the use of iodonium salts for indole functionalization was reported by Olofsson and co-workers[69] (**Scheme II-2**). The authors reported a C-2 selective arylation with nanopalladium and diaryliodonium salts. The reaction is susceptible to steric hindrance and electronic deactivation, since indoles with *tert*-Butyldimethylsilyl (TBDMS) or *tert*-butyloxycarbonyl (Boc) protecting groups were shown to be inert under the reaction conditions.

Another important factor for the outcome of the reaction was the influence of the anion of the iodonium salt, where the coordination ability of the anion to the metal center seems to be crucial for the reaction. In general, the reaction proceeds in water under mild conditions being compatible with N-H and N-protected indoles with a large variety of substituents, including halogenated indoles.

The first steps in the use of hypervalent iodine reagents for the functionalization of indoles have already been given and allowed the development of site selective approaches and milder reaction conditions. However, the need to develop greener (metal-free) methodologies with a broad scope for the construction of arylated indoles is still emerging and in this aspect, we

believe that benziodoxole derivatives could emerge as a great alternative to emulate more toxic and expensive late transition metals.

II.2.2.2 - Arylation of 1-methylindole

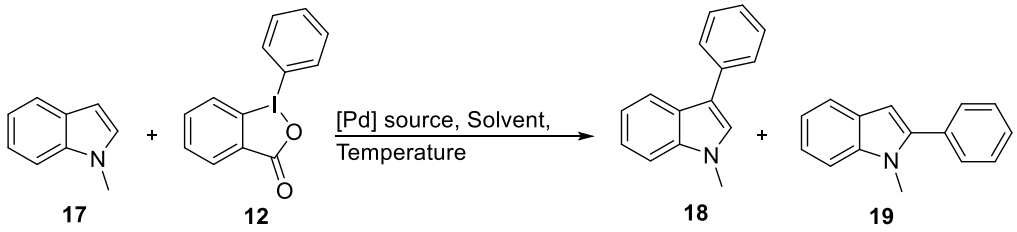


***Scheme II-3**: Conditions for the arylation of 1-methylindole.*

Despite the results achieved by Waser and co-workers in the palladium alkynylation of indoles, where the protection of the nitrogen atom is not necessary for the outcome of the reaction, we decided to investigate whether this would be an important factor to obtain the desired arylated indole, since it is known that N-protected indoles are more easily arylated[69].

Thus, 1-methylindole was synthetized and some experiments performed as described in **Table II-2**.

Table II-2:** Conditions and results of the catalytic trials with 1-methylindole and 1-phenylbenziodoxolone **12.



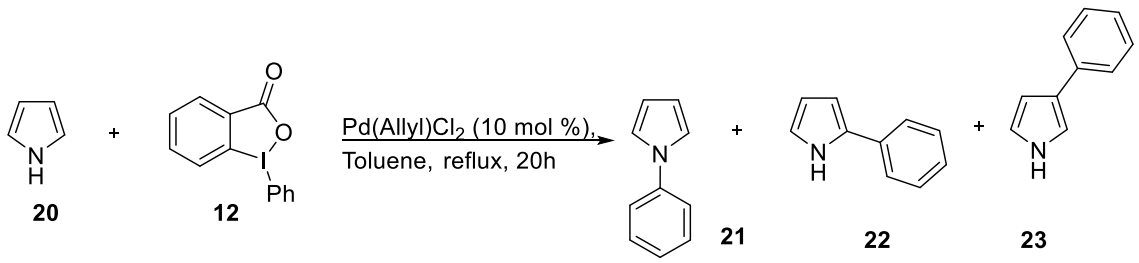
Entry	Catalyst (mol%)	Solvent	Temperature	Time (h)	Observations
1[a]	$Pd(Allyl)Cl_2$ (10)	DCM/H_2O (98:2)	rt	42	Complex mixture -
2[a]	$Pd(Allyl)Cl_2$ (2)	DCM/H_2O (98:2)	rt	44	Complex mixture -
3[a]	$Pd(Allyl)Cl_2$ (10)	Toluene	reflux	42	Complex mixture -
4[a]	$Pd(Allyl)Cl_2$ (2)	Toluene	reflux	48	Complex mixture -

a– Experiment made with 3 equiv. of **12**.

In this approach the procedure reported by Waser *et al.* [39] was adapted, since this appeared to be the most promising during the assays with the indole nucleus. Sadly, once again, in all experiments carried a complex mixture was observed and the desired product was not isolated.

II.2.2.3 - Arylation of pyrrole

Based on the results report by Waser *et al.* in the direct alkynylation of pyrroles[12] we perform one experiment envisioning the arylated pyrrole (**Scheme II-4**).



***Scheme II-4**: Conditions for the arylation pf pyrrole.*

Following the pattern observed for the indole arylation, under Pd-catalyzed conditions, we also observe a complex mixture and consumption of the starting material, in the TLC, during the reaction. This result reinforces the observation that **12** is not inert under Pd-catalyzed conditions and that the presence of one or more of the desired products in the reaction mixture or decomposition of the benziodoxole derivative used is plausible

It is known from the literature that the Pd-catalyzed arylation of indoles require protection of the NH group[70], thus more experiments with N-protected pyrroles would be needed to confirm if the protection of the nitrogen atom is critical to the outcome of the reaction.

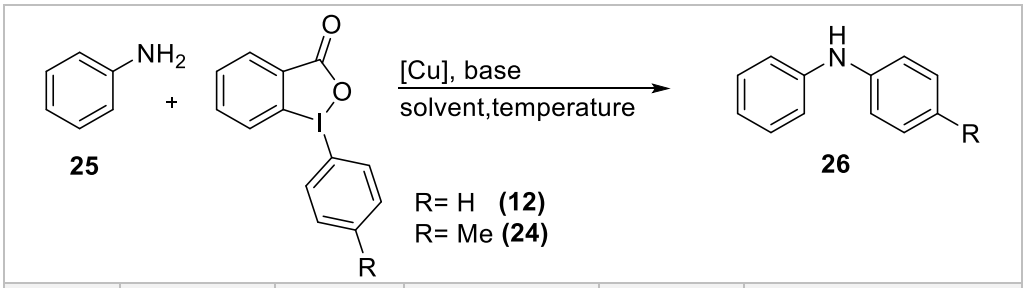
II.2.3 - Arylation of amines

After the experiments carried with the indole nucleus, further experiments were performed with anilines, that despite of being aromatic are more basic than indoles, and possess an exocyclic nitrogen atom.

II.2.3.1 - Arylation of aniline

Table II-3 summarize the results obtained in the experiments with aniline.

Table II-3: *Conditions and results of the catalytic trials with aniline and 1-phenylbenziodoxolone* ***12****.*



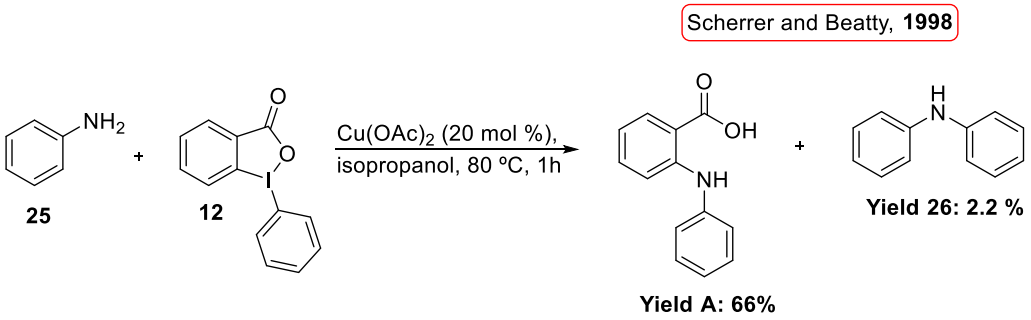
Entry	Catalyst (mol %)	Solvent	Temperature	Time(h)	Observations/Yield of (26)
1[a]	-	THF	reflux	26	Unreacted starting material
2[a]	$Cu(OAc)_2$ (20)	THF	reflux	20	Unreacted starting material
3[b]	$Cu(OAc)_2$ (20)	THF	reflux	20	Unreacted starting material-
4[a.c]	-	THF	reflux	18	26%

a- Experiment made with 1-phenylbenziodoxolone **12**; **b**- Experiment made with 4-methoxyphenylbenziodoxolone **24**;.**c**- Prior the addition of **12** a solution of aniline and *t*-BuOK (3 equiv.), in THF, was stirred for 10 min. at 0 ºC.

For the first experiments, in order to perform the N-arylation of aniline, we adapt and applied the conditions reported by Hao and co-workers[71].

In our first approach we wanted to investigate if the reaction would occur in the absence of catalyst. However, in these conditions, no product was observed other than the unreacted compounds **25** and **12** (**Table II-3: Entry 1**).

Regarding the use of **12** under Cu-catalyze conditions, to our surprise, we were not able to reproduce the result obtained by Scherrer and Beatty[54] and isolate the N-phenylanthranilic acid (**Scheme II-5**).



***Scheme II-5**: Conditions for the preparation of N-phenylanthranilic acid (**A**).*

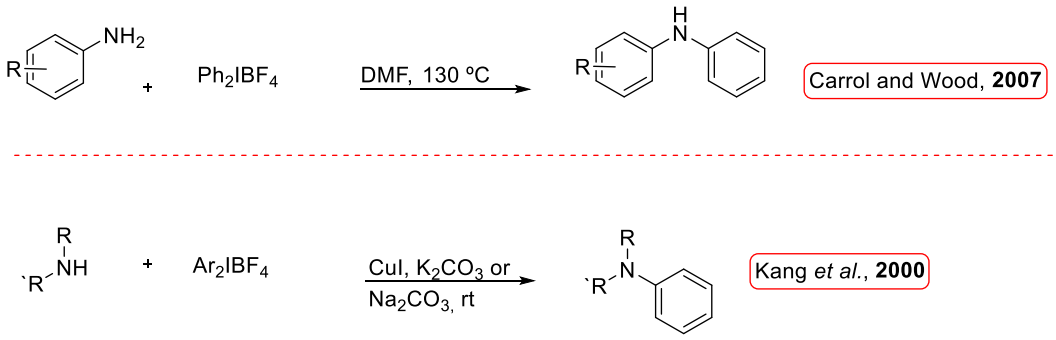
The author also reported that trace amounts of the arylated amine were isolated, but in the experiments carried, under Cu-catalyzed conditions, (**Table II-3: Entry 2 and 3**) the correspondent product were not observed.

Concerning the solvent, the authors used, a protic polar solvent such as isopropanol. Additionally, they also reported that the reaction occurs in the presence of N,N-Dimethylacetamide (polar aprotic solvent), standing in contrast with the result attained when carbon tetrachloride (nonpolar solvent) was used and no N-phenylanthranilic acid was observed. These results may suggest that, in fact, the utilization of polar solvents could be an important factor in the reaction. Therefore, the results obtained, with benziodoxoles **12** and **24** under Cu-catalyzed conditions, may not be related to the solvent used and other factors may be influencing the outcome of the reaction. However, the choice of solvent by the authors, may be only due to the fact that **12** exhibits high solubility in solvents such as, methanol and isopropanol.

The first results were very discouraging, since none of the conditions tested were able to achieve the arylated amine. Surprisingly, when the reaction was carried in the absence of Cu catalyst and a strong base was used, the desired diphenylamine **26** was observed (**Table II-3: Entry 4**).

Under metal-free conditions and in the presence of *t*-BuOK the arylated product **26** was obtained in 26 % yield (**Table II-3: Entry 4**). This result, to the best of our knowledge, represent the first time that 1-arylbenziodoxolone was efficiently used as an aryl transfer reagent.

Concerning the arylation of amines with hypervalent iodine, Carroll and Wood reported a metal-free route to diarylamines in good yields, where the chemeoselectivity and influence of the anion were also investigated[72] (**Scheme II-6**).



***Scheme II-6**: N-arylation of amines with iodonium salts[72, 73].*

If we compared the procedure reported by the authors and the one that we present, it is clear that the use of 1-phenylbenziodoxolone allows the reaction to occur under milder conditions, even though the condition were not optimized.

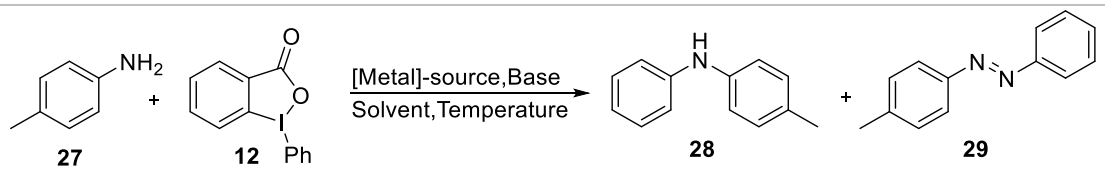
Curiously, in the results reported by Kang in the copper-catalyzed N-arylation of amines with hypervalent iodonium salts, in the presence of base, the use of CuI is crucial for the reaction[73] (**Scheme II-6**).

The diphenylaniline **26** has a similar Rf to the starting material in the eluents tested, and for that reason it was difficult to detect by TLC analysis. When analyzing the ^{1}H-NMR spectra of a compound isolated, that was believed to be recovered aniline, product **26** was found. It is important to refer, that only during thesis writing, this result was found and was previously neglected since it was attributed to the unreacted aniline. For this reason, no further investigation of these conditions were done. In the future this reaction will be optimized and other amines tested, since this route consists on a metal-free procedure to N-arylation of anilines, opening room for improvement in this field.

II.2.3.2 - Arylation of *p*-toluidine

The study proceeds with the investigation of the reaction of benziodoxole **12** with *p*-toluidine (**Table II-4**).

***Table II-4**: Conditions and results of the catalytic trials with p-toluidine and 1-phenylbenziodoxolone **12**.*



27 **12** **28** **29**

Entry	Catalyst (mol%)	Solvent	Temperature	Time (h)	Observations/ Yield 28 (%)
1[a]	-	THF	rt to reflux	20	Formation of **29**
2[a,b]	-	THF	reflux	24	Complex mixture
3[a]	$Cu(OAc)_2$ (20)	THF	reflux	72	5
4[a]	$Cu(OAc)_2$ (20)	THF (degassed)	reflux	26	3
5[a]	$Cu(OAc)_2$ (100)	THF	reflux	70	Unreacted starting material
6[a]	AgOH (20)	THF	reflux	22	Unreacted starting material
7[a]	$Cu(OAc)_2$ (20)	DMF	rt to 110 ºC	26	Unreacted starting material
8[a]	$Cu(OAc)_2$ (10)	THF	reflux	20	Unreacted starting material
9[a]	CuI (10)	THF	reflux	20	Unreacted starting material
10[a]	$(CuOAc)_2$ (20)	Toluene	reflux	18	Unreacted Starting material
11[a,c]	-	THF	reflux	20	44

a– experiment made with **12**; **b**– experiment made in the presence of *t*-BuOK (3 equiv.); **c**– Experiment made in the presence of *t*-BuONa (3 equiv.)

In the first experiment, the formation of azocompound **29** was observed and isolated with 15 % yield. The formation of **20** was suppressed by degasification of the solvent (**Table II-4: Entry 4**) and minimized, in the remaining experiments, by doing cycles of evacuation of the vessel, containing the solids, under vacuum and refilling it with nitrogen prior the addition of the solvent.

After several experiments the expected product **28** was obtained with low yield (**Table II-4: Entries 3 and 4**).

Curiously, when 4-methoxphenylaniline (**27**) was use for the arylation of aniline (**Table II-3: Entry 3**) the arylated amine was not observed, but when *p*-toluidine was used with 1-phenylbenziodoxolone (**12**) the desired product **28** was isolated. This result indicates that the outcome of the reaction is much more influenced by alterations in the nucleophile (amine) than in the electrophile (benziodoxole derivative).

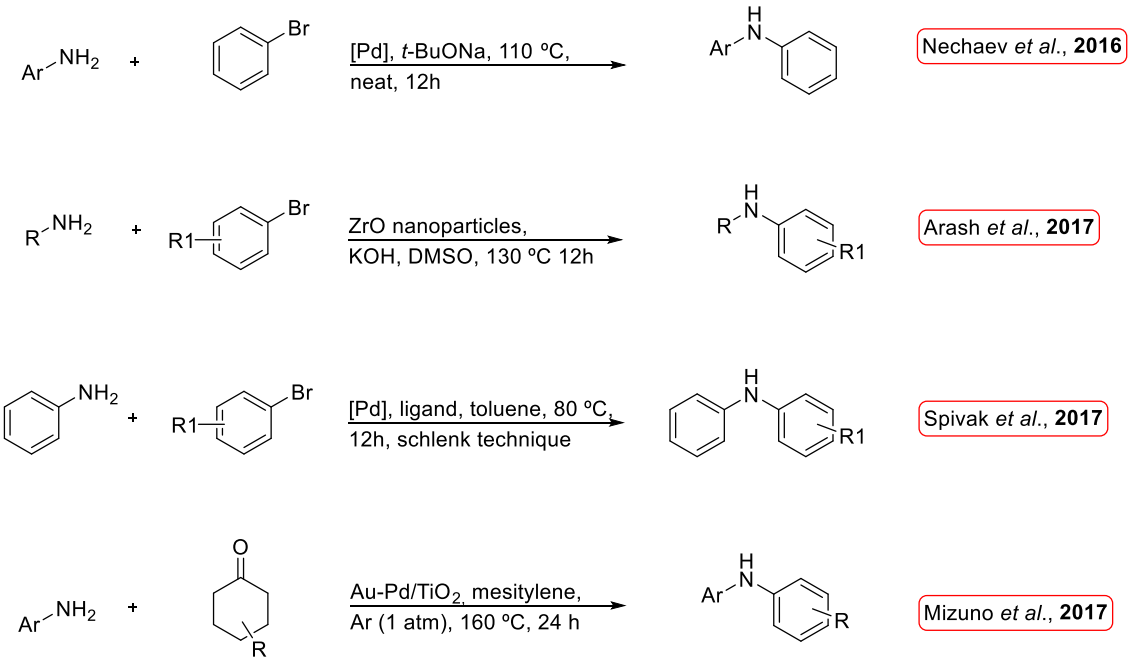
It is also interesting to note that the reaction is much faster in the absence of oxygen (**Table II-4: Entry 4**) which is according with the findings reported by Roberts *et al.*[74] for the hydrolysis of unsymmetrical diaryliodonium salts. The authors reported that Cu(I) is the catalyst of the reaction and the rate of the reactions with Cu(II) is reduced in the presence of oxygen, since the reduction of Cu(II) to Cu(I) is retarded. However, if this were true for **12**, formation of product would be expected in **entry 9**.

This might suggest, as previously attained in **entry 4**, that this case may not be reproducible and the catalytic specie is Cu(II). Being in agreement with the result obtained by Scherrer and Beatty[54].

It is worth to mention, that, in **entry 2**, a complex mixture was observed throughout the reaction, which may indicate a result similar to that obtained with aniline. Therefore, in the future, further investigation is required.

In a later stage of the project, a trial with *t*-BuONa under metal free conditions was performed (**Table II-4: Entry 11**) and for our surprise **28** was obtained with 44 % yield. This remarkable result represents the first time that a benziodoxole derivative was used for amine arylation and shows the potential of this reagent as an alternative to the Buchwald reaction.

Some of the most recent reports in the literature concerning the synthesis diarylamines (**Scheme II-7**) normally require metal-catalyzed conditions, ligands and harsh conditions.



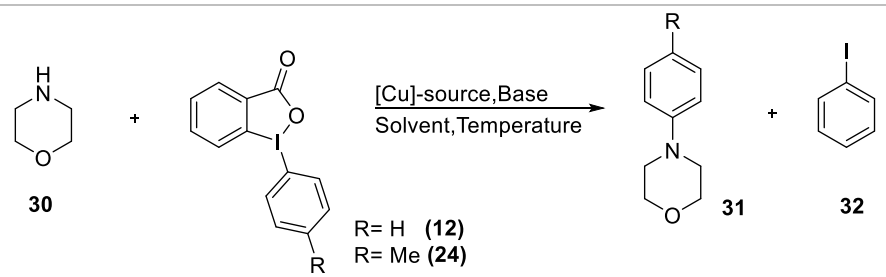
***Scheme II-7**: Recent reports on the synthesis of diarylamines*[75-77]

It is evident that the development of metal-free methods is emergent and undoubtedly this result is a major step towards the development of a more sustainable chemistry in the functionalization of amines.

II.2.3.3 - Arylation of morpholine

Next, morpholine was investigated since it is more nucleophilic than the previously tested amines (**Table II-5**).

***Table II-5**: Conditions and results of the catalytic trials with morpholine and 1-phenylbenziodoxolone **12** or 4-metoxyphenylbenziodoxolone **24**.*



Entry	Starting Material Mass (mg)	Catalyst (mol%)	Base(equiv.)	Solvent	Temperature	Time (h)	Observations
1[a,e]	80	$Cu(OAc)_2$ (20)	-	THF	rt to reflux	62	Unreacted starting material

2[a,b,d]	80	$Cu(OAc)_2$ (20)	-	THF	rt to reflux	20	Unreacted starting material
3[d]	80	$Cu(OAc)_2$ (20)	-	THF	reflux	22	Unreacted starting material
4[d]	50	$Cu(OAc)_2$ (20)	*t*-BuONa (3)	Toluene	reflux	20	Complex mixture-
5[c,d]	50	$Cu(OAc)_2$ (20)	*t*-BuONa (3)	Toluene	reflux	18h	Decomposition of **12**
6[d]	80	CuI (20)	-	THF	reflux	22	Unreacted Starting material
7[d]	80	CuI (20)	TEA (1)	THF	rt	22	Unreacted starting material-
8[d]	80	CuI (20)	TEA (1)	MeOH	reflux	24	Unreacted starting material /Fomation of **32**
9[d]	80	CuI (20)	TEA (1)	$CHCl_3$	reflux	24	Unreacted starting material/ Formation of **32**
10[d]	80	$Cu(OAc)_2$ (20)	TEA (1)	$CHCl_3$	reflux	22	Unreacted starting material

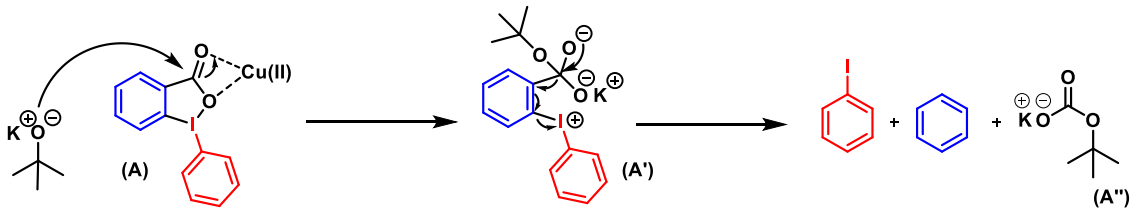
a- 2 equiv. of morpholine **30**; b- Experiment made with 4-methoxyphenylbenziodoxolone **24**; c- Experiment in the absence of morpholine **30**: d– Experiment made with **12**.

