NOVEL HALOGEN(I) REAGENTS IN THE CSP2- AND CSP3-BOND FUNCTIONALIZATION

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Novel Halogen(I) Reagents in the Csp^2- and Csp^3-Bond Functionalization

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Novel Halogen(I) Reagents in the Csp^2- and Csp^3-Bond Functionalization

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Doctoral Thesis

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Prof. Dr. Kilian Muñiz Klein, Group Leader of Institute of Chemical Research Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

I confirm that the present study, entitle "Novel Halogen(I) Reagents in the Csp^2- and Csp^3-Bond Functionalization", presented by María Belén García de la Concepción for the award of the degree of Doctor, was carried out under my supervision at the Institute of Chemical Research Catalonia (ICIQ).

Tarragona, July 2nd, 2018

Doctoral Thesis Supervisor

Prof. Dr. Kilian Muñiz Klein

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LIST OF PUBLICATION RESULTING FROM THE THESIS

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Some of the results presented in this thesis have not been published.

LIST OF ABBREVATIONS

PIDA…….....	(Diacetoxyiodo)benzene
PIFA…….....	[Bis(trifluoroacetoxy)iodo]benzene
HTBI…….	[Hydroxy(tosyloxy)iodo]benzene
MO……	Molecular orbital
3c-4e……..	Three-centre-four-electron
D……	Donor
A……	Acceptor
L……	Ligand
SET……	Single-electron-transfer
EDA……..	Electron donor-acceptor-complex
IPy ……	Barluenga´s reagent
$I(coll)_2PF_6$……	Bis(collidine)iodine(I) hexafluorophosphate
$Br(coll)_2PF_6$…….	Bis(collidine)bromine(I) hexafluorophosphate
DMSO……..	Dimethyl sulfoxide
TEA……..	Triethylamine
NaOMe…….	Sodium methoxide
NaOH……	Sodium hydroxide
AcOH……	Acetic acid
HNPhth……..	Phthalimide
TFA……...	Trifluoroacetic acid
TFAA……	Trifluoroacetic anhydride
$PhI(NPhth)_2$……..	Varvoglis´ reagent
TBAI…….	Tetrabutylammonium iodide
m-CBA……..	*m*-chlorobenzoic acid
$CDCl_3$……...	Deuterated chloroform
CH_3CN……..	Acetonitrile
THF……..	Tetrahydrofuran
DMF……..	Dimethylformamide
DCM…….	Dichloromethane
DCE……..	Dichloroethane
DDAB……...	Dimethyldioctadecylammoniumbromide
DBU……..	1,8-Diazabicyclo[5.4.0]undec-7-ene
ee……...	Enantiomeric excess
Equiv…….	Equivalent
i-PrOH……...	Isopropanol

IUPAC……...…	International Union of Pure and Applied Chemistry
m.p……	Melting point
NMR…….	Nuclear magnetic resonance
Py……..	Pyridine
r.t……..	Room temperature
d.e…….	Diastereomeric excess
H.G……	Hoveyda-Grubbs II
TBAF……	Tetrabutylammonium fluoride
DIAD……	Diisopropyl azodicarboxylate
LDA……..	Lithium diisopropylamide

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SUMMARY OF THE THESIS

The work presented in this Thesis represents some major developments in halogen(I) reagents, specifically towards the oxidative functionalization of C(sp^2)-H and C(sp^3)-H bonds through application of monomeric iodine(I) and bromine(I) reagents.

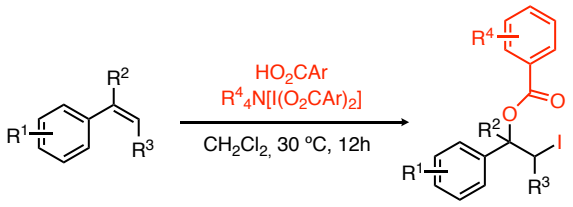
The present manuscript is divided into three general parts:

1-Iodine(I) reagents for vicinal alkene difunctionalization.

2-Oxidative amination of C(sp^3)-H bonds of tetrahydrocarbazoles.

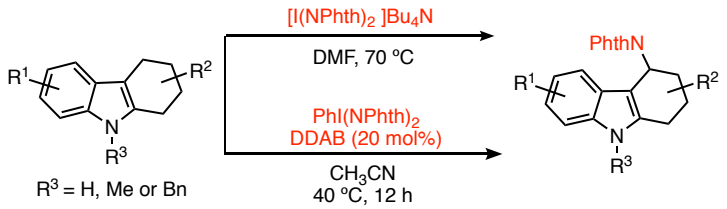
3-Application of iodine(I) reagents or bromine catalysis to the formal total synthesis of (±)-aspidospermidine.