Despite what was initially thought, the increasing nucleophilicity of the nucleophile did not contribute to the formation of the intended product **22**.

When just $Cu(OAc)_2$ was used, both **12** and **24** fails to react with morpholine to afford the desired product **31** (**Table II-5: Entries 1 and 2**). Additionally, to investigate whether the excess of morpholine would be affecting the reaction outcome a trial with 1 equiv. of morpholine was performed (**Table II-5: Entry 3**). However, the same result of the previously trials was attained. Based on the pattern observed (formation of a complex mixture) with the previously amines when bases, such as *t*-BuOK, were used we decide to inspect if the use of base would be crucial for the result of the reaction (**Table II-5: Entry 4**). Surprisingly, the pattern remains and a complex mixture was observed.

Standing in contrast with the results reported by Scherrer and Beatty[54], we observed that 1-arylbenziodoxolone decomposes in the presence of *t*-BuONa and Cu catalyst (**Table II-5: Entry**

5). This decomposition may be due the fact that an alkoxide ion is being formed in the reaction and reacting with the ring bearing the carbonyl group (**Scheme II-8**).



Scheme II-8 *Proposed mechanism for the decomposition of 1-phenylbenziodoxolone in the presence of t-BuONa.*

This hypothesis is in agreement with the result obtained by Scherrer and Beatty[54], where under Cu(II) catalyzed conditions the phenoxide ion reacts with **A** to form the correspondent benzoic acid. It is important to mention that we are not capable of isolate the product **A``**, since the reaction TLC indicates the formation of several decomposition products.

Surprisingly, now that is known that amines, such as aniline, can be arylated with 1-phenylbenziodoxolone **12** in the presence of base, it was unexpected that no product was attained in the presence of *t*-BuONa and copper(II) (**Table II-5: Entry 4**). This result can be attributed to the presence of the Cu-catalyst. Additionally, there might be a coordination of the amine with Cu, preventing the reaction to occur under the tested conditions

The result observed **in entry 5** reinforces the previous statement and show that 1-phenylbenziodoxolone **12** is susceptible to decomposition in the presence of a combination of copper and base, such as *t*-BuONa. Probably, in the presence of copper, the zwitterionic form is favored and **12** become prone to being attacked by the phenoxide ion (**Scheme II-7**). Interestingly, this predisposition to nucleophilic attack, in the presence of copper, seems to be affected by the base, considering that we did not observe a complex mixture in the TLC`s when triethylamine (TEA) was used (**Table II-5: Entries 7, 8 and 9**).

It is intriguing to observe, that even in the presence of a nucleophile, such as morpholine, the reaction occurs with the base acting as a nucleophile. It would be interesting to know to what extent the chelating effect of the nitrogen atom, in the presence of copper, would be inhibiting the nucleophilicity of the morpholine.

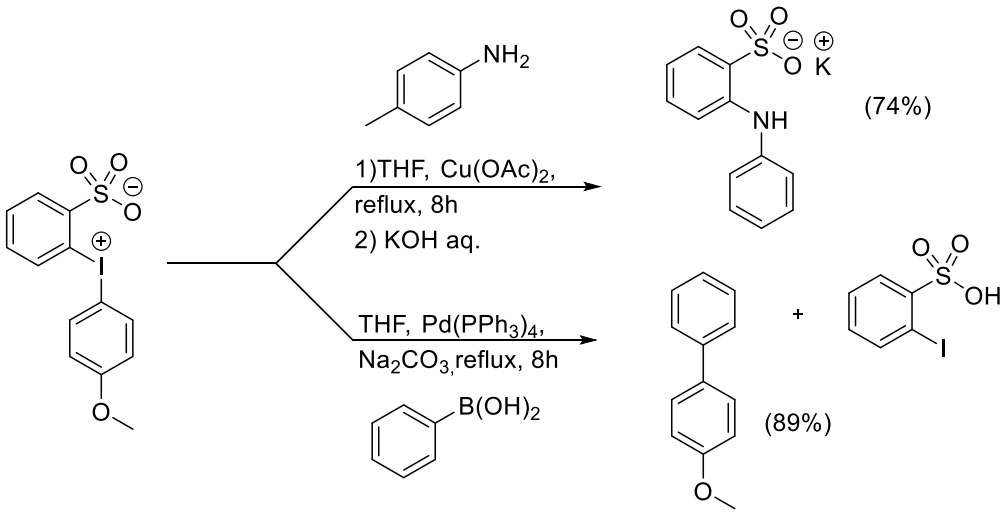
Curiously, in the experiments made with $CHCl_3$ and MeOH in the presence of CuI (**Table II-5: Entries 8 and 9**) iodobenze (**32**) was isolated. Even knowing that decarboxylation of aromatic acids require harsh conditions[78], it was investigated whether **32** was formed by decarboxylation of the benziodoxole ring or from any reaction involving the catalyst. A trial was conducted (**Table II-5: Entry 10**), where the catalyst was changed for $Cu(OAc)_2$ and, in fact, the formation of **32** was inhibited. To access if the iodine was coming from de catalyst, a trial with a different source of Cu(I), such as CuOAc, would be necessary.

II.2.4 - Synthesis of 2-[(aryl)iodonio]benzenesulfonates

After the experiments with 1-arybenziodoxolone derivatives, was found that, in 2009, Justik and co-workers reported the use of 2-[(aryl)iodonio]benzenesulfonates as an aryl-carrier for metal-catalyzed cross-coupling reactions[79].

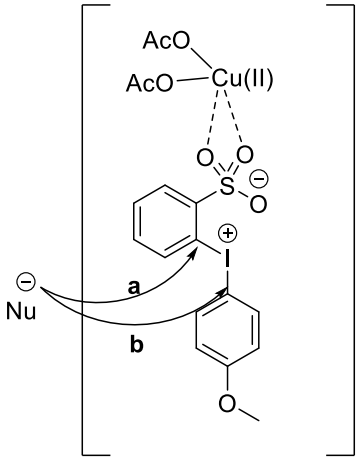
Contrary to what is observed for the structure of 1-arylbenziodoxolone, in the 2-[(aryl)iodonio]benzenesulfonate the I-O bond is longer (2.478 Å vs 2.676 Å)[79], implying a greater contribution from the betaine form, due the reduced covalent character of the I-O bond.

This zwitterionic character might explain why 2-[(aryl)iodonio]benzenesulfonates succeed in Pd-catalyzed reactions, such as Suzuki-Miyaura coupling (**Scheme II-9**), allowing these reagent emulate the reactivity of iodonium salts that are well known in this reaction[80].



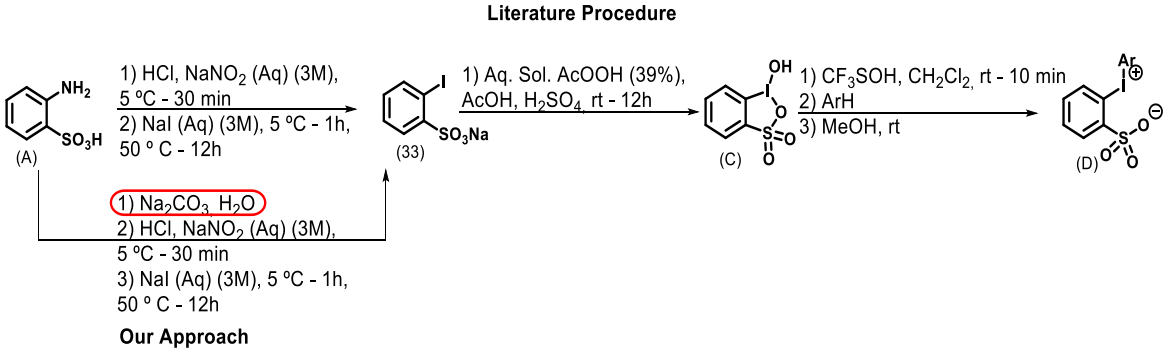
***Scheme II-9**: Reactivity of 2-[(aryl)iodonio]benzenesulfonates under Cu and Pd-catalyzed conditions.*

Surprisingly, the reagent exhibits a distinct reactivity, in copper catalyzed conditions, to the reactivity observed for 1-arylbenziodoxolone. In the presence of copper catalyst the reaction occurs in the ring bearing the SO_3 anion. These reactivity might be due two factors: 1) to the Lewis acid character of $Cu(OAc)_2$ that coordinate with the oxygens atoms and 2) to the excellent leaving group ability of aryl iodide[80]. These factors combined favor the pathway **a** over **b** (**Scheme II-10**).



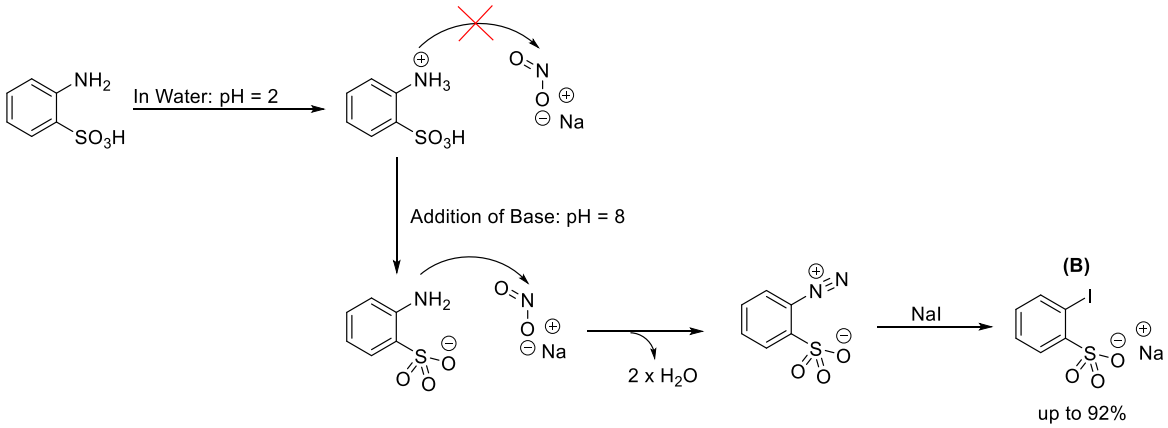
***Scheme II-10**: Proposed mechanism for the reaction of 2-[(aryl)iodonio]benzenesulfonates under Cu-catalyzed conditions in the presence of nucleophiles.*

The synthetic strategy for the preparation of 2-[(aryl)iodonio]benzenesulfonates consist in three steps: 1) Diazotization and iodination of commercial 2-aminobenzene-sulfonic acid; 2) Oxidation with peracetic acid to afford HBI (1H-1-hydroxy-1,2,3-benziodoxathiole 3,3-dioxide – **B**) and 3) Aryl insertion (**Scheme II-11**).



***Scheme II-11**: Adapted approach for the synthesis of **33**.*

For the synthesis of **33** we followed the procedure reported by Ishihara and co-workers[81] (**Scheme II-11**), but after several attempts we were never able to afford the desired product (**33**). We were intrigued by these results and in order to try to find out why the reaction was not working we decided to verify if the amine, in the reported condition, would be able to attack the sodium nitrite. We observe that a solution of **A** in water presented a pH = 2 and therefore, the amine (aniline pKa = 4.6) is protonated and unable to attack the sodium nitrite (**Scheme II-12**).



***Scheme II-12**: Proposed explanation for iodination reaction in basic media.*

After this finding, we decided to change the procedure and proceed to the adding of base (Na_2CO_3 (Aq) (1M)) in the first step (**Scheme II-12**). We basified the solution to pH = 8 and proceed with the second and third step of the synthesis, affording **B** with 92% of yield.

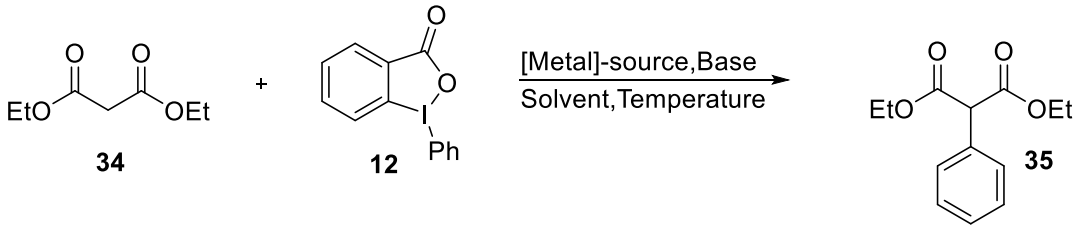
Based on the previous results and in the data collected, the synthesis of **A** in the absence of base it is not possible. However, later, it was discovered that Ishihara and co-workers[81] used base, for the same reaction, for starting materials other than **A**.

It is worth to mention that, even after one month of several trials adapted from the procedure described on the literature, the desired product **B** were never attained and only with the modification presented the desired product was obtained. Initially, the objective was to explore the potential of 2 - [(aryl) iodonium] benzenesulfonate for aryl transfer. However, given the difficulties encountered, during the synthesis of the first intermediate 33, this approach was abandoned because it would not be practical during the time of the thesis and because there are more direct alternatives.

II.2.5 - Arylation of diethyl malonate

Considering that the reactivity of the benziodoxolone derivatives might be substrate dependent, it was decided to test the potential of **12** for alpha carbon arylation following the conditions of Buchwald and co-workers[82] (**Table II-6**).

***Table II-6**: Conditions and results of the catalytic trials with diethyl malonate and 1-phenylbenziodoxolone **12**.*



Entry	Catalyst (mol%)	Base (equiv.)	Solvent	Temperature	Reation time (h)	Observations
1	CuI (10)	Cs_2CO_3 (3)	$CHCl_3$	reflux	32	Unreacted starting material
2	-	Cs_2CO_3 (3)	$CHCl_3$	rt	30	Unreacted starting material
3	CuI (10)	NaH (1)	$CHCl_3$	reflux	28	Unreacted starting material
4	-	NaH (1)	$CHCl_3$	reflux	30	Unreacted starting material
5	$Zn(OTf)_2$ (5)	-	$CHCl_3$	reflux	30	Unreacted starting material

Despite all efforts, the arylated product **35** was not observed and any product was isolated. With these results, concerning the benziodoxole derivatives, the alpha carbon functionalization remains exclusive for CBX and ABX and contrast with the results obtained with iodonium salts for α-arylation[8], including the arylation of diethyl malonate[83].

Chang *et al.*[83] proposed that the arylation of diethyl malonate occur by an addition-elimination mechanism, as no radical by product were detected. The authors used conditions ((1) NaH, DMF; 2) Ar_2X)) similar to the ones tested (**Table II-6: Entry 4**). Therefore, if the mechanism proposed by Chang and co-workers is correct, the lack of product is due the low reactivity of **12**, under the tested conditions, and not the non-formation of the enolate.

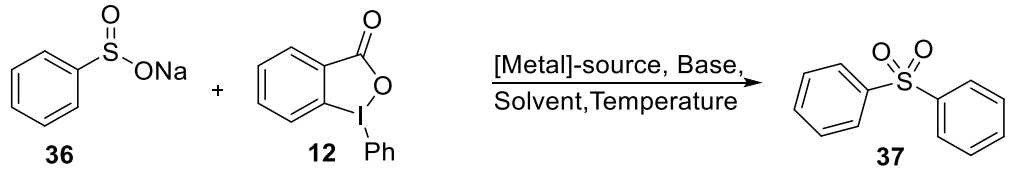
So far as functionalization of alpha carbons is concerned, Szpillman *et al.*[84] reported, recently, the first characterization and identification of enolonium species. Showing, that these species act as intermediated in a variety of reactions and that the regioselective stand in contrast with the reactive of enolates, where the reaction occurs in the less sterically hindered position of unsymmetrical allylating agent.

The authors observed that, in the case of the reaction of enolonium species with allylsilanes, the regiochemistry is controlled by the electronic predilection of the allylic silanes to go through an attack at the γ position of the trimethylsilane (TMS) moiety.

II.2.6 - Arylation of sodium benzenesulfinate

Driven by the results attained in our group, in the synthesis of sulfonamides with benziodoxole derivatives, we wondered if **12** could be applied in the synthesis of aryl sulfones (**Table II-7**).

Table II-7**: Conditions and results of the catalytic trials with sodium benzenesulfinate and 1-phenylbenziodoxolone **12.



Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	Solvent	Temperature	Time (h)	Observations
1[a]	-	-	-	DCM	rt	36	Unreacted starting material
2[a]	-	-	-	Toluene	reflux	30	Unreacted starting material
3[c]	-	-	-	DMF	90 ºC	42	Unreacted starting material
4[c]	-	-	-	$CHCl_3$	reflux	32	Unreacted starting material
5[a]	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	rt	48	Complex mixture
6[c]	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	reflux	42	Complex mixture
7[c]	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	$CHCl_3$	rt	36	Complex mixture-
8[c]	$Pd_2(dba)_3$ (2.5)	BINAP (5)	Cs_2CO_3 (1.5)	Toluene	reflux	40	Complex mixture
9[b.c]	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	reflux	32	Decomposition of **12**

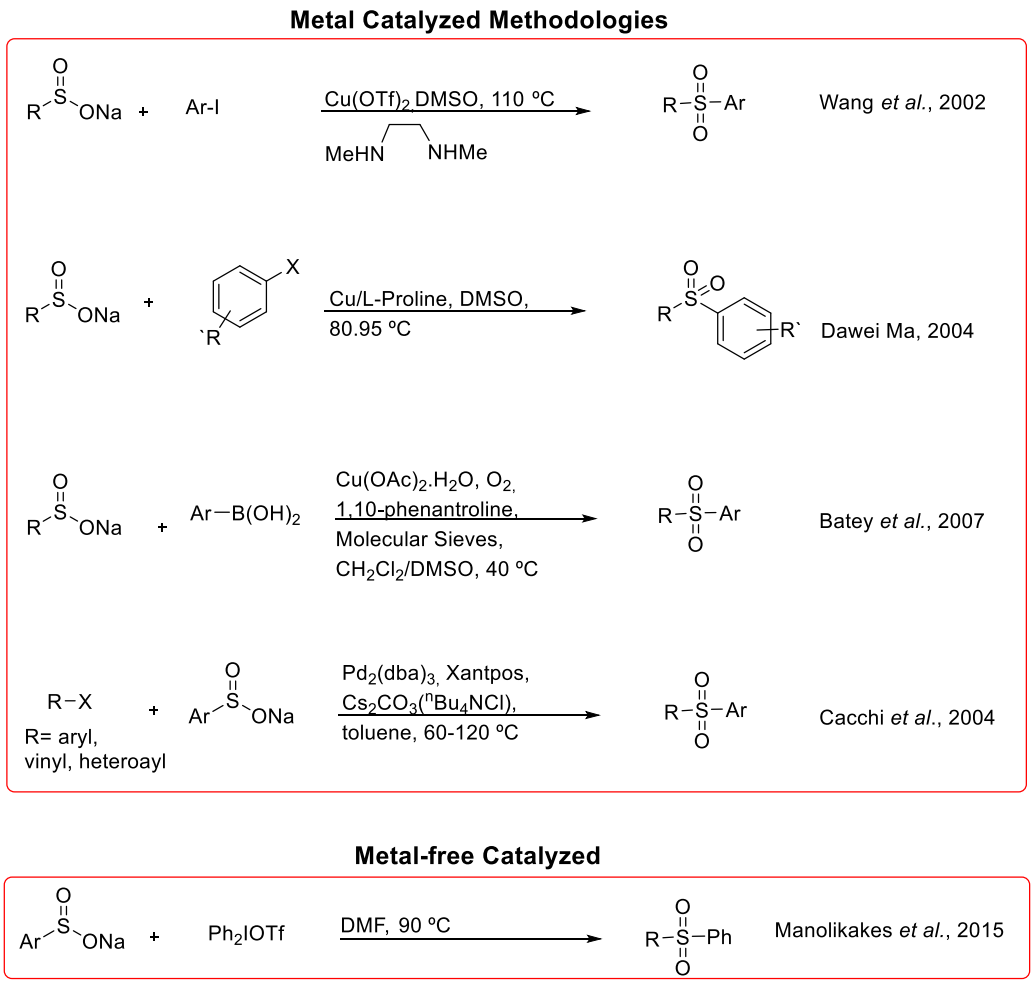
a- Experiment made with 4-bromophenylbenziodoxolone **38**; **b**- Experiment made in the absence of sodium benzenesulfinate.; **c**- Experiment made with 1-phenylbenziodoxolone **12**.

It is known from the literature that, EBX,CBX[1] and Togni´s reagent[49] can react with sulfur nucleophiles, which unfortunately does not seem to be the case with **12**.

Concerning the reaction of iodonium salts with sulfur nucleophiles, they are compatible with Cu and Pd-catalyzed conditions[8].

In these experiments, it was observed that 1-phenylbenziodoxole (**12**) does not react under metal-free conditions (**Table II-2: Entries 1-4**) and Pd-catalyzed conditions, and the later lead to decomposition of the reagent (**Table II-7: Entry 9**). This result, further enhances the unique reactivity of each benziodoxole and the distinction between this class of compounds and iodonium salts.

As far as the synthesis of diaryl sulfones, with hypervalent iodine, is concerned, several methods based on Cu-catalyzed conditions were reported and normally require the use of ligands, halogenated starting materials and high temperatures[85-88] (**Scheme II-13**). Regarding the palladadium catalyzed synthesis of diaryl sulfones, similar requirements were needed for the outcome of the reaction[89](**Scheme II-13**).

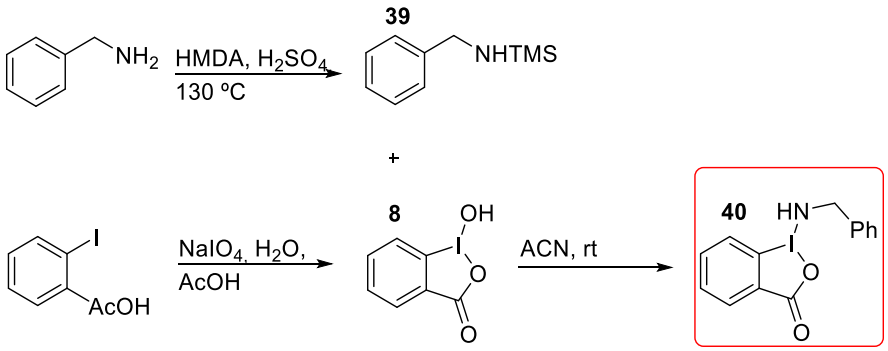


***Scheme II-13**: Construction of diaryl sulfones with iodonium salts.*

II.2.7 - Synthesis of 1-benzylamine-1,2-benzodioxol-3-(1*H*)-one

Since the first approach to explore the reactivity of 1-arylbenziodoxolones, towards a variety of nucleophiles, was not successful, we decided to explore the potential of the hypervalent bond for the transfer of different groups, namely amine groups.

Based on the typical strategy for the synthesis of benziodoxole derivatives, where the sylylated moiety (**39**), that will bind the iodine atom, react with hydrobenziodoxolone (**8**) to afford the benziodoxolone derivative (**40**) (**Scheme II-14**).



***Scheme II-14**: Synthetic strategy for the synthesis of 1-benzylamine-1,2-benzodioxol-3-(1H)-one (**40**).*

Surprisingly, in the first experiment, **C** was isolated with 74 % yield as white crystalline solid, which allowed us the confirmation of the structure by X-ray crystallography (**Figure II-1**)

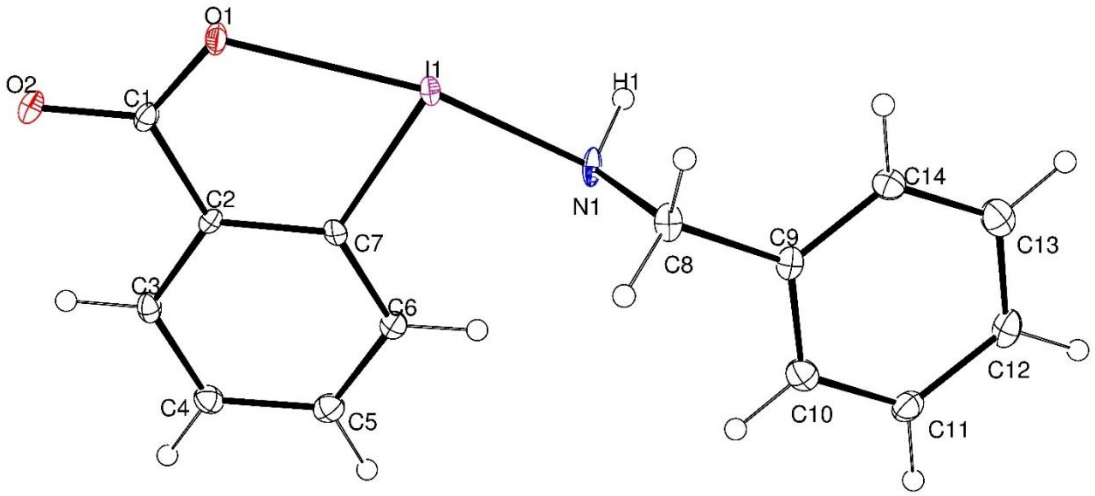


***Figure II-10**:* ORTEP-3 diagram of the title compound, using 30% probability level ellipsoids, with labelling. Selected distances [Å] and angles [°]: I(1)-N(1) 2.031(5), I(1)-C(7) 2.103(7), I(1)-O(1) 2.379(4), N(1)-C(8) 1.500(8), N(1)-I(1)-C(7) 91.6, N(1)-I(1)-O(1) 166.57(19), C(7)-I(1)-O(1) 75.0(2), C(1)-O(1)-I(1) 113.3(4)

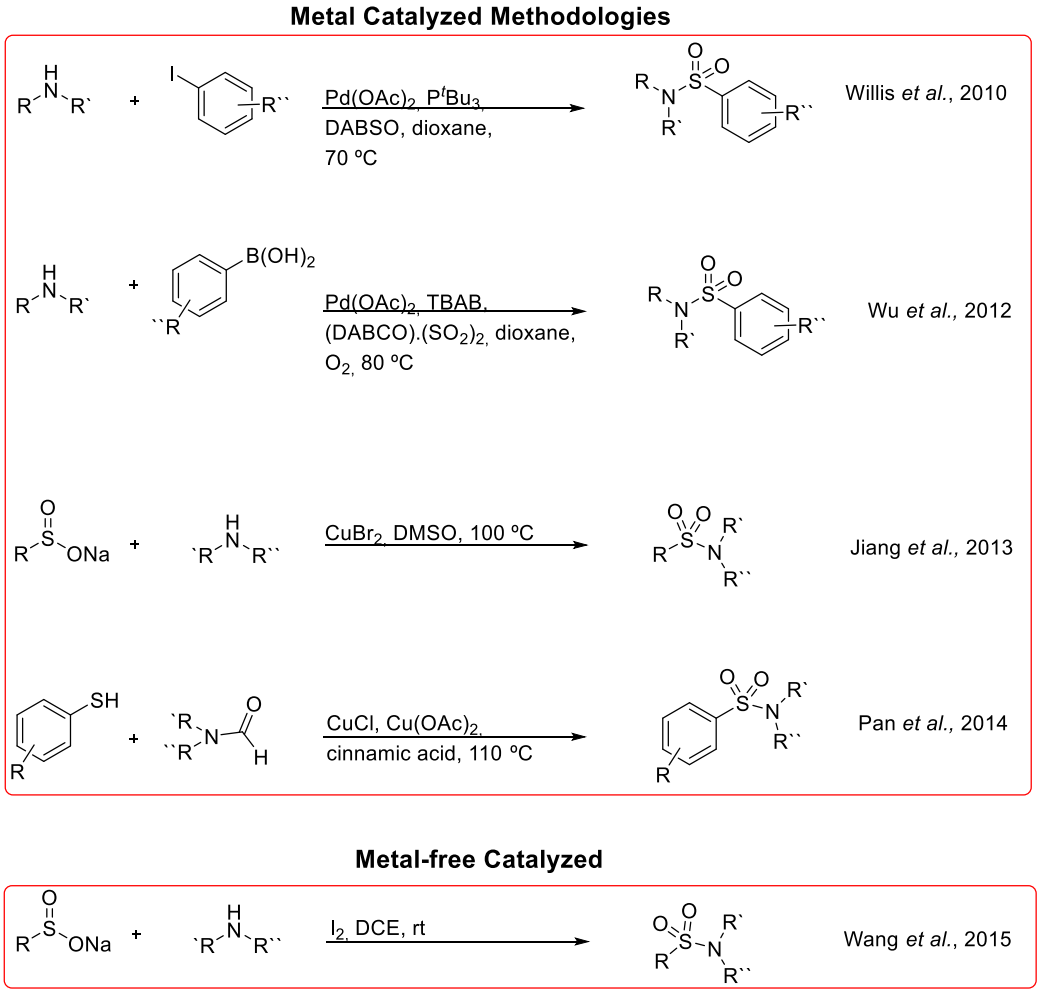
For the best of our knowledge, that was the first time that a benziodoxole derivative carrying an amine group was synthetized.

To showcase the synthetic utility and understand the reactivity, of this novel benziodoxole derivative, some preliminary studies were carried out.

II.2.7.1 - Synthesis of sulfonamides

Traditionally, sulfonamides are prepared by the reaction between an amine and a sulfonyl chloride in the presence of base. Despite the efficiency of the method, it requires the synthesis of sulfonyl chlorides, some of which are difficult to prepare and sensitive to moisture.

To overcome these drawbacks, several alternatives, such as the amino sulfonylation reactions of haryl halides[90], diazonium salts[91], boronic acids[92]; the triphenylphosphine ditriflate-mediated coupling reaction of sulfonic acids with amines[93]; the copper catalyzed sulfonamide formation reported by Jiang *et al.*[94] and Pan *et al.*[95] (**Scheme II-15**), others have thus been developed. However, these methods usually present some limitations, such as severe or complex reaction conditions, use of strong oxidants and the production of toxic wastes.

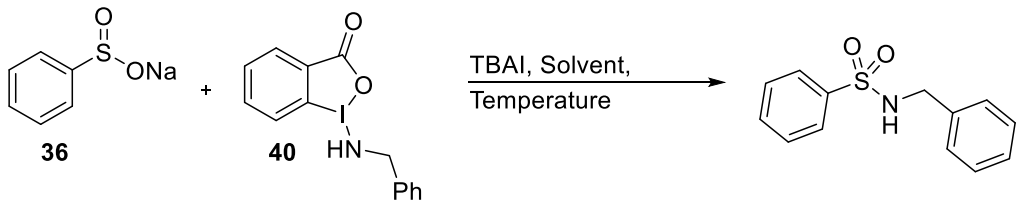


***Scheme II-15**: Some of the methodologies described for the synthesis of sulfonamides.*

Recently, Wang and co-w*orkers* reported an metal-free procedure for the construction of sulfonamides at room temperature[96] (**Scheme II-15**). The reaction shows to be compatible with a broad range of functional groups and proceeds well under air at room temperature. The

authors propose the formation of a sulfonyl iodide intermediate that undergoes nucleophilic attack by the amine, leading to the desired sulfonamide. Although the mild conditions required and the good yields attained, the use of 1,2-dichloroethane (DCE), as solvent, limits the application of the reaction. DCE is toxic, especially by inhalation, and carcinogenic[97, 98].

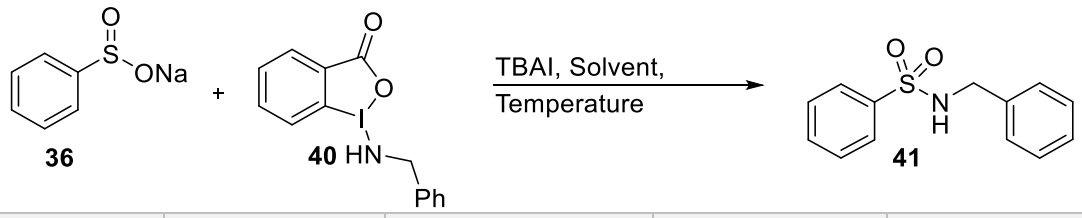
Envisioning a new methodology for the synthesis of sulfonamides we perform some experiments with sodium benzenesulfinate (**Table II-8**).



Scheme II-16*: Conditions for the formation of sulfonamides.*

The choice of nucleophile and conditions were based on other ongoing project, in our lab, for the synthesis of sulfonamides with hypervalent iodine and in the conditions reported by Hamashima and co-workers[99].

Table II-8*: Conditions and results of the catalytic trials with sodium benzenesulfinate and 1-benzylamine-1,2-benzodioxol-3-(1H)-one (**40**)*

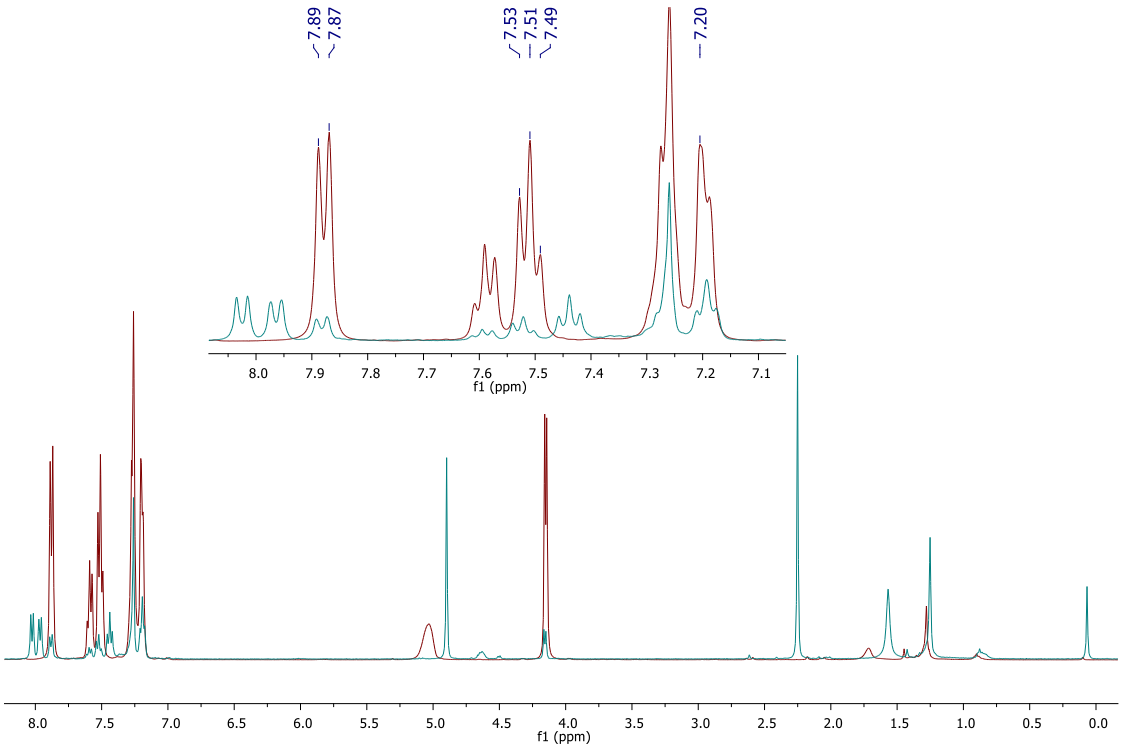


Entry	Solvent	Temperature	Time (h)	Observations
1	DCM	rt	22	Traces of product
2	DCM	reflux	18	Unreacted starting material
3	ACN	reflux	22	Unreacted starting material
4	ACN	-40 ºC to rt	30	Unreacted starting material
5[a]	DCM	rt	28	No decomposition of **40**

a- experiment made in the absence of sodium benzenesulfinate.

During the experiments, was possible identify traces of the desired sulfonamide (**Table II-8: Entry 1**) in the reaction crude (**Scheme II-17**).

It is worth to mention that unlike the reactions with 1-phenylbenziodoxolone (**1**), which is easily detected by TCL, it was difficult to find an eluent that would allow us to monitor, by TLC, the behavior of **40** throughout the reaction.



***Scheme II-17**: Overlapping of the ^{1}H NMR spectra of the reaction crude (blue) and the desired sulfonamide (red).*

This result shows, that **40** is able to react with the sulfinate salt to form the correspondent sulfonamide. Being this, the first time that a benziodoxole derivative is used for sulfonamide synthesis.

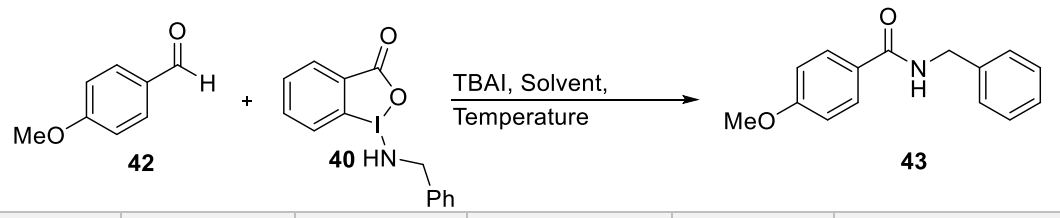
In a future approach, would be interesting to explore the reaction under metal-catalyzed condition and optimize the reaction conditions.

As far as the preparation of sulfonamides with hypervalent iodine is concerned, there was no reports of the use of hypervalent iodine in the synthesis of those valuables synthetic targets.

II.2.7.2 - Synthesis of amides

Driven by the results attained by Zhdankin and co-workers in the C−H azidation of aldehydes with azidobenziodoxolone (ABX)[16], some experiments were conducted to ascertain the potential of the reagent **40** in the C-H amidation of *p*-anisaldehyde (**Table II-9**).

Table II-9**: Conditions and results of the catalytic trials with p-anisaldehyde and 1-benzylamine-1,2-benzodioxol-3-(1H)-one **(40)



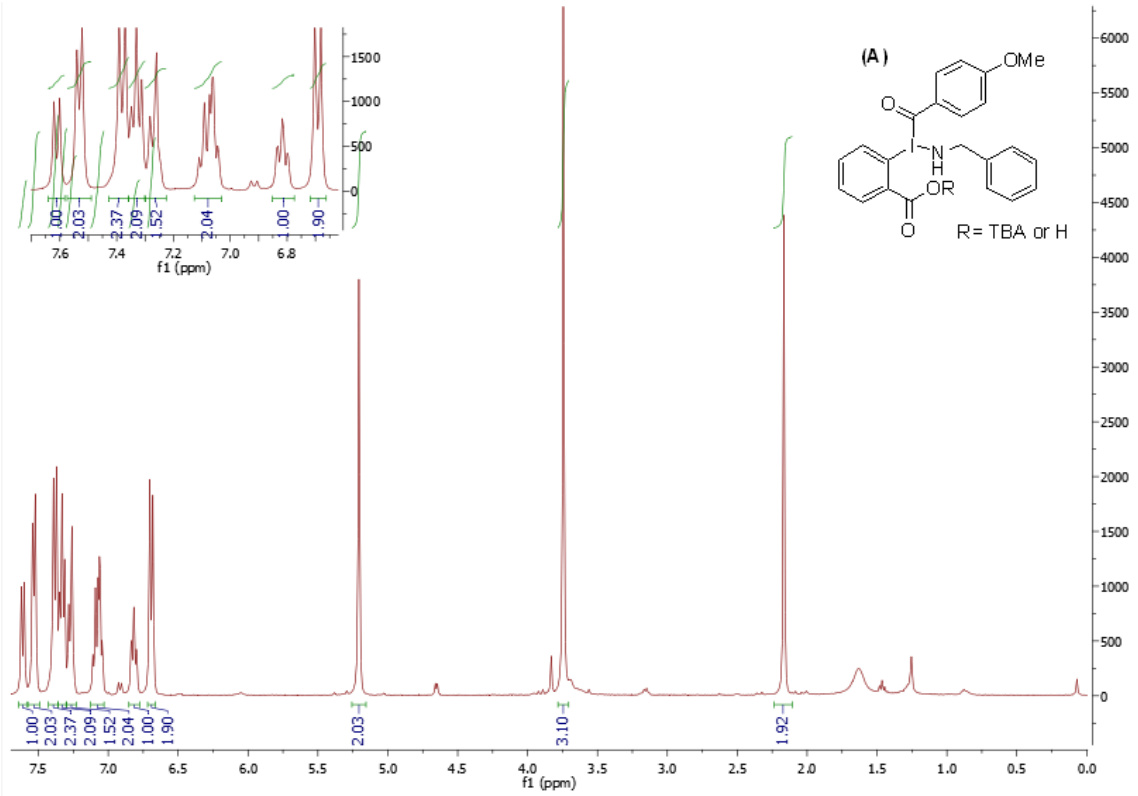
Entry	TBAI (equiv.)	Solvent	Temperature	Time (h)	Obsevations/Yield 44 (%)
1	0.1	DCM	rt	72	3
2	1	DCM	rt to reflux	74	Unreacted starting material
3[c]	-	DCM	rt to reflux	74	Unreacted starting material
4	1	ACN	reflux	144	Unreacted starting material-
5	0.1	ACN	reflux	120	5
6[a]	1	ACN	reflux	46	Unreacted starting material
7[b]	1	ACN	reflux	48	Absence of **43**

a- experiment made in the absence of *p*-anisaldehyde and **43**; **b**- experiment made in the presence of TEMPO (1 equiv.); **c-** experiment made in the absence of TBAI.

Following the exact same conditions, reported by the authors, N-benzyl-4-methoxybenzamide **43** was isolated although in low yield (**Table II-9**: **Entry 1**). As well as in the results reported by Zhdankin *et al*[16]., the reaction does not occur in the absence of tetra-*n*-butylammonium Iodide (TBAI) (**Table II-9**: **Entry 3**).

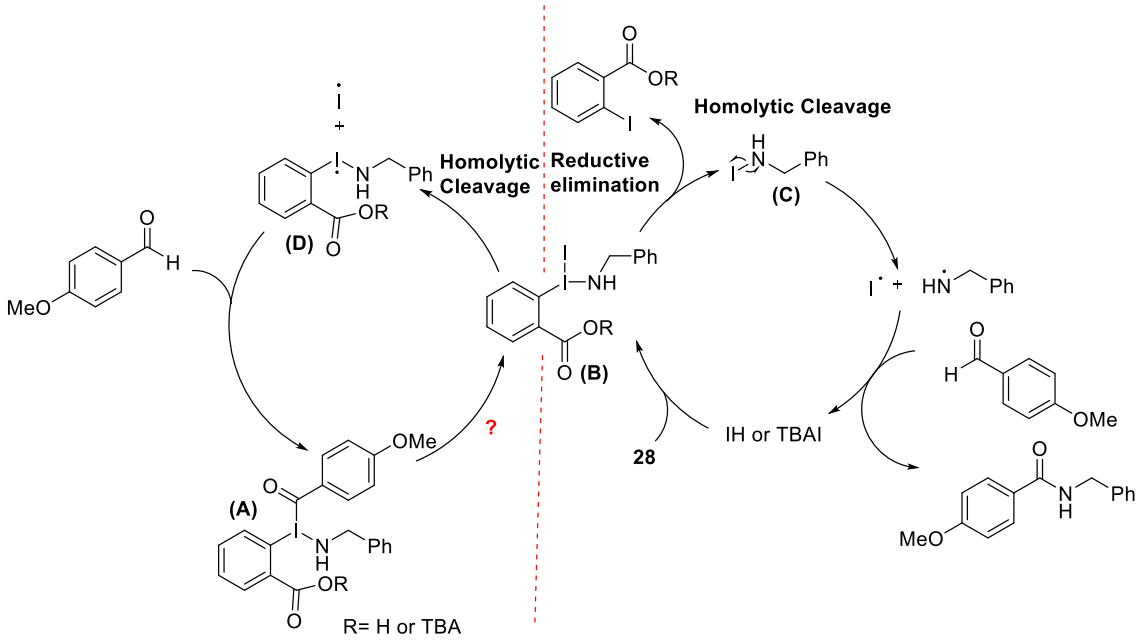
It is also important to mention tha the TBAI-catalyzed amidation was repressed by the addition of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as a radical inhibitor, which suggest a radical mechanism for this reaction (**Table II-9**: **Entry 7**). The change of solvent for ACN and the increase of the reaction temperature did not provide a significant enhancement in the yield (**Table II-9: Entry 5**). Also, greater catalytic loading seems to inhibit the amide formation (**Table II-9: Entries 2, 4 and 6**).

In many of the trials it was possible to isolate a specie that presents 13 aromatic protons, which might correspond to a specie that possesses the aldehyde, the amine and the benziodoxolone ring in their structure (**Scheme II-18**).



Scheme II-18**: ^{1}H NMR ($CDCl_3$) of intermediate **A

Based on the results obtained, a plausible mechanism is proposed (**Scheme II-19**), where the specie specie (**A**) could be a possible intermediate in the amidation reaction.



***Scheme II-19**: Proposed mechanism for the amidation reaction and for the formation of intermediate **A**.*

For the amide formation, it is plausible, that an analogous catalytic cycle to that reported by Zhdankin and co- workers is taking place under the tested conditions. In that case **C** would be formed by the reductive elimination of **B**. The formation of a similar specie is also observed in the mixture of Togni`s reagent and TBAI[100].

From the homolytic cleavage of **C**, an benzylamine and iodine radical are released and the later abstract a proton from the aldehyde, generating HI and an acyl radical. The benzylamine radical specie, leads to the formation of the correspondent amide by the coupling with acyl radical.

For the formation of **A** an alternative pathway is proposed, where the homolytic cleavage of the I-I bond of **B** occur giving rise to **D** and an iodine radical. Again, the iodine radical will abstract the proton of the aldehyde and generate an acyl radical. The coupling of **D** with the acyl radical generate the intermediate **A**.

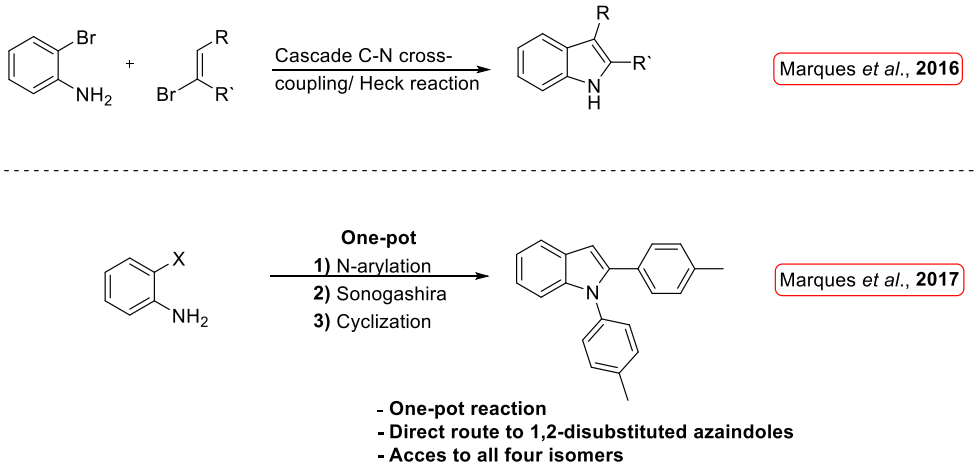
In order to know whether the intermediate could be converted into the amide or another product, **A** was exposed to UV radiation and temperature, but no product was observed.

The formation of **A** was substantially greater than of the amide. This might be due the fact that the formation of **D** is more favored than the formation of the benzylamine radical. In **D**, the radical is far more stabilized by resonance than in the benzylamine radical and this might be the reason for the preferential formation of **A**. For a more accurate proposal about the mechanism, computational studies would be necessary to calculate the energies associated with the intermediates **C** and **D**.

Finally, a novel reagent for the formation of amides is proposed, along with all his unexplored potential. The discovery of this reagent shows the great versatility of the benziodoxole derivatives and the endless possibilities for the bond of new groups to the iodine atom. With these recent accomplishments, the eventual discovery of the adequate catalytic system and synthesis of the desired amides using this method is definitely within reach.

II.2.8 - One-pot Synthesis of 1,2-Disubstituted Azaindoles

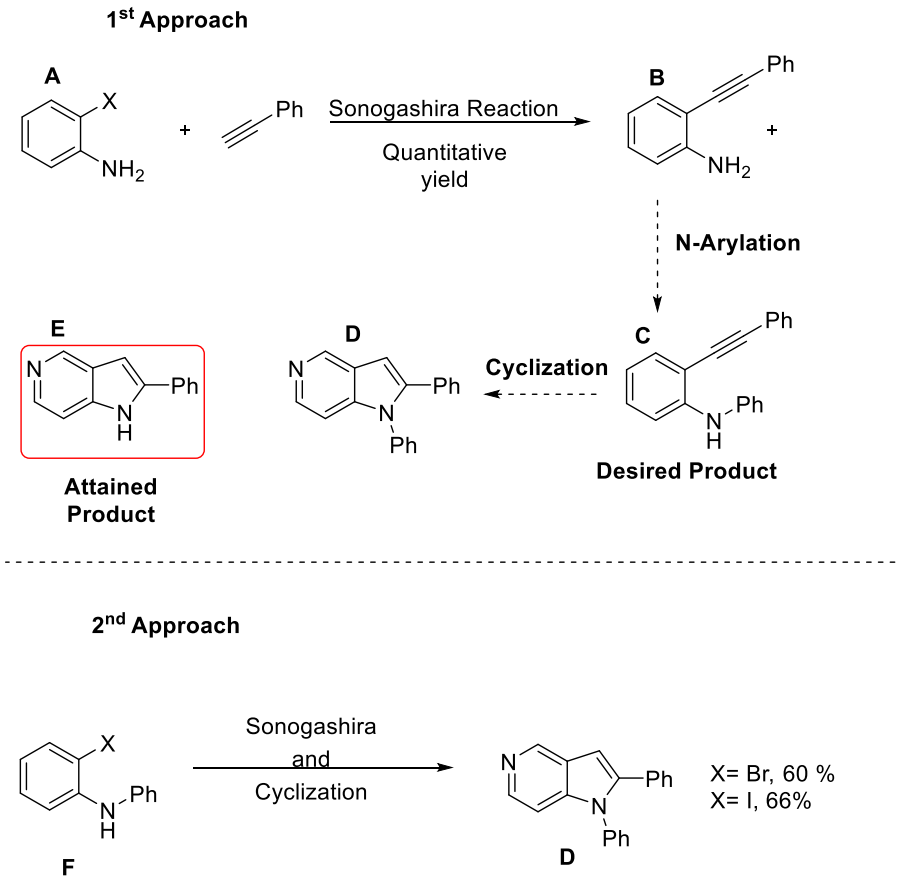
As previously mentioned, in parallel with the thesis, I was involved in a project that envisioned the construction of 1,2-disubstituted-azaindoles. This project was the continuation of a work that has been carried out since 2016. In 2016, Marques reported a palladium-catalyzed cascade C−N cross-coupling/Heck reaction of alkenyl bromides with amino-*o*- bromopyridines for the synthesis of substituted 4-, 5-, 6-, and 7-azaindoles using a $Pd_2(dba)_3$/ XPhos/ *t*-BuONa system[25] (**Scheme II-20**). This work consisted in one of the first example of a cascade amination/Heck reaction of alkenyl bromides with amino-*o*-bromopyridines, and provided an elegant alternative for the preparation of 2-substituted azaindoles. However, the reported methodology, when applied to N-aryl amino-*o*-bromopyridines was unable to afford 1,2-diaryl-azaindoles.



***Scheme II-20**: Methods report by Marques and co-workers for the preparation of functionalized azaindoles[25, 26].*

With substituted azaindoles being a promising scaffold in drug discovery since, different substitution patterns give rise to different properties[25, 26]. Efforts toward efficient strategies for the synthesis of substituted azaindoles have been developed[26]. However, 1,2-disubstituted azaindoles are almost unexplored, especially 1,2-diaryl azaindoles. Therefore, we reported a new, efficient and direct protocol to attain several 1,2-disubstituted-azaindoles (4-, 5-, 6-, and 7-azaindoles) via a one-pot N-arylation/Sonogashira/cyclization reaction[26] (**Scheme II-21**).

Initially, a Sonogashira reaction to amino-*o*-halopyridines followed by N-arylation of the corresponding products and subsequent cyclization to afford the azaindole core (**Scheme II-21**) was envisaged. However, only trace amounts of the 2-phenyl-5-azaindole **E** were observed instead of the desired compound **D**. These results suggested that, under heating conditions, cyclization of the Sonogashira product **B** occurs before N-arylation, affording **E**.

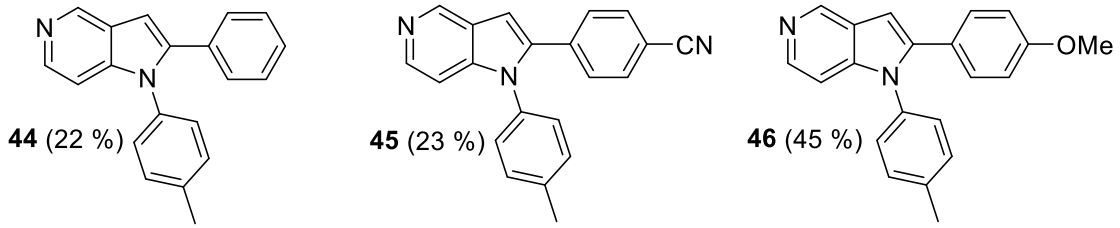


***Scheme II-21**:1st Approach: Sonogashira Followed by N-Arylation; 2nd Approach: N-Arylation Followed by Sonogashira/ Cyclization Reaction.*

As the N-arylation of **B** proved to be difficult, we decided to investigate the Sonogashira reaction of N-arylated amino-*o*-halopyridines (**Scheme II-22**). The reaction was carried out at 110 °C and azaindole **D** was directly obtained and isolated in 66% yield. At 110 °C, both bromide and iodide were suitable coupling partners in the Sonogashira reaction with no significant change in **E** yield.

Having established the best route to attain **E**, we next investigated whether the reaction could be performed in a one-pot approach, directly from the amino-*o*-halopyridines while avoiding isolation of both the N-arylation and Sonogashira products. To our satisfaction, azaindole **E** was isolated in 49% yield by treatment of 1a (X = Br) with $Pd_2(dba)_3$/XantPhos/*t*-BuONa in toluene at 110 °C for 6 h, followed by solvent removal and resuspension in dry DMF, addition of $PdCl_2(PPh_3)_2$/CuI/phenyl acetylene, and heating at 110 °C for 24 h[26].

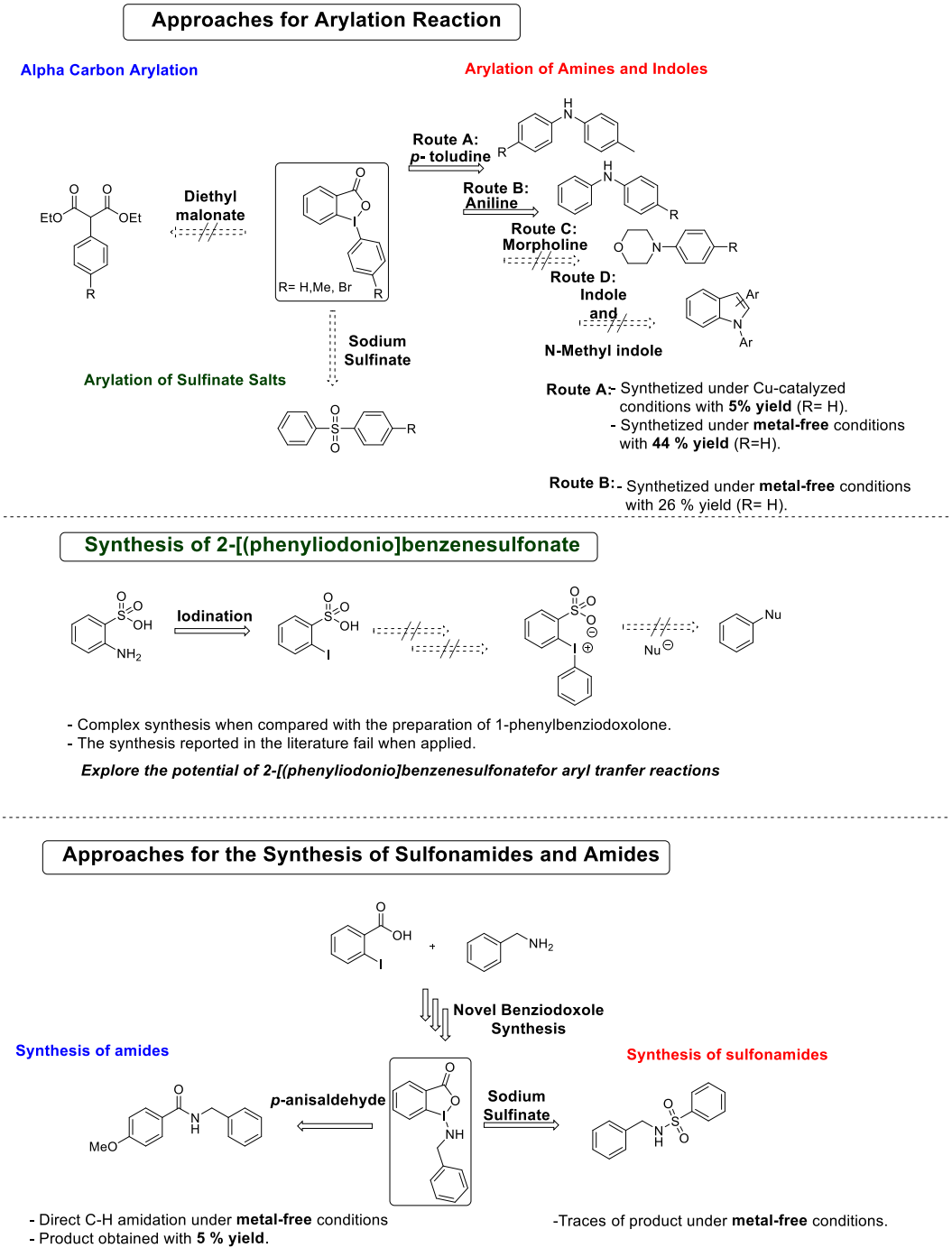
Encouraged by these results, we next examined the scope of the one-pot protocol, that proved to be versatile and compatible with both EWG and EDG at both the phenylacetylene and aryl iodide, allowing the synthesis of 18 different 1,2-disubstituted azaindoles, of which three of them were synthetized by me (**Scheme II-22**).



***Scheme II-22**: Synthetized 1,2-Disubstituted azaindoles.*

II.2.9 - Final Remarks

In a project involving the development of novel approaches for arylation and amidation reactions, a new synthetic methodology was investigated in order to provide arylated amines, along with a novel benziodoxole derivative for direct C-H amidation of aldehydes (**Scheme II-23**).



***Scheme II-23**: Attempted procedures in the several approaches performed during the project.*

Thus, two benziodoxole derivatives were prepared (**12** and **40**). Those, were used for different approaches. 1-phenybenziodoxolone **12** was used in 4 different approaches, being the arylation of amines the one with the most promising results.

The first approach envisaged the arylation of amines and indoles. With the indole and 1-methyl indole nucleus we observe that under Pd-catalyzed conditions, there may have been formation of one or more of the desired products, due the complex mixture observed in the TLC plate. In

the trials with *p*-toluidine, under Cu-catalyzed conditions, 4-methyl-N-phenylaniline was obtained with 5% yield and under meta-free conditions with *t*-BuONa, the product was attained with 44 % yield. Regarding the trials with aniline, diphenylamine was isolate with 22% yield under metal free conditions.

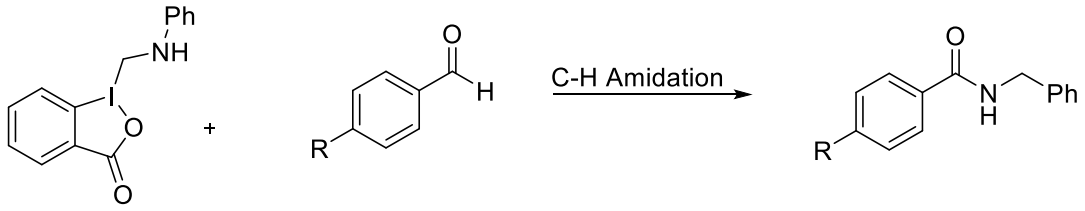
The remaining approaches fail to provide the desired products, under the tested conditions, and further investigation is required.

Regarding the novel benziodoxole derivative **40**, in the first approach to construct sulfonamides, traces of the desired product, at room temperature, under metal free catalyzed conditions were observed. Regarding the synthesis of amides from aldehydes, in the second approach, N-benzyl-4-methoxyamide was attained with 5% yield and a radicalar mechanism was proposed.

Furthermore, an one-pot approach towards 1.2-diarylazaindoles was developed involving N-arylation/Sonogashira/Cyclization reaction.

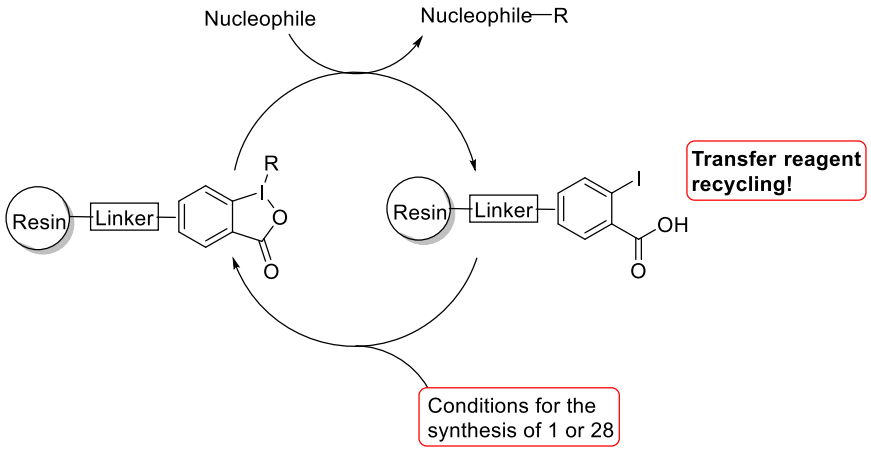
II.2.10 - Future perspectives

For the future work in this project, it is intended to optimize the reaction conditions and to fully explore the C-H amidation with 1-benzylamine-1,2-benzodioxol-3-(1*H*)-one with a variety of aldehydes to produce different amides (**Scheme II-24**).



***Scheme II-24**: Planned future work: synthesis of different amides with 1-benzylamine-1,2-benzodioxol-3-(1H)-one*

Since the reaction appears to be slow under the conditions tested and preferably forms the intermediate A, it would be interesting to perform some test under microwave radiation. Additionally, it will be interesting to immobilize **12** and **40** in a solid support and perform some tests, exploring, this way, the potential for group transfer reactions and recyclability of these reagents (**Scheme II-25**).



***Scheme II-25**: Imobilization of benziodoxole derivatives for functional group transfer.*

On a later stage, it is also intended to explore the potential to bond different amines to the iodine atom, giving rise to new benziodoxole derivatives.

Finally, it is envisioned the selective modification of amino acids and peptides. That, would be a breakthrough in the field of hypervalent iodine and allowed the development of new strategies for peptide functionalization.

It is also intended to optimize the conditions for the arylation of amine and explore the potential of 1-phenyllbenziodoxolone for amine functionalization.

Unquestionably, the future of these type of benziodoxole derivates is yet to be discovered and here we present the preliminary results of a reagent that, we believe, has an enormous hidden potential.

III. Experimental Section

III.1 - General Information

The experimental part of this work involved the use of general laboratory procedures.

All reagents and solvents were acquired commercially and used without further purification, unless otherwise mentioned. All of the mentioned solvents were, when necessary, dried using typical methods. Molecular sieves were activated by heating at 300 °C in a muffle furnace for 3h.

Analytical TLC was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Keiselgel 60GS254 silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Keiselgel 60A silica gel (70-200 mesh) and the described eluent for each case.

Melting points were measured using a Reichert Thermovar melting point apparatus, equipped with a Kofler plate. Measured melting points were not corrected.

IR spectra were acquired using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Transmittance of the sample was acquired on between 4000 and 600 cm-1 and the samples were supported on KBr pellets. The IR bands are classified as weak (w), medium (m) or strong (s), and broad (br) when such is the case.

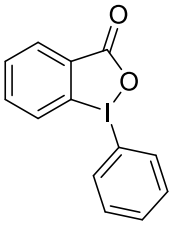
NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-RMN and ^{13}C-RMN spectra were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ or DMSO-d_6 as solvents and the corresponding trace $CHCl_3$ or DMSO as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), doublet (d), triplet (t) and multiplet (m) with coupling constant (*J*) being given in Hz.

III.2 - First Approach: Arylation with Hypervalent Iodine

III.2.1 - General procedure for the synthesis of benziodoxole derivatives

A rounded bottom flask was charged with oxone (2.6 mmol) and 2-iodobenzoic acid (4.03 mmol) and cooled with ice to 5 ºC, to which precooled H_2SO_4 (3.2 ml) was added, dropwise, via syringe. The reaction was mixed during 10 min at 5 ºC resulting in a yellow mass and then stirred at room temperature for 30 min. The mixture was cooled at 5 ºC, and CH_2Cl_2 (4 mL) and ArH (7-9 mmol) were added. The reaction mixture was stirred, at 5 ºC, during 1 h and then at room temperature for 3 h. The reaction temperature was kept at 5 ºC and CH_2Cl_2 (10 mL), and saturated aqueous solution of $NaHCO_3$ was slowly added until pH 8.0. The resulting aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried under Na_2SO_4, filtered, concentrated under vacuum. to give 602 mg of 1 as a white crystalline solid

III.2.1.1 - Synthesis of 1-phenylbenziodoxolone (12)



12

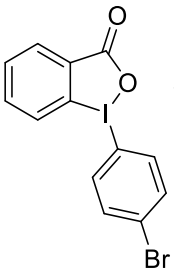
Following the previously described general procedure for the synthesis of benziodoxolone derivatives, 2-iodobenzioc acid (1 g, 4.03 mmol), oxone (1.6 g, 2.6 mmol), H_2SO_4 (3.2 mL), and benzene (8.95 mmol, 0.8 mL) was used and afford 1.05 g of **12** as a white solid.

Mp: 176 – 178 ºC

IR (KBr) ν_{max} (cm^{-1}) 3054 (w), 1608 (m, C=O), 1440 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 2H), 7.76 (s, 1H), 7.59 (s, 3H), 7.38 (t,*J*= 7.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H). Spectral data is according to the literature[51].

III.2.1.2 - Synthesis of 4-Bromophenylbenziodoxolone (38)



38

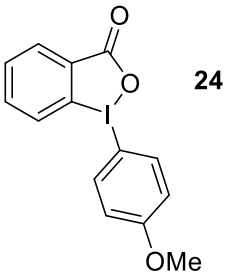
Following the previously described general procedure for the synthesis of benziodoxolone derivatives, 2-iodobenzioc acid (1 g, 4.03 mmol), oxone (1.6 g, 2.6 mmol), H_2SO_4 (3.2 mL), and bromobenzene (7.6 mmol, 0.8 ml) was used and afforded 1.3 g of **38** as a white solid.

Mp: 174 – 177 ºC

IR (KBr) ν_{max} (cm^{-1}) 3037 (m), 1607 (m, C=O), 1472 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H). Spectral data is according to the literature[51].

III.2.1.3 - Synthesis of 4-Metoxyphenylbenxiodoxolone (24)



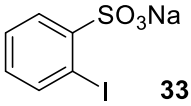
24

Following the previously described general procedure for the synthesis of benziodoxolone derivatives, 2-iodobenzioc acid (1 g, 4.03 mmol), oxone (1.6 g, 2.6 mmol), H_2SO_4 (3.2 mL), and anisole (0.96 mL, 8.86 mmol) was used and gave 314 mg of **24** as a brown solid.

IR (KBr) ν_{max} (cm^{-1}) 3082 (w), 1596 (s, C=O), 1488 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.58 (t, *J* = 7.1 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 3H).

III.2.2 - Synthesis of Sodium 2-Iodobenzenesulfonate (33)



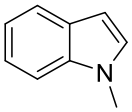
33

To a round-bottom flask with a solution 2-aminobenzenesulfonic acid (1.0 g, 5.78 mmol) in 6 mL of H_2O was added Na_2CO_3 (306 mg, 2.89 mmol). The solution was mixed for 10 min and cooled with ice to 0 ºC, then $NaNO_2$ was slowly added and the stirring continued for 30 min. To the resulting mixture concentrated HCl (1mL) was added at 0 ºC. The reaction mixture was stirred for 5 min and a solution of NaI (952 mg in 2 mL of H_2O) was then added dropwise with stirring at 0 ºC. The stirring was continued for 10 min at ºC after the end of the addition and the resulting mixture was allowed to warm to room temperature and then heated to 50 ºC for 12 h.The mixture was than refrigerated, and the insoluble component was separated. After the solid was treated with boiling EtOH (some Et_2O), the mixture was cooled to separate the insoluble solid, that was later washed with cold EtOH and Et_2O to isolate **33** as brown solid.

IR (KBr) ν_{max} (cm^{-1})**:**

^{1}H NMR (400 MHz, DMSO) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.4Hz, 1H).

III.2.3 - Synthesis of 1-methylindole (17)



17

To a dry round bottom flask with a solution of indole (500 mg, 4.27 mmol) in THF (12.8 mL) at 0 ºC was added NaH (150mg, 60 % dispersion in mineral oil, 6.4 mmol). The reaction mixture was stirred, under inert atmosphere, for 30 min at 0 ºC and 1 h at room temperature. The reaction was cooled at 0 ˚C and iodomethane (345 µL, 5,6 mmol) was added, after which the reaction mixture was allowed to warm to room temperature. After 1 h of stirring the reaction mixture was cooled at 0 ˚C and saturated NH_4Cl (20 mL) was added, and the resulting mixture extracted with ether (4 x 10 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford a greenish oil. The obtained oil was purified by flash chromatography (eluent: petroleum ether/EtOAc 10:1) to give 478 mg of **17** as a colorless oil.

IR (KBr) ν_{max} (cm^{-1})**:** 3050 (s), 2923 (m), 1512 (m), 1465(s), 1323(s),

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 3H). Spectral data is according to the litearture[101].

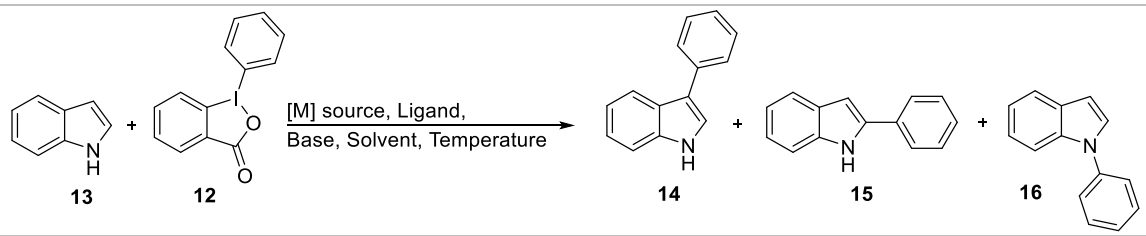
III.2.4 - General procedure for the arylation of heterocycles.

A dried round-bottom flask was charged with the catalyst and 1-phenylbenziodoxolone (1.2 equiv.). To the vessel was added the correspondent solvent, previously dried, (volume to make a 0.1 M solution of the substrate) and the indole. The solution was stirred under inert atmosphere at room temperature or reflux.

III.2.4.1 - Arylation of Indole

Following the previously general procedure several experiments were carried out envisaging the arylation of the indole nucleus (**Table 1**).

Table III-1**: Conditions of the experiments made with indole **13** and 1-phenylbenziodoxolone **12.



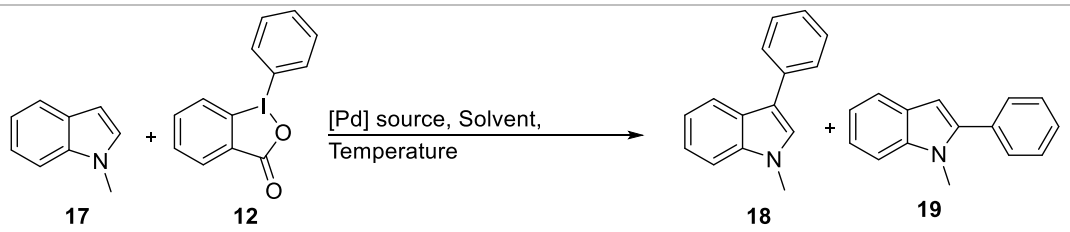
Entry	Starting Material Mass (mg)	Catalyst (mol%)	Base (equiv)	Solvent	Temperature	Time (h)	Observations
1[c]	50		-	MeOH	rt	72	Unreacted starting material
2[c]	50	CuI (10)	-	MeOH	rt	72	Unreacted starting material
3[c]	50	$Cu(OAc)_2$ (10)	DMEDA (1.3)	Toluene	reflux	76	Unreacted starting material
4[a,b]	80	$Pd(OAc)_2$ (10)	Cs_2CO_3 (1.3)	Toluene	reflux	72	Complex mixture
5[a]	80	$Pd(Allyl)Cl_2$ (10)	-	DCM/H_2O (98:2)	rt	48	Complex mixture
6[c]	50	$InCl_3$ (10)	-	Toluene	reflux	56	Unreacted starting material-
7[c]	50	$InCl_3$ (10)	-	ACN	reflux	72	Unreacted starting material

a– Experiment made with 3 equiv. of **12**; **b**– Experiment made in the presence of BINAP (20 mol%);.**c**– Experiment made with **12**

III.2.4.2 - Arylation of 1-methylindole

Following the previously general procedure several experiments were carried out envisaging the arylation of 1-methylindole (**Table III-2**).

***Table III-2**: Conditions of the experiments made with 1-methylindole **17** and 1-phenylbenziodoxolone **12**.*



17 12 18 19

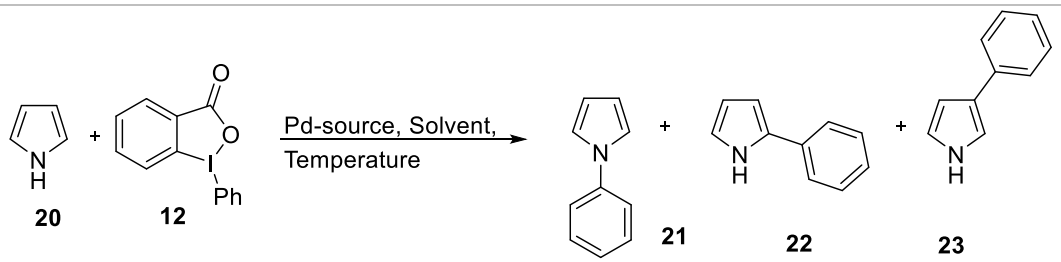
Entry	Starting Material Mass (mg)	Catalyst (mol%)	Solvent	Temperature	Time (h)	Observations
1[a]	80	$Pd(Allyl)Cl_2$ (10)	DCM/H_2O (98:2)	rt	42	Complex mixture -
2[a]	80	$Pd(Allyl)Cl_2$ (2)	DCM/H_2O (98:2)	rt	44	Complex mixture -
3[a]	80	$Pd(Allyl)Cl_2$ (10)	Toluene	reflux	42	Complex mixture -
4[a]	80	$Pd(Allyl)Cl_2$ (2)	Toluene	reflux	48	Complex mixture -

a– Experiment made with 3 equiv. of **12**.

III.2.4.3 - Arylation of Pyrrole

Following the previously general procedure for the arylation of heterocycles, we made one experiment with pyrrole (**Table III-3**).

***Table III-3**: Conditions of the experiments made pyrrole **20** and 1-phenylbenziodoxolone **12**.*



20 12 21 22 23

Entry	Starting Material Mass (mg)	Catalyst (mol%)	Solvent	Temperature	Reaction time (h)	Observations
1[a]	100	$Pd(Allyl)Cl_2$ (10)	Toluene	reflux	20	Unreacted starting material

a– Experiment made with 3 equiv. of pyrrole.

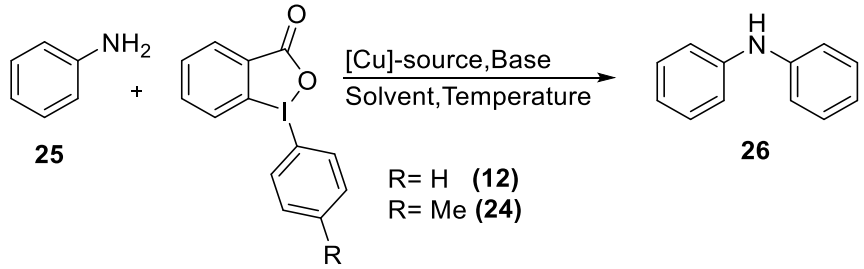
III.2.5 - General procedure for the arylation of amines

A round-bottom flask was charged with the correspondent benziodoxole derivative (1-1.2 equiv.), catalyst (10-20 mol %) and dry solvent (volume to make a 0.2 M solution of substrate). The mixture was stirred for 10 min and the correspondent amine (1-2 equiv.) was added. The reaction was mixed (time and temperature of the reactions are indicated in the following tables). The resulting mixture was diluted with AcOEt and washed with saturated aqueos $NaHCO_3$ and separated. The organic phase was dried under Na_2SO_4 and concentrated under vacuum. The crude product was purified by PTLC.

III.2.5.1 - Arylation of aniline

Following the previously general procedure for the arylation of amines a few experiments were performed envisioning the arylation of aniline (**Table III-4**).

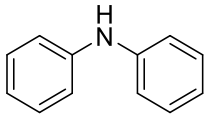
***Table II-4**: Conditions of the experiments made with aniline **25** and 1-phenylbenziodoxolone **12**.*



Entry	Starting Material Mass (mg)	Catalyst (mol %)	Solvent	Temperature	Time(h)	Observations/Yield of 26 (%)
1	50	-	THF	reflux	26	Unreacted starting material
2[a]	80	$Cu(OAc)_2$ (20)	THF	reflux	20	Unreacted starting material
3[b]	80	$Cu(OAc)_2$ (20)	THF	reflux	20	Unreacted starting material
4[a.c]	80	-	THF	reflux	18	22%

a- R=H; **b**- R= Me; **c**- Prior the addition of **12** a solution of aniline and *t*-BuOK (3equiv.) in THF was stirred for 10 min. at 0 ºC.

III.2.5.1.1- Synthesis of diphenylamine (26)



26

Following the general procedure for the arylation of amines, the conditions presented in entry 4 of table III-4 afforded **26** as a white solid. The crude was purified by PTLC with 3 elutions in 8:2 hexane/ethyl acetate.

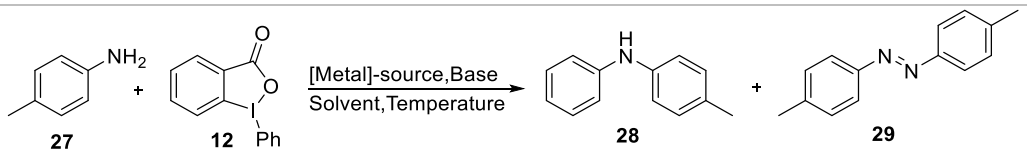
IR (NaCl) ν_{max} (cm^{-1}) 3397 (s, N-H), 3298 (m), 2915 (m), 1590 (s), 1324 (m), 751 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 6H), 7.09 (d, *J* = 7.7 Hz, 4H), 6.94 (t, *J* = 7.3 Hz, 2H), 5.7 (s, 1H). Spectral data is according with the literature[102].

III.2.5.2 - Arylation of *p*-toluidine

Following the previously general procedure for the arylation of amines a few experiments were performed envisioning the arylation of p-toluidine (**Table III-5**).

***Table III-5**: Conditions of the experiments made with p-toluidine **27** and 1-phenylbenziodoxolone **12**.*



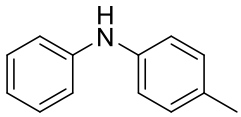
27 **12** **28** **29**

Entry	Starting Material Mass (mg)	Catalyst (mol%)	Solvent	Temperature	Time (h)	Observations/ Yield 28 (%)
1[a]	50	-	THF	rt to reflux	20	-Formation of **29**
2[a,b]	50	-	THF	reflux	24	-Complex mixture
3[a]	80	$Cu(OAc)_2$ (20)	THF	reflux	72	5
4[a]	80	$Cu(OAc)_2$ (20)	THF(degassed)	reflux	26	3
5[a]	80	$Cu(OAc)_2$ (100)	THF	reflux	28	Unreacted starting material
6[a]	100	AgOH (20)	THF	reflux	22	Unreacted starting material

7[a]	80	$Cu(OAc)_2$ (20)	DMF	rt to reflux	26	Unreacted starting material
8[a]	80	$Cu(OAc)_2$ (10)	THF	reflux	20	Unreacted starting material
9[a]	80	CuI (10)	THF	reflux	20	Unreacted starting material -
10[a]	80	$(CuOAc)_2$ (20)	Toluene	reflux	18	Unreacted starting material -
11[a,c]	40	-	THF	reflux	20	44

a– Experiment made in the presence of **12**; **b**– Experiment made in the presence of *t*-BuOK (3equiv.); **c**– Experiemnt made in the presence of *t*-BuONa (3equiv.).

II.2.5.2.1 - Synthesis of 4-methyl-N-phenylaniline (28)



28

Following the general procedure for the arylation of amines, the conditions presented in entries 3, 4 and 11 afforded **28** as a yellow oil. The crude was purified by PTLC with 2 elutions in 5:1 hexane/ethyl acetate.

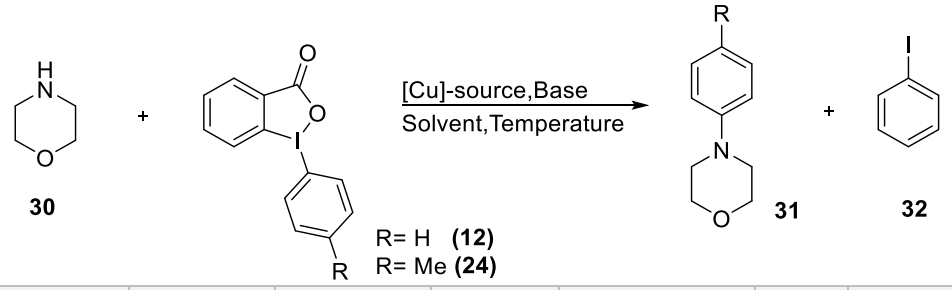
IR (NaCl) ν_{max} (cm^{-1}) 3396 (m, N-H), 3037 (m), 2345 (m), 1592 (s), 1376 (m), 1091 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.7 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.04 – 6.98 (m, 4H), 6.89 (t, *J* = 7.2 Hz, 1H), 5.60 (s, 1H), 2.30 (s, 2H). Spectral data is according with the literature[103]

III.2.5.3 - Arylation of morpholine

Following the previously general procedure for the arylation of amines a few experiments were carried out envisioning the arylation of morpholine (**Table III-6**).

***Table III-6**: Conditions of the experiment made with morpholine **30** and 1-phenylbenziodoxolone **12** or 4-metoxyphenylbenziodoxolone **24**.*



Entry	Starting Material Mass (mg)	Catalyst (mol%)	Base (equiv.)	Solvent	Temperature	Time (h)	Observations
1[a,d]	80	$Cu(OAc)_2$ (20)	-	THF	rt to reflux	62	Unreacted starting material
2[a,b]	80	$Cu(OAc)_2$ (20)	-	THF	rt to reflux	20	Unreacted starting material
3[d]	80	$Cu(OAc)_2$ (20)	-	THF	reflux	22	Unreacted starting material-
4[d]	50	$Cu(OAc)_2$ (20)	*t*-BuONa (3)	Toluene	reflux	20	Complex mixture-
5[c,d]	50	$Cu(OAc)_2$ (20)	*t*-BuONa (3)	Toluene	reflux	18h	Decomposition of benziodoxole
6[d]	80	CuI (20)	-	THF	reflux	22	Unreacted starting material
7[d]	80	CuI (20)	TEA (1)	THF	rt	22	Unreacted starting material
8[d]	80	CuI (20)	TEA (1)	MeOH	reflux	24	Unreacted starting material/ Fomation of **32**
9[d]	80	CuI (20)	TEA (1)	$CHCl_3$	reflux	24	Unreacted starting material/ Formation of **32**

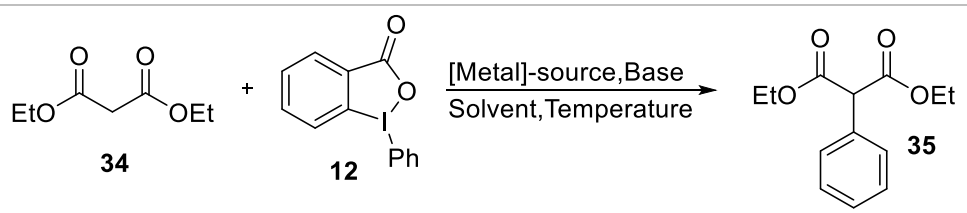
10[d]	80	$Cu(OAc)_2$ (20)	TEA (1)	$CHCl_3$	reflux	22	Unreacted starting material

a- 2 equiv. of morpholine **30**; **b** - experiment made with 4-methoxyphenylbenziodoxolone **24**; **c**- Experiment in the absence of morpholine **30**; **d**– Experiment made with **12**.

III.2.6 - General procedure for the α-arylation of diethyl malonate.

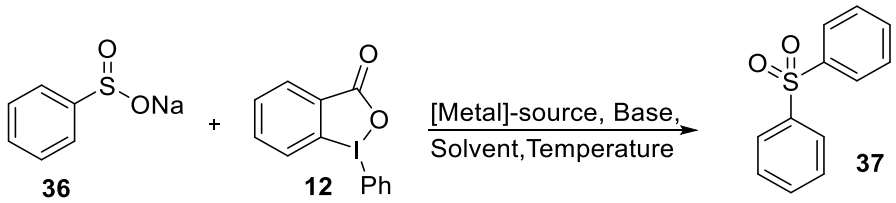
A rounded bottom flask was charged with diethyl malonate, base (3 equiv.), catalyst (10 mol %) and dry solvent (volume to make a 0.2 M solution of substrate). The mixture was stirred for 30 min. under inert atmosphere at room temperature and then 1-phenylbenziodoxolone (1.2 equiv.) was added. After the designated time (**Table III-7**) the reaction mixture was filtered under celite and purified by PTLC.

Table III-7*: Conditions of the experiment made with diethyl malonate **34** and 1-phenylbenziodoxolone **12**.*



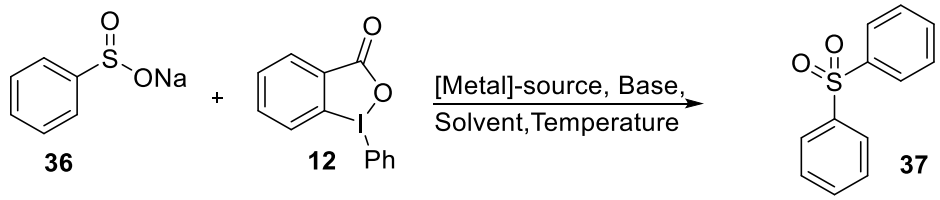
Entry	Starting Material Mass (mg)	Catalyst (mol%)	Base (equiv.)	Solvent	Temperature	Time (h)	Observations
1	100	CuI (10)	Cs_2CO_3 (3)	$CHCl_3$	reflux	32	Unreacted starting material
2	100	-	Cs_2CO_3 (3)	$CHCl_3$	rt	30	Unreacted starting material
3	100	CuI (10)	NaH (1)	$CHCl_3$	reflux	28	Unreacted starting material
4	100	-	NaH (1)	$CHCl_3$	reflux	30	Unreacted starting material
5	80	$Zn(OTf)_2$ (5)	-	$CHCl_3$	reflux	30	Unreacted starting material

III.2.7 - General Procedure for the arylation of Sodium benzenesulfinate



A round-bottom flask was charged with sodium benzenesulfinate, TBAI (20 mol %), the correspondent benziodoxolone (1.2 equiv.) derivative and solvent (volume to make a 0.2 M solution of substrate). The reaction time and temperature of each experiment are given in **Table III-8**.

***Table III-8**: Conditions of the experiments made with sodium benzenesulfinate **36** with 1-phenylbenziodoxolone **12** or 4-bromophenylbenziodoxolone **38**.*

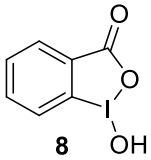


Entry	Starting Material Mass (mg)	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	Solvent	Temperature	Time (h)	Observations
1[a]	100	-	-	-	DCM	rt	36	Unreacted starting material
2[a]	100	-	-	-	Toluene	reflux	30	Unreacted starting material
3	100	-	-	-	DMF	90 ºC	42	Unreacted starting material
4	80	-	-	-	$CHCl_3$	reflux	32	Unreacted starting material
5[a]	80	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	rt	48	Complex mixture -
6	80	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	reflux	42	- Complex mixture

7	80	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	$CHCl_3$	rt	36	- Complex mixture
8	80	$Pd_2(dba)_3$ (2.5)	BINAP (5)	Cs_2CO_3 (1.5)	Toluene	reflux	40	Complex mixture -
9[b]	80	$Pd_2(dba)_3$ (2.5)	XantPhos (5)	Cs_2CO_3 (1.5)	Toluene	rt	32	Decomposition of **12**-

a- Experiment made with 4-bromophenylbenziodoxolone **38**; **b**- Experiment made in the absence of sodium benzenesulfinate.; **c**- Experiment made with 1-phenylbenziodoxolone **12**

III.2.8 - Synthesis of 1-hydroxy-1,2-benzodioxol-3-(1*H*)-one (8)



8

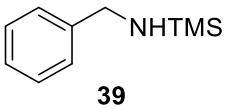
To rounded bottom flask charged with 2-iodobenzoic acid (2 g, 8.06 mmol) and sodium periodate (1.81 g, 8.47 mmol) an aq. solution (40 mL) of 30% (v:v) acetic acid was added. The reaction mixture was protected from the light and stirred at reflux for 4 h. The reaction was then diluted with cold water (40 mL) and was allowed to cool to rt. The crude was filtered, washed with cold water (4 x10 mL) and acetone (4 x 10 mL) and air dried to give 2 g of **8** as a white solid.

Mp: 233- 235 ºC

IR (NaCl) ν_{max} (cm^{-1}) 2286 (b, O-H), 2416 (m), 1605 (s, C=O), 1440 (m)

^{1}H NMR (400 MHz, DMSO) δ 8.06 – 7.98 (m, 2H), 7.95 (t, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H)

III.2.9 - Synthesis of N-Benzyltrimethylsilylamine (39)

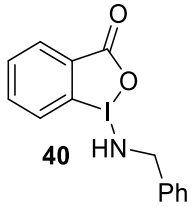


39

To a rounded bottom flask charged with benzylamine (0,18 mol, 19,4 mL), hezamethyldisilazane (0,098 mol, 20.5 mL) one drop oh H_2SO_4 was added and the reaction mixture was stirred at 130 ºC for 12 h. The reaction crude was purified by reduced pressure distillation to afford 24.4 g of **39** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 3.90 (s, 2H), 0.12 (m, 7H).

III.2.10 - Synthesis of 1-benzylamine-1,2-benzodioxol-3-(1*H*)-one (40)



40

To a rounded bottom flask charged with **8** (100 mg, 0.38 mmol) and ACN (3,8 mL) was added **39** (143 mg, 0.76 mmol). The reaction mixture was stirred for 4 h. at room temperature. The reaction crude was filtered and washed with acetone (4 x 15 mL) and air dried to afford 100 mg of **40** as a white crystalline solid.

Mp: 109 – 111 ºC

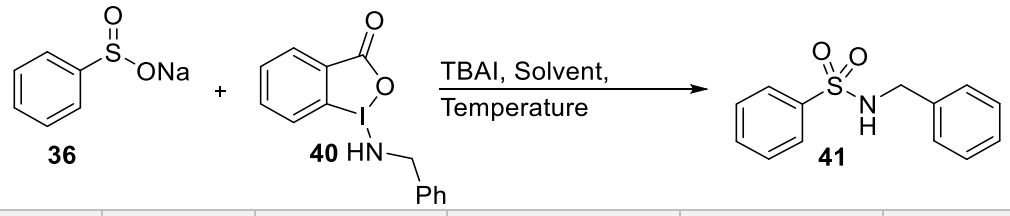
IR (NaCl) ν_{max} 3200 (N-H, m), 2980 (Ar-H, w), 1600 (C=O, s), 1496 (C=C, s), 1378 (C=C, s)

^{1}H NMR (400 MHz, DMSO) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 7.1 Hz, 1H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.40 (m, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 5.83 (t, *J* = 5.9 Hz, 1H), 4.47 (d, *J* = 5.9 Hz, 2H).

III.2.11 - General procedure for the synthesis of sulfonamides.

A round-bottom flask was charged with sodium benzenesulfinate (1.5 equiv), TBAI (20 mol %), **40** and solvent (volume to make a 0.2 M solution of substrate). The crude was filtered under celite and purified by PTLC in 3:7 ethyl acetate/hexane.

***Table III-9**: Conditions of the experiments made with sodium benzenesulfinate **36** and 1-benzylamine-1,2-benzodioxol-3-(1H)-one **40**.*



36 **40** **41**

Entry	Starting Material Mass (mg)	Solvent	Temperature	Time (h)	Observations
1	80	DCM	rt	22	Unreacted starting material
2	80	DCM	reflux	18	Unreacted starting material

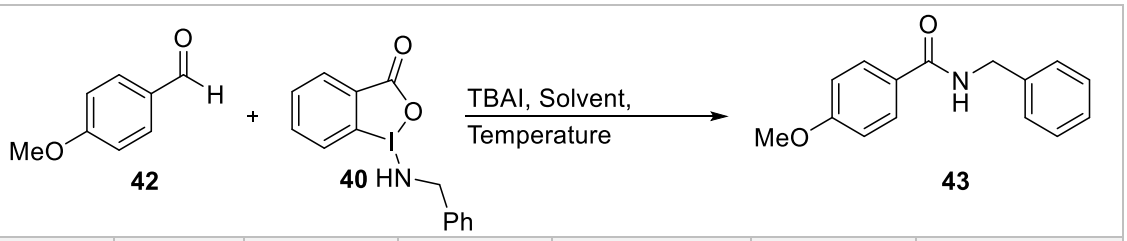
3	80	ACN	reflux	22	Unreacted starting material
4	100	ACN	-40 ºC to rt	30	Unreacted starting material
5[a]	80	DCM	rt	28	Unreacted starting material

a- Experiment made with 4-bromophenylbenziodoxolone **38**; **b**- Experiment made in the absence of sodium benzenesulfinate; **c**- Experiment made with 1-phenylbenziodoxolone.

III.2.12 - General procedure for the synthesis of N-benzyl-4-methoxybenzamide.

To A round-bottom flask charged with **40** (1.2 equiv.), solvent (volume to make a 0.2 M solution of substrate) and TBAI (0.1-1 equiv.), *p*-methoxybenzaldehyde was added. The crude was filtered under celite and purified by PTLC in 3:7 ethyl acetate/hexane.

Table III-10*: Conditions of the experiments made with p-methoxybenzaldehyde* ***42*** *and 1-benzylamine-1,2-benzodioxol-3-(1H)-one* ***40****.*

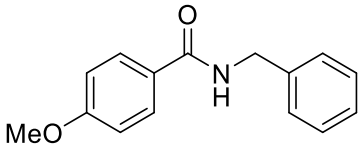


Entry	Starting Material Mass (mg)	TBAI (equiv.)	Solvent	Temperature	Reaction time (h)	Observations/ Yield 32 (%)
1	80	0.1	DCM	rt	72	3
2	80	1	DCM	rt to reflux	74	-Unreacted starting material
3	80	-	DCM	rt to reflux	74	-Unreacted starting material
4	80	1	ACN	reflux	144	-Unreacted starting material
5	80	0.1	ACN	reflux	120	5
6[a]	80	1	ACN	reflux	46	-Unreacted starting material

7[b]	80	1	ACN	reflux	48	Absence of **43**

a- experiment made in the absence of *p*-methoxybenzaldehyde and **40**;.**b** - experiment made in the presence of TEMPO (1 equiv.)

III.2.12.1 - Synthesis of N-benzyl-4-methoxybenzamide (43)



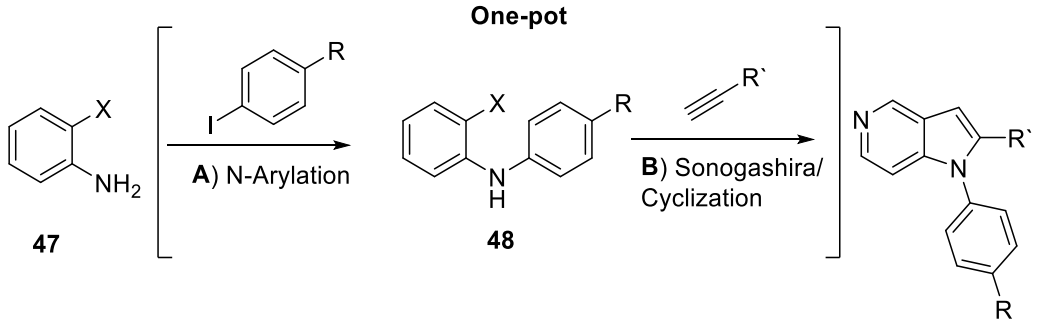
43

Following the previously general procedure for the synthesis of N-benzyl-4-methoxybenzamide, *p*-methoxyaldehyde (44.7 µl, 0 37 mmol), TBAI (13.6 mg, 0.1 mmol), **40** (155.6 mg, 0.44 mmol) and ACN (1.9 mL) were used and afford 5 mg of **43** as a white solid.

IR (NaCl) ν_{max} (cm^{-1}) 3062 (N-H, m), 2893(m), 2852 (m), 1608 (C=O, s), 1550 (s), 1452 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 1H), 7.36 (m, 5H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.64 (d, *J* = 5.5 Hz, 1H), 3.85 (s, 1H). Spectral data is according to the literature[104].

III.2.13 – General procedure for the one-pot synthesis of 1,2-disubstituted azaindoles.



A) A sealed tube equipped with a magnetic stir bar was charged with $Pd_2(dba)^3$ (4 mol %, 42.34 mg, 0.04 mmol), XantPhos (8 mol %, 53.51 mg, 0.092 mmol), *t*-BuONa (2 equiv, 222.2 mg, 2.31 mmol) and amino-*o*-bromopyridine (**47**) (1 equiv, 200 mg, 1.16 mmol). The tube was sealed with a suba-seal, evacuated and backfilled with N_2 thrice, then dry toluene (C = 0.2 M, 5.8 mL) was added, followed by the aryl iodide (1.2 equiv, 158.67 µL, 1.39 mmol), and the tube sealed under N_2. The reaction was stirred for 6 hours at 110 ºC. The crude reaction product (**48**) was concentrated and vacuum dried.

B) DMF was previously degassed 7 times by applying vacuum when the mixture is completely frozen and then flushed with N_2.

Three solutions were prepared with the degassed DMF and the solids were dried under vacuum before DMF addition:

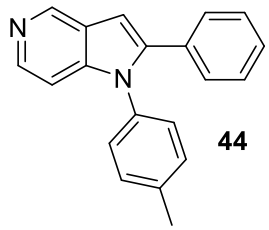
Solution A – A round-bottom flask was charged with the crude product 7 (1 equiv, 287.97 mg, 1.16 mmol), DIPEA (3.2 equiv, 644.35 µL, 3.7 mmol) and DMF (2.4 mL) and the final solution degassed thrice.

Solution B – A round-bottom flask was charged with CuI (5 mol %, 11.01 mg, 0.058 mmol), PdCl2(PPh3)2 (3 mol %, 4.87 mg, 0.035 mmol) and DMF (2.4 mL) and the final solution degassed twice.

Solution C – A round-bottom flask was charged with phenylacetylene (2.1 equiv, 266.6 µL, 2.43 mmol) and DMF (4.8 mL) and the final solution degassed thrice.

To solution B, solution A was added via syringe, then degassed twice; and finally, solution C. The mixture was degassed one more time and then allowed to warm up to 110 ºC and stirred for 24 h. Toluene was added to the residue and washed thrice with water, then sat. NH_4Cl. The combined aqueous layers were then washed with toluene to take off remain product. Combined organic layers were dried with anhydrous sodium sulphate, filtered and concentrated. The desired product was isolated after purification by chromatography.

III.2.13.1 - Synthesis of 2-Phenyl-1-(*p*-tolyl)-5-azaindole (44)



44

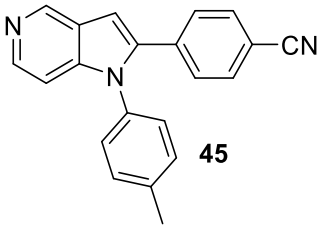
Following the general procedure for the preparation of 1,2-disubstituted indoles, 40.7 mg, 0.14 mmol of **44**, as a brown oil, was obtained from 40 mg, 0.23mmol of the starting 4-amino-3-bromopyridine. The crude was purified by PTLC using EtOAc/hexane (1:1) followed by PTLC using EtOAc/hexane (1:2).

IR (NaCl) ν_{max} (cm^{-1}) 3037, 2926, 2852, 1597, 1514, 1463

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.28 (d, *J* = 5.8 Hz, 1H), 7.26 – 7.20 (m, 7H), 7.15 (d, *J* = 5.8 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.83 (s, 1H), 2,40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 142.7, 142.0, 141.6, 137.9, 134.8, 130.2, 131.8, 129.1, 128.4, 128.0, 127.5, 125.2, 105.9, 102.4, 21.3.

2.13.2 – Synthesis of 4-(2-Benzonitrile)-1-(*p*-tolyl)-5-azaindole (45)



45

Following the general procedure for the preparation of 1,2-disubstituted indoles, 12.5 mg, 0.04 mmol of **45**, as a pale yellow solid, was obtained from 30 mg, 0.17 mmol of the starting 4-amino-3-bromopyridine. The crude was purified by PTLC using EtOAc/hexane (1:1) followed by PTLC using EtOAc/hexane (2:1).

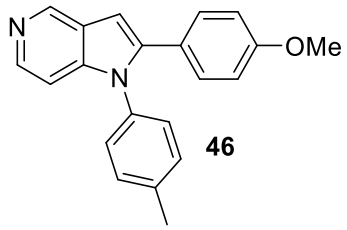
Mp: 127-130 °C

IR (NaCl) ν_{max} (cm^{-1}) 3042, 2923, 2853, 2225, 1512, 1457

^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.96 (s, 1H), 8.26 (d, *J* = 5.1 Hz, 1H), 7.49 (d, *J* = 8.04 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 5.8 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.92 (s, 1H), 2.37 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 143.3, 141.4, 138.9, 135.9, 134.2, 132.3, 130.7, 129.3, 128.7, 127.3, 124.8, 118.6, 111.7, 106.4, 104.4, 21.3

2.13.3 – Synthesis of 2-(4-Methoxyphenyl)-1-(*p*-tolyl)-5-azaindole (46)



46

Following the general procedure for the preparation of 1,2-disubstituted indoles, 32.7 mg, 0.1 mmol of **46**, as a yellow oil, was obtained from 40 mg, 0.23 mmol of the starting 4-amino-3-bromopyridine. The crude was purified by PTLC using EtOAc/hexane (1:1) followed by PTLC using EtOAc/hexane/EtOH (5:5:0.5).

IR (NaCl) ν_{max} (cm^{-1}) 3041, 2926, 2833, 1607, 1500, 1459, 1255

^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.89 (s, 1H), 8.19 (d, *J* = 5.84 Hz, 1H), 7.19 – 7.08 (m, 6H), 7.03 (d, *J* = 8.08 Hz, 1H), 6.74 – 6.71 (m, 3H), 3.72 (s, 3H), 2.34 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 142.7, 140.8, 140.5, 137.4, 134.7, 130.4, 130.3, 127.8, 127.5, 125.2, 124.0, 113.9, 106.0, 101.5, 55.4, 21.3

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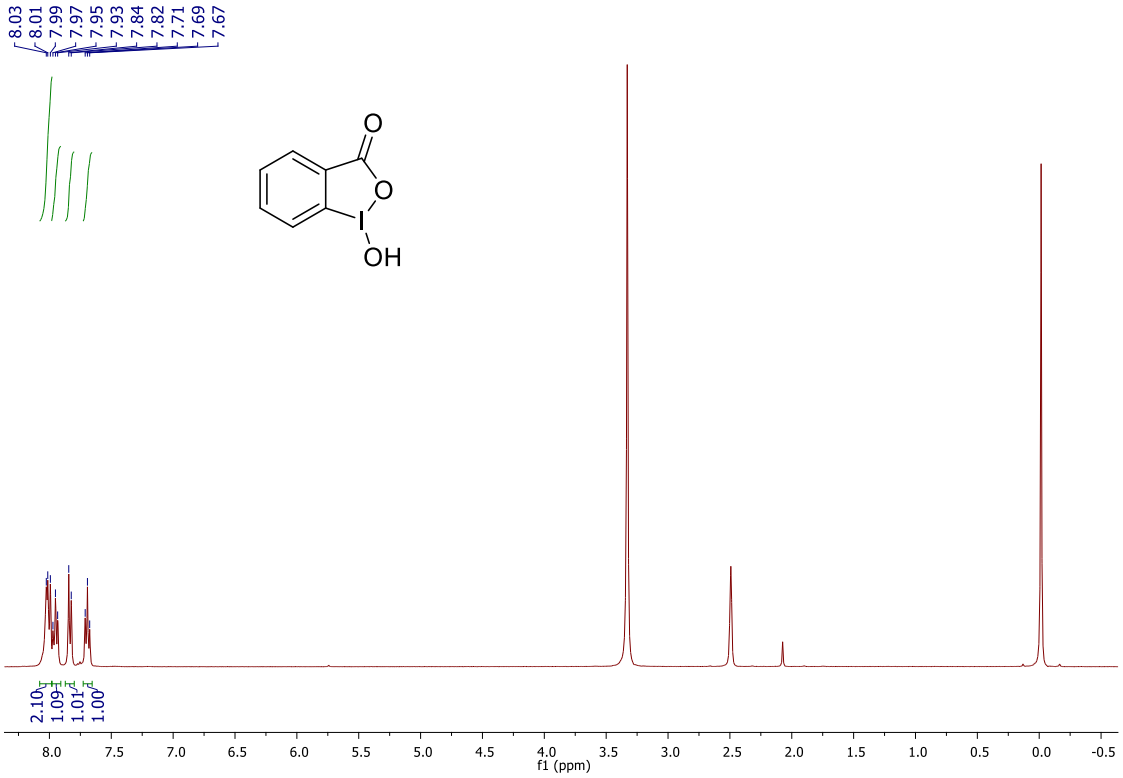
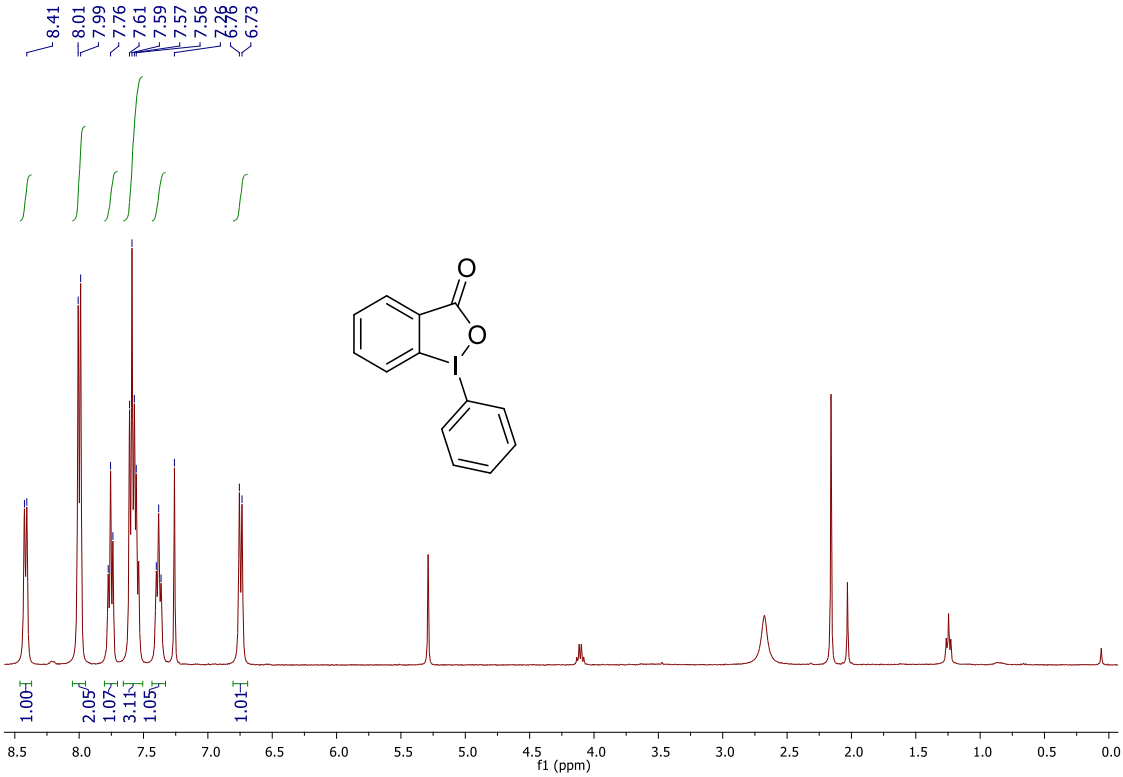
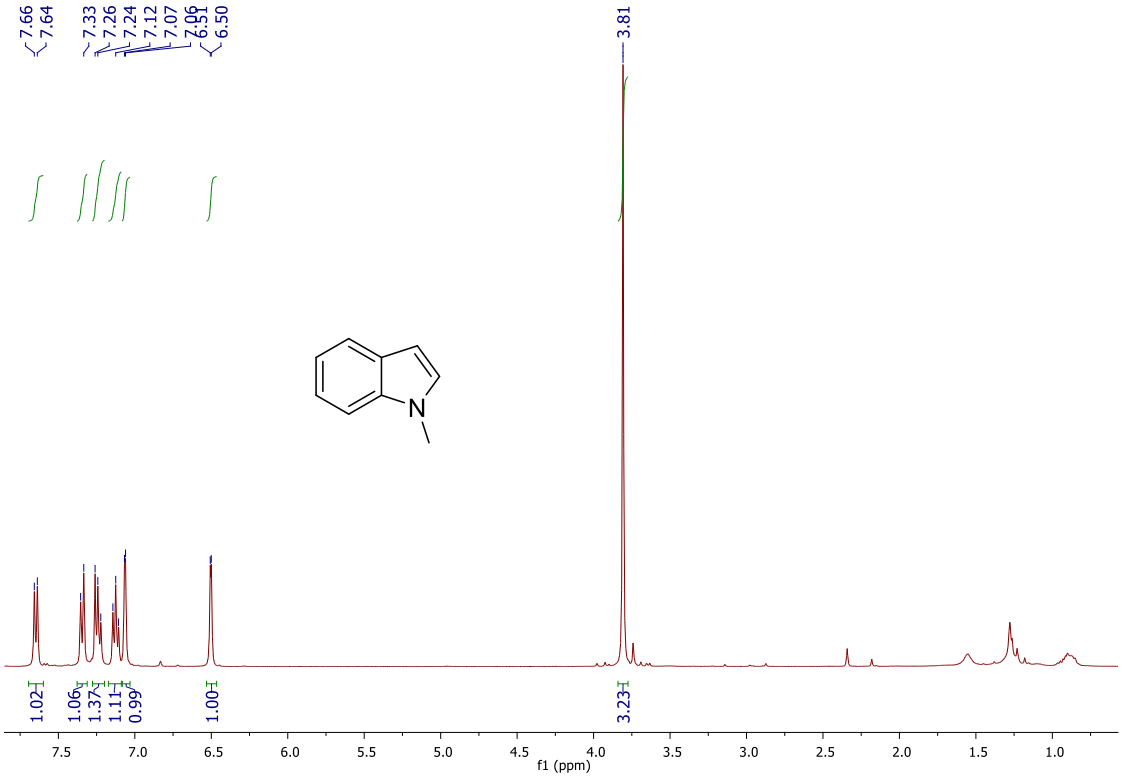
Appendix



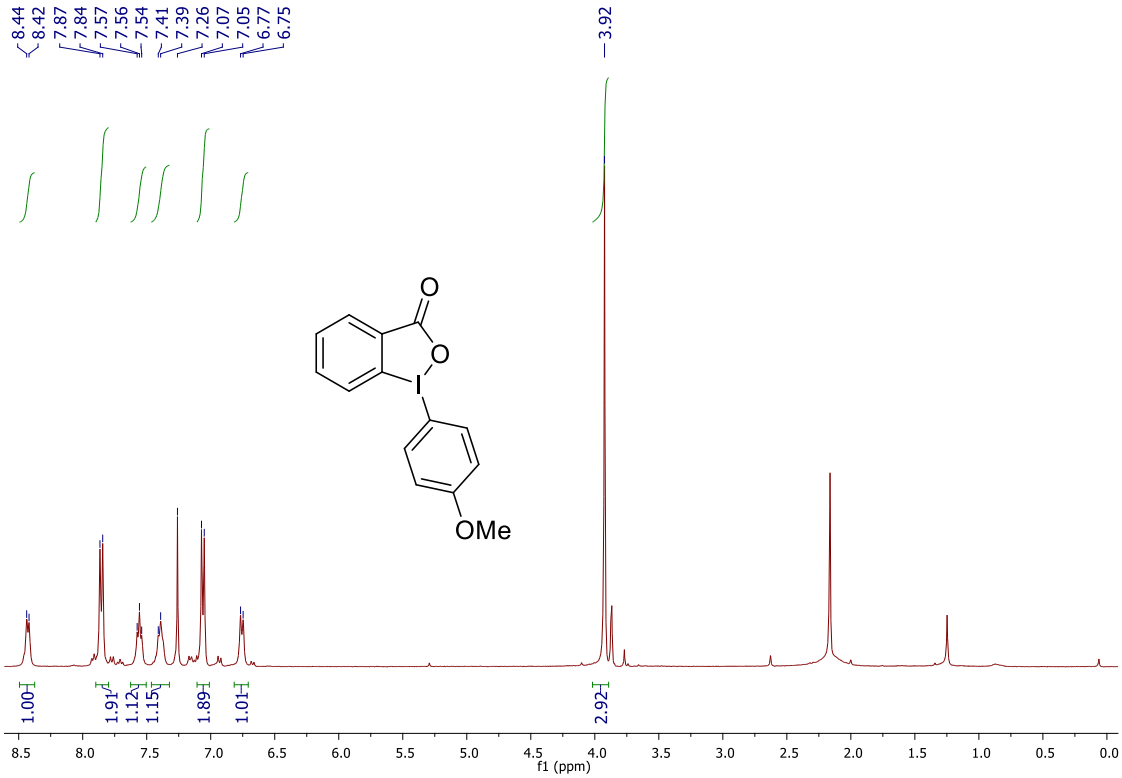
Spectrum 1 *- ^{1}H-NMR spectrum of 1-Hydroxy-1,2-benziodoxole-3-(1H)-one (**8**).*



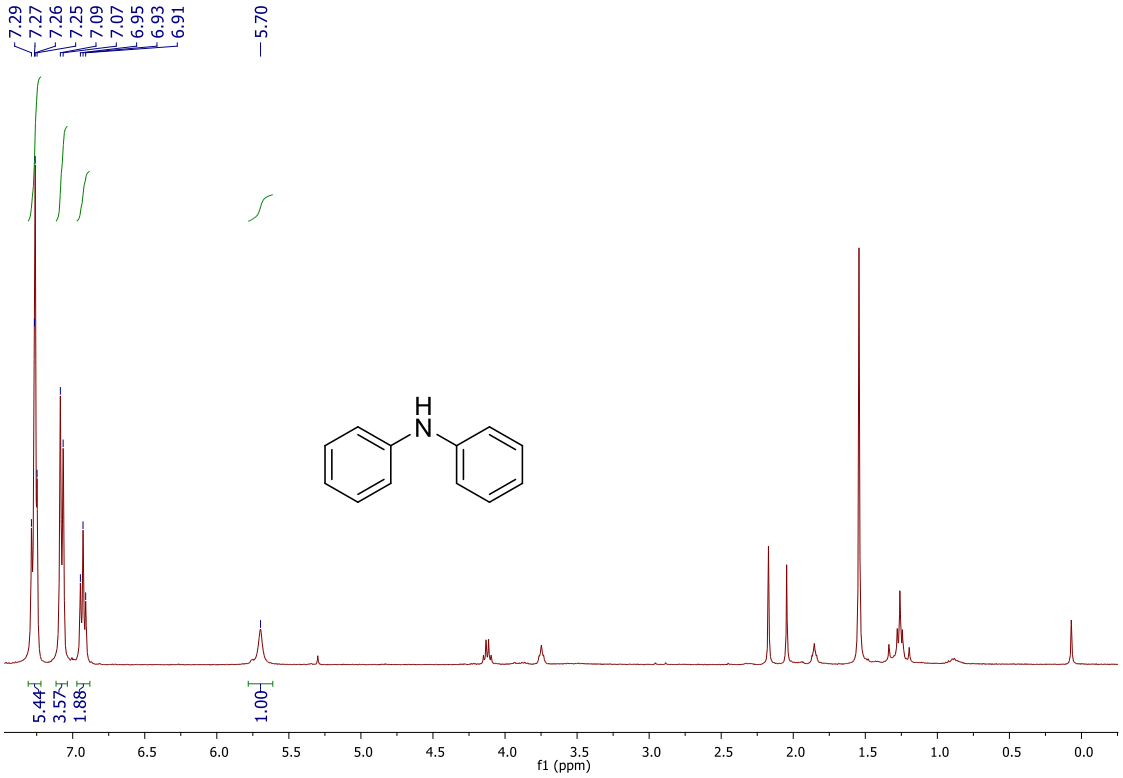
Spectrum 2 *- ^{1}H-NMR spectrum of 1-phenylbenziodoxolone (**12**).*



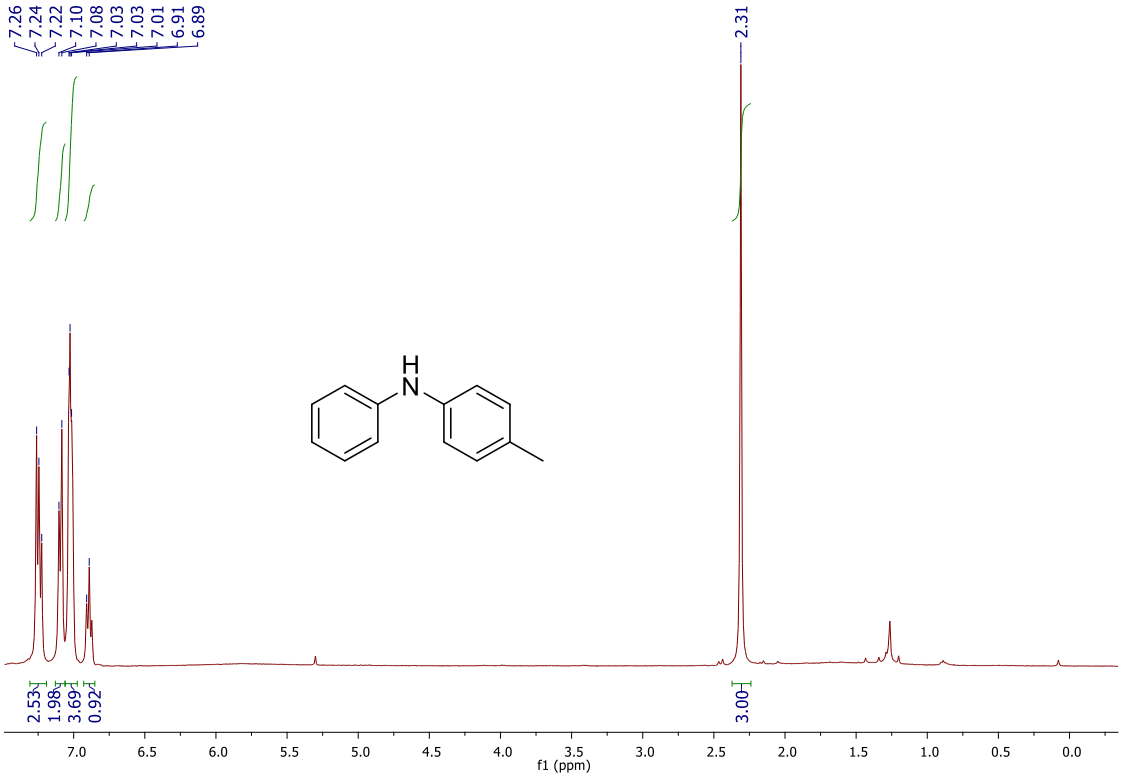
Spectrum 3 *- ^{1}H-NMR spectrum of 1-Methylindole (**17**).*



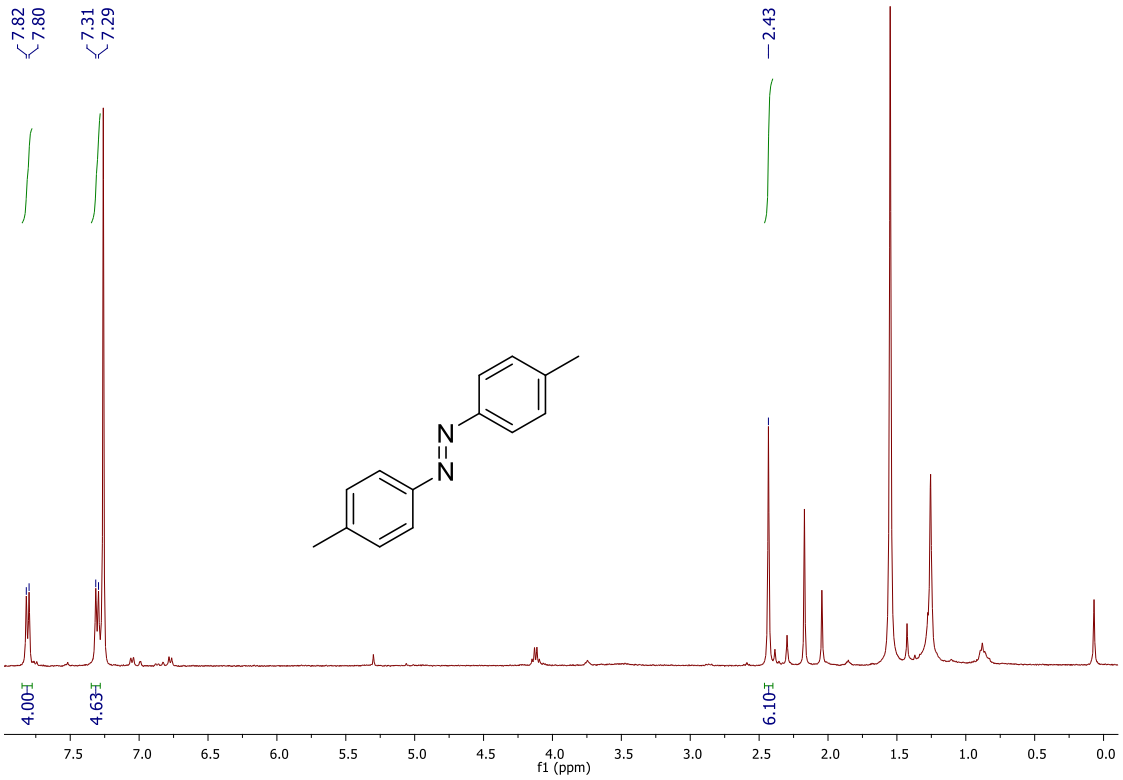
Spectrum 4 *- ^{1}H-NMR spectrum of 4-methoxyphenylbenziodoxolone (**24**).*



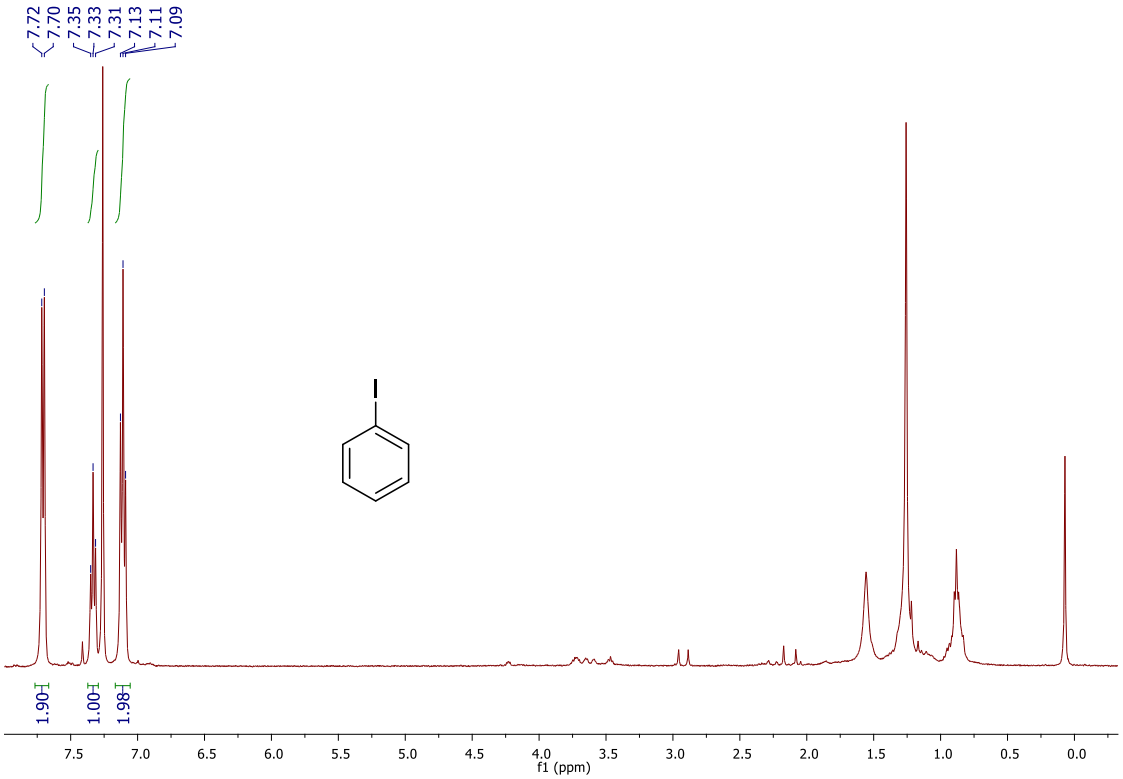
Spectrum 5 *- ^{1}H-NMR spectrum of diphenylaniline (**26**).*



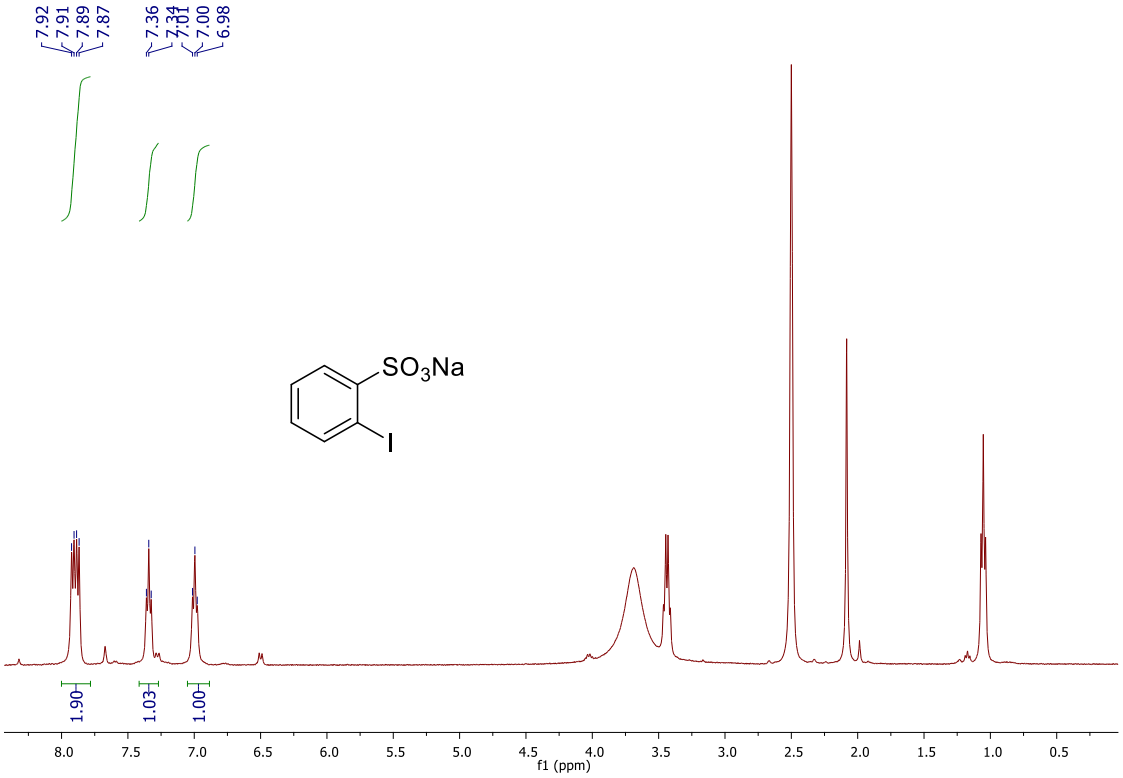
Spectrum 6 *- ^{1}H-NMR spectrum of 4-methyl-N-phenylaniline (**28**).*



Spectrum 7 *- ^{1}H-NMR spectrum of 4,4`-dimethylazobenzene (**29**).*

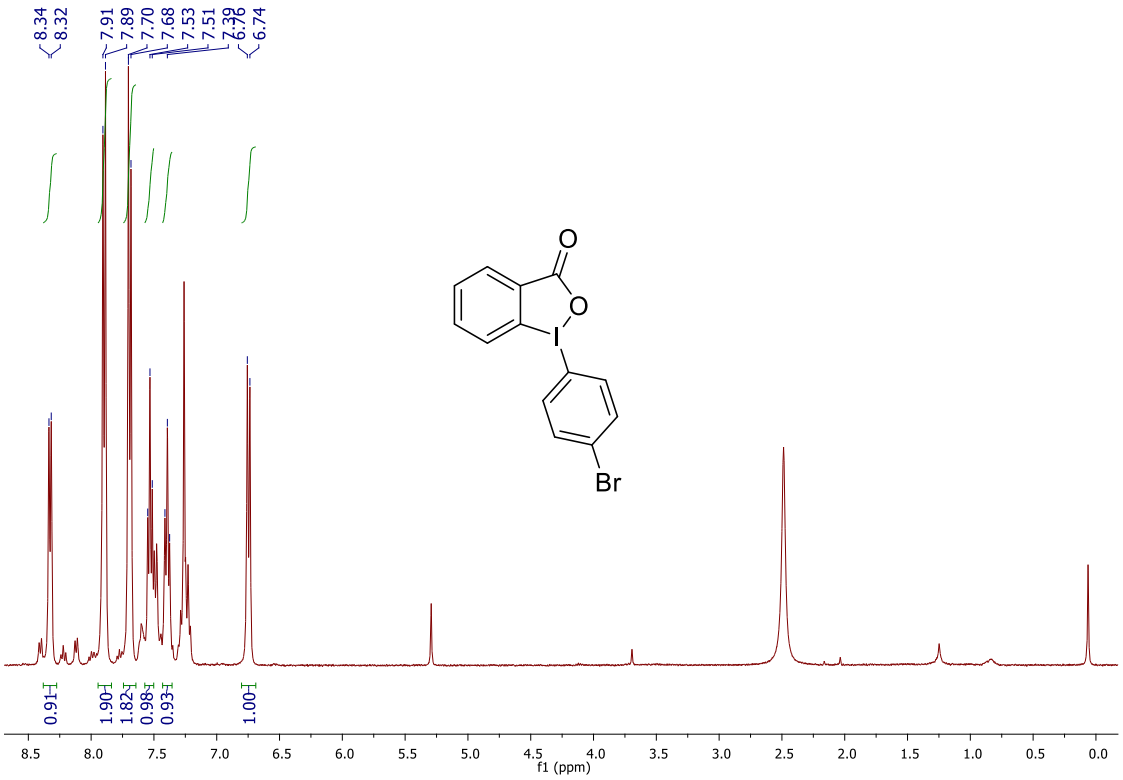


Spectrum 8 *- ^{1}H-NMR spectrum of iodobenzene (**32**).*

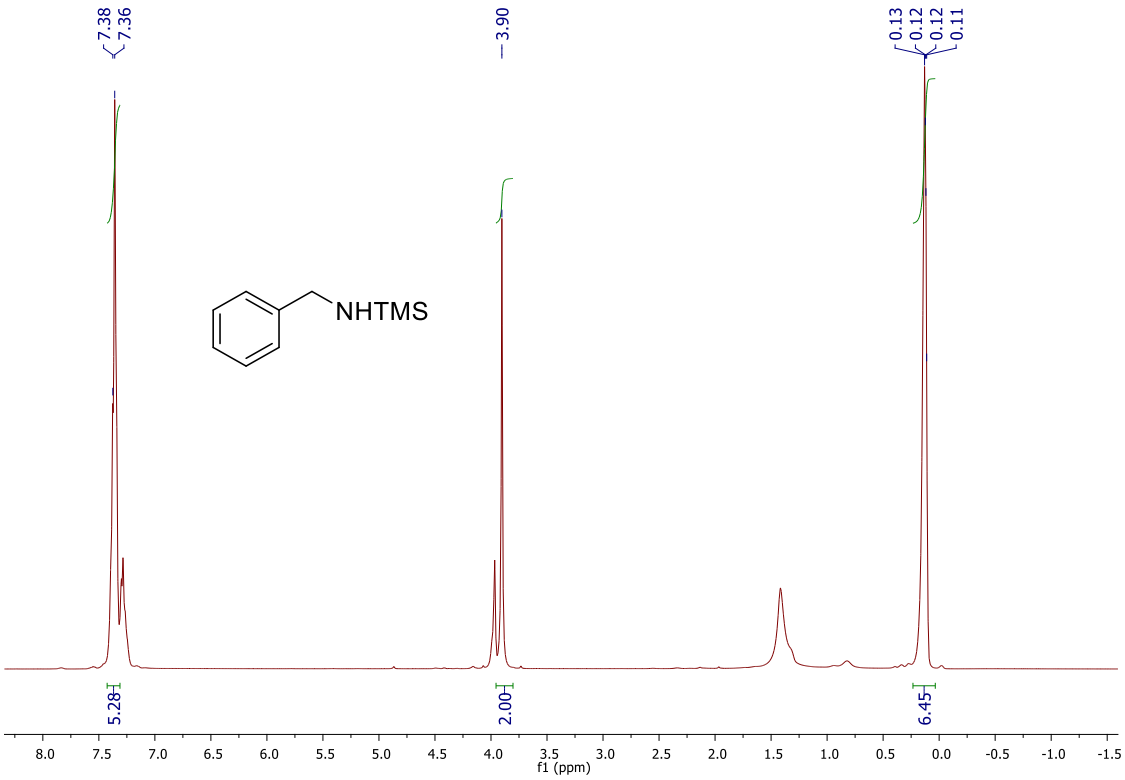


Spectrum 9 *- 1H-NMR spectrum of Sodium-2-iodobezenesulfonate (**33**).*

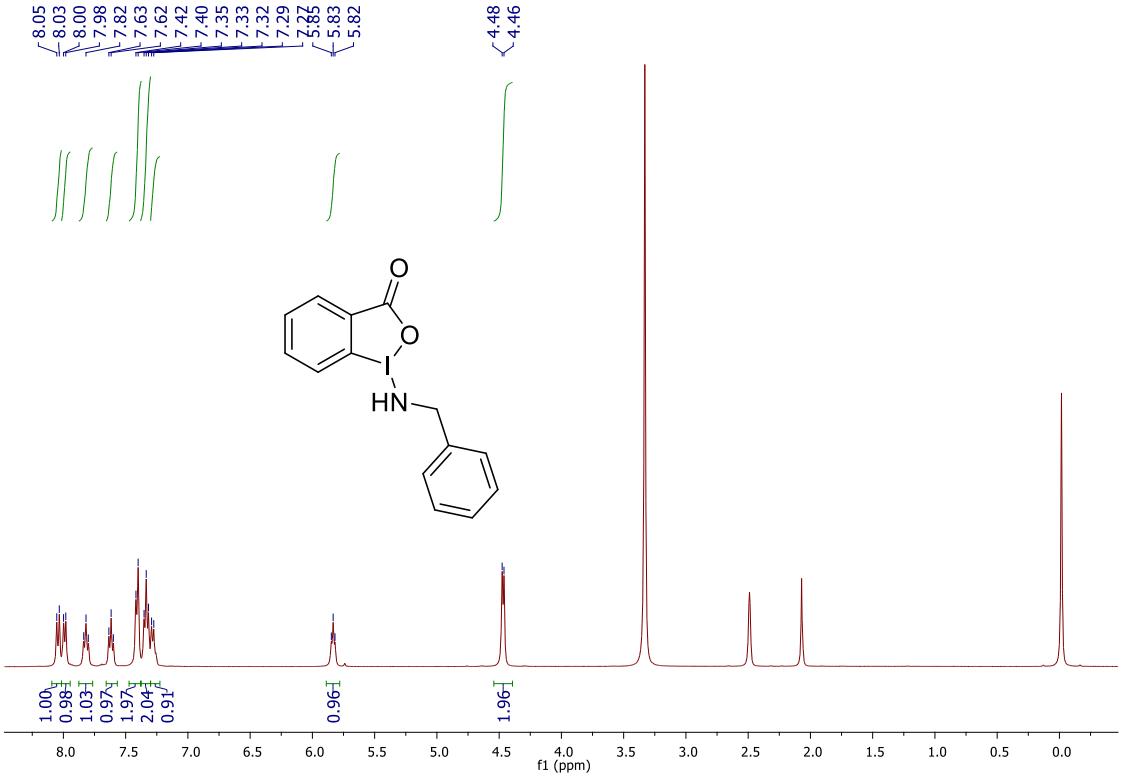
Benzenesulfonate



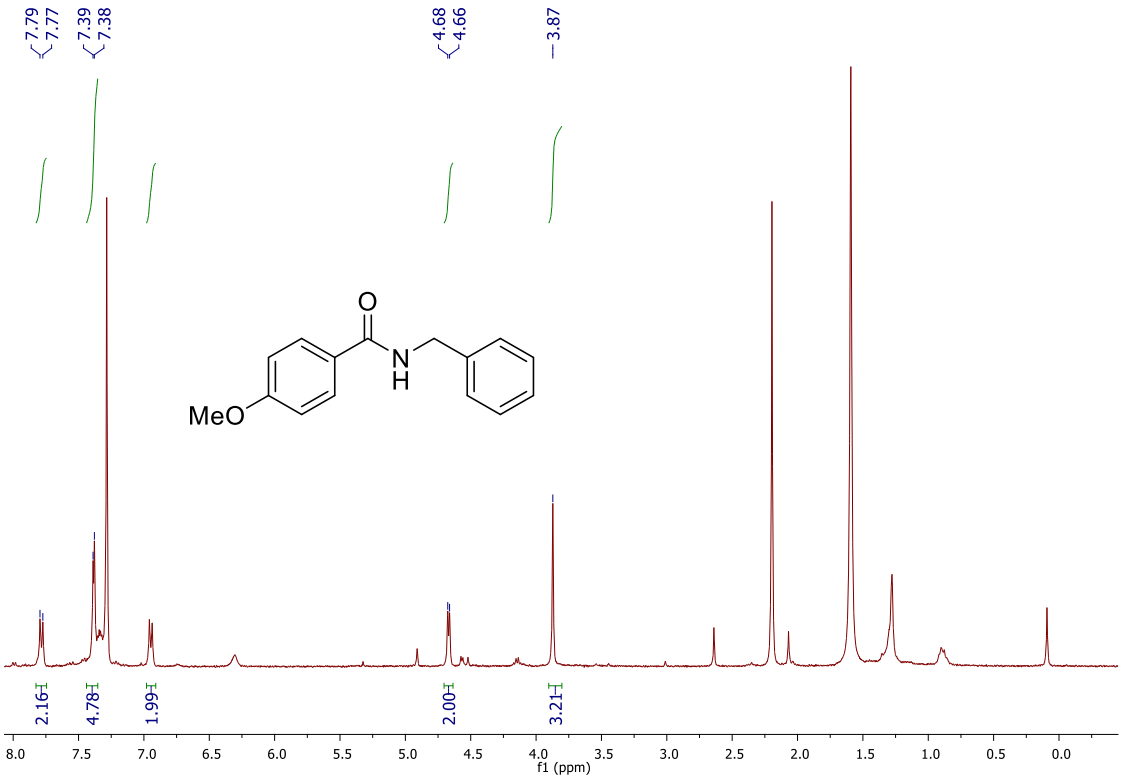
Spectrum 10 *- [1]H-NMR spectrum of 4-bromophenylbenziodoxolone (**38**).*



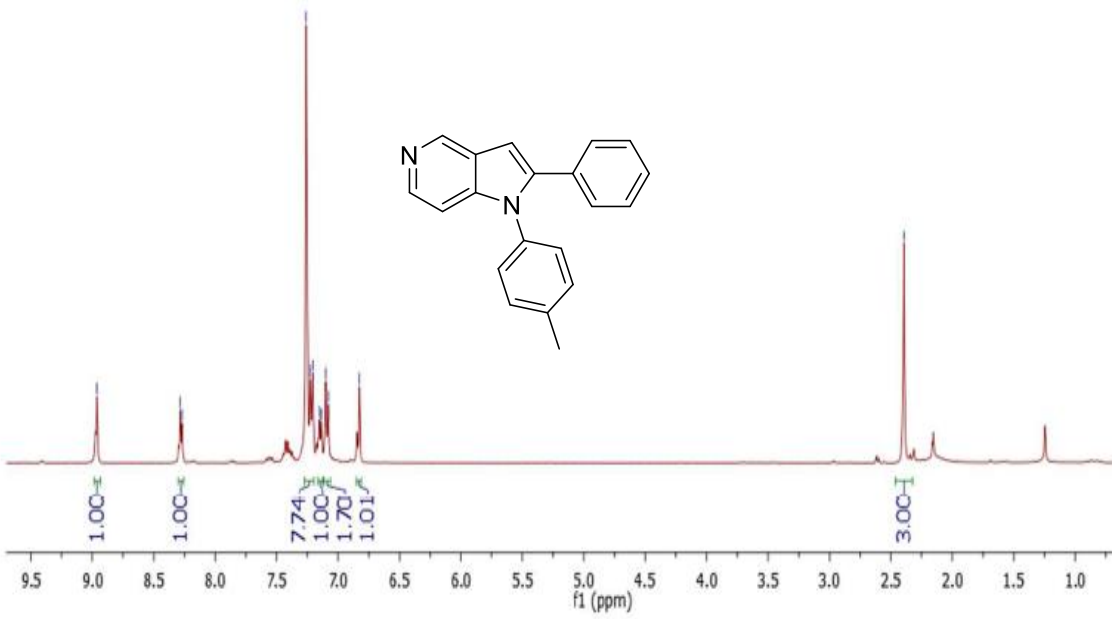
Spectrum 11 *- ^{1}H-NMR spectrum of N-benzyltrimethylsilylamine (**39**).*



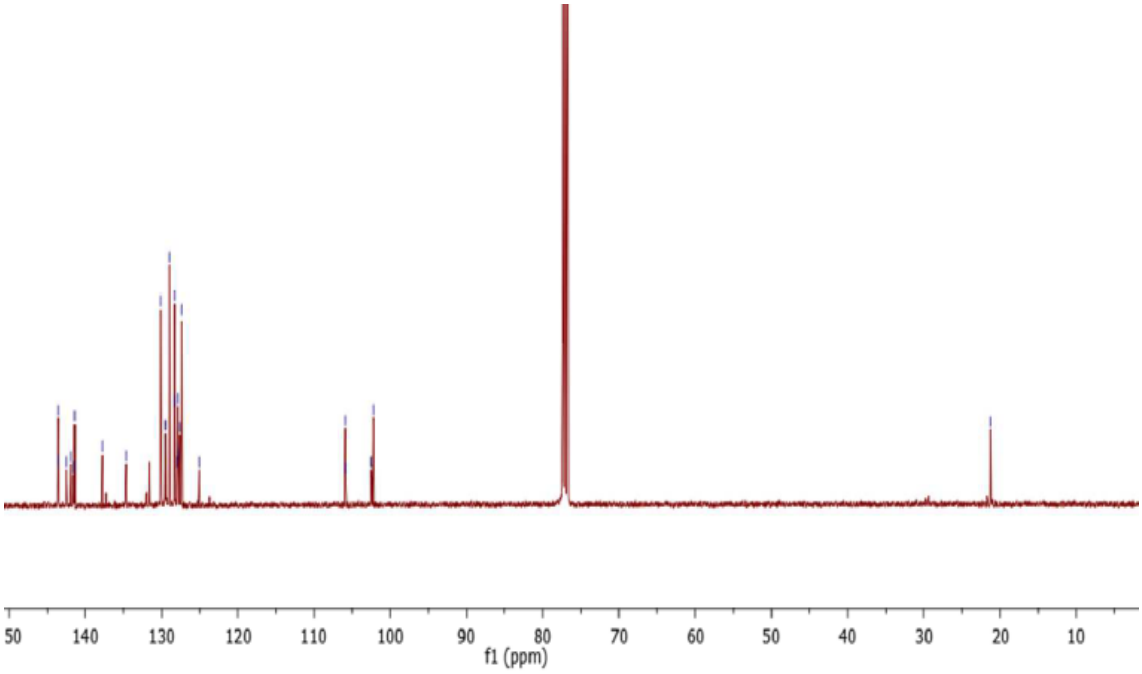
Spectrum 12 *- ^{1}H-NMR spectrum of 1-benzylamine-1,2-benziodoxole-3-*(1*H*)-one *(**40**).*



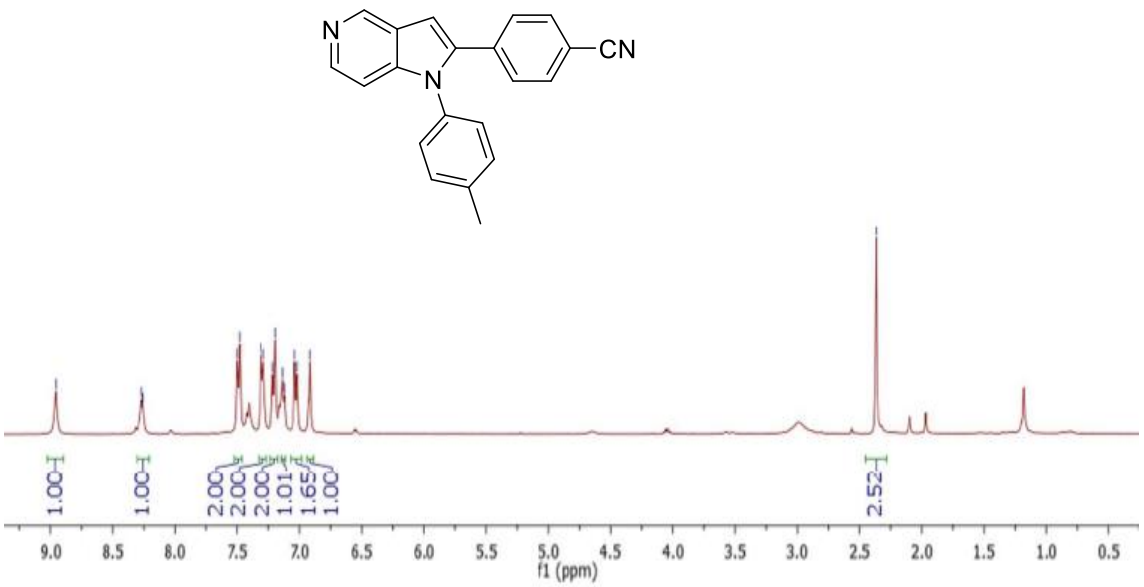
Spectrum 13 *- ^{1}H-NMR spectrum of N-benzyl-4-methoxybenzamide (**43**).*



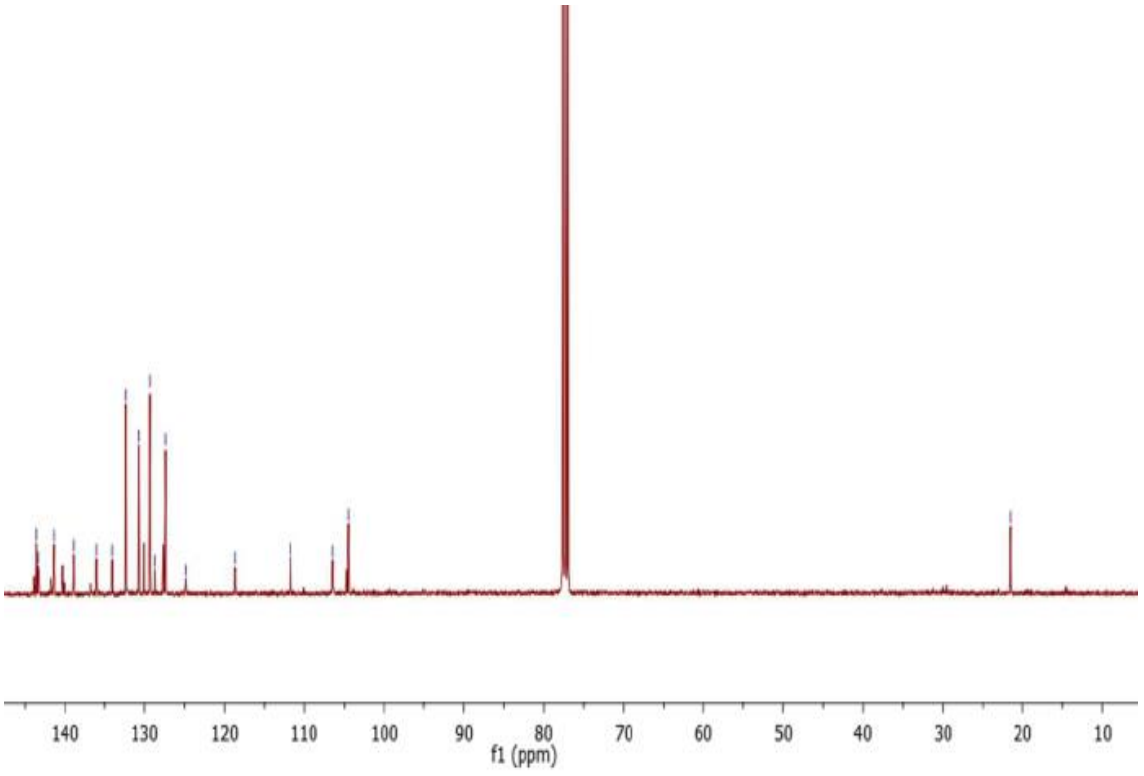
Spectrum 14 *- ^{1}H-NMR spectrum of 2-Phenyl-1-(p-tolyl)-5-azaindole (**44**).*



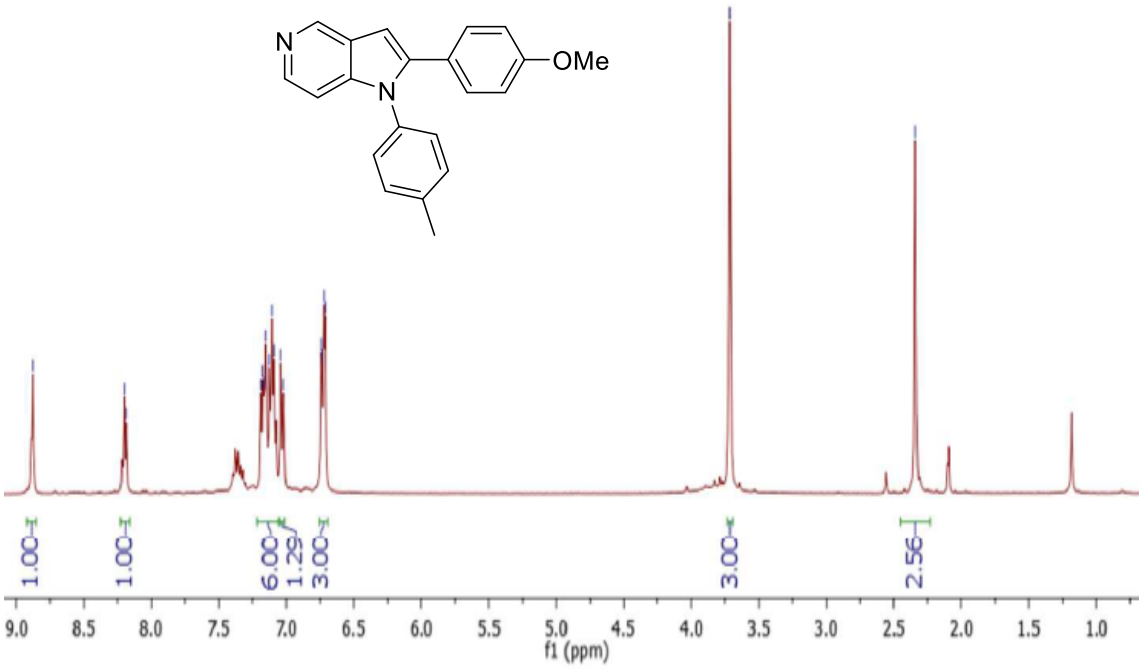
Spectrum 15 *- ^{13}C-NMR spectrum of 2-Phenyl-1-(p-tolyl)-5-azaindole (**44**)*



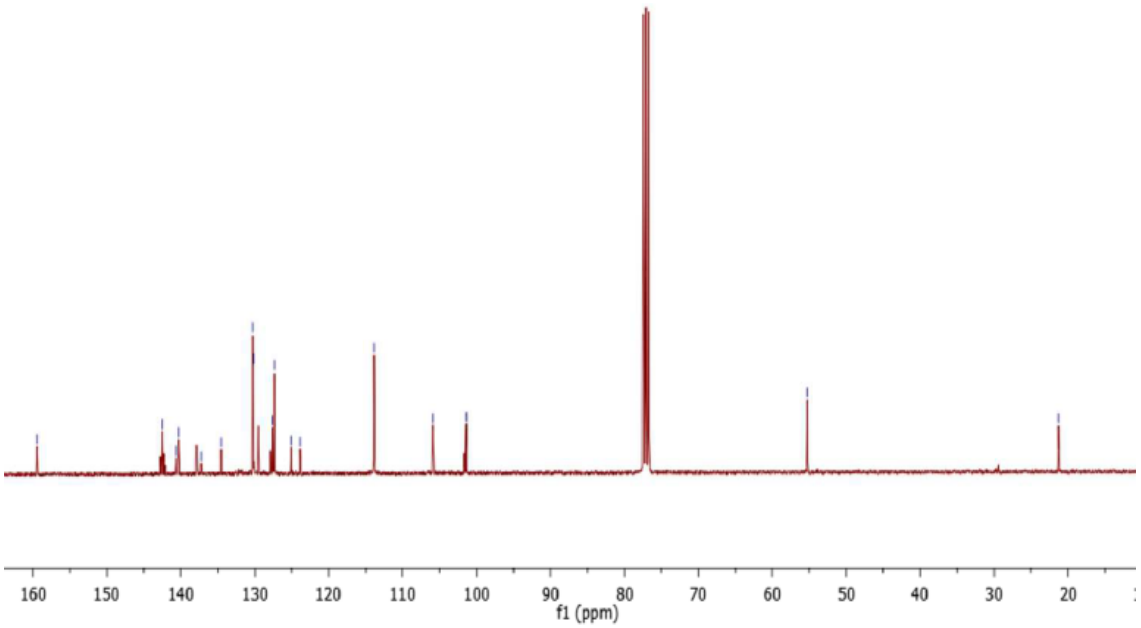
Spectrum 16 *– ^{1}H-NMR spectrum of 4-(2-Benzonitrile)-1-(p-tolyl)-5-azaindole (**45**).*



Spectrum 17 *– ^{13}C-NMR spectrum of 4-(2-Benzonitrile)-1-(p-tolyl)-5-azaindole (**45**)*



Spectrum 18 *- ^{1}H-NMR spectrum of 2-(4-Methoxyphenyl)-1-(p-tolyl)-5-azaindole (**46**).*



Spectrum 19 *– ^{13}C-NMR spectrum of 2-(4-Methoxyphenyl)-1-(p-tolyl)-5-azaindole (**46**)*