In the first section on alkene difunctionalization, we present a concise synthesis, isolation and characterization of several novel iodine(I) reagents with the general formula $R_4N[I(O_2CAr)_2]$. These compounds exhibit high air and moisture stability. We have been interested in the exploration of reactions promoted by these electrophilic iodine reagents towards alkenes and have elaborated a vicinal iodooxygenation of styrene derivatives (Scheme i).



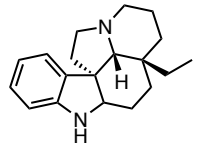
Scheme i: Iodooxygenation of styrene derivatives.

In the second section, an exploration on the use of Varvoglis´ reagent $PhI(NPhth)_2$ is discussed. This reagent is used in the synthesis of novel iodine(I) and bromine(I) reagents with two phthalimide ligands as stabilizers for the electrophilic halogen center. As C-H amination of tetrahydrocarbazoles in the 4-position had not been explored previously, we have developed an innovative methodology to carry out such an C(sp^3)-H oxidative amination of tetrahydrocarbazole derivatives using an iodine(I) reagent or a novel bromine(-I/I) catalysis (Scheme ii).



Scheme ii: Oxidative amination of tetahydrocarbazole derivatives.

Finally, in the third chapter, we demonstrate the versatility of the performance of the halogen reagents, that have been introduced in the previous chapters, within different synthetic approaches towards the synthesis of (±)-aspidospermidine (Scheme iii).



(±)-Aspidospermidine

Scheme iii: Synthesis of (±)-aspidospermidine by electrophilic halogen mediated C(sp^3)-H amination

OVERALL OBJECTIVES

The general objectives of this thesis were to carry out the synthesis, isolation and characterization of several halogen(I) reagents and to probe the high potential of these new compounds in organic chemistry:

-Novel iodine(I) reagents containing two carboxylic acid derivatives as ligands with the general formula $R_4N[I(O_2CAr)_2$ were used as powerful reagents for the vicinal iodooxygenation of alkenes.

-Varvoglis´ reagent containing two phthalimide ligands allowed for the synthesis of new iodine(I) and bromide(I) compounds, which in turn showed to be useful reagents toward oxidative amination at the 4-position of tetrahydrocarbazole derivatives.

-Onces that the expected methodology based on the new halide reagents containing two phthalimides was developed, the subsequent objective consisted in a concise total synthesis of (±)-aspidospermidine relying on an intramolecular C-H amination as the key s

CHAPTER 1: INTRODUCTION

1.1 HYPERVALENT IODINE(III): A VERSATILE TOOL IN ORGANIC SYNTHESIS

Iodine is an element that belongs to the p-block of the periodic table and is quite different in reactivity to its halogen homologues. It is the largest, least electronegative and, as a consequence, the most polarizable element among the halides. These properties allow iodine to form stable polycoordinated derivatives and its behaviour often tends to resemble that of a transition metal when it is employed in organic transformations. As a result of this similarity in reactivity, it has been used successfully as a versatile alternative to highly toxic heavy-metal oxidants such as lead(IV), mercury(II), and thallium(III).

1.1.1. Hypervalent bonding and general structures.

Iodine can be present in the three different oxidation states +1, +3, and +5 in organic compounds and in addition is encountered with oxidation states -1 and +7 in inorganic compounds. In 1969, J. I. Musher suggested the definition of hypervalent species as "molecules and ions formed by elements in Groups 15-18 bearing more than eight electrons in their valence shells"[1]. According to this convention, trivalent and pentavalent iodine compounds fall into this category. In 1886, Willgerodt[2] had synthesized the first aryliodine(III) derivative in form of $PhICl_2$, and a very rich structural derivatisation followed in a surprisingly short period of time, which includes the discovery of PIDA, that represents the most commonly used derivative until the day of today.

The most common iodine(III) reagents are shown in Figure 1, including the most representative compounds such as [bis(trifluoroacetoxy)iodo]benzene (PIFA), (diacetoxyiodo)benzene (PIDA) and [hydroxy(tosyloxy)iodo]benzene (HTBI, Koser´s reagent)[3].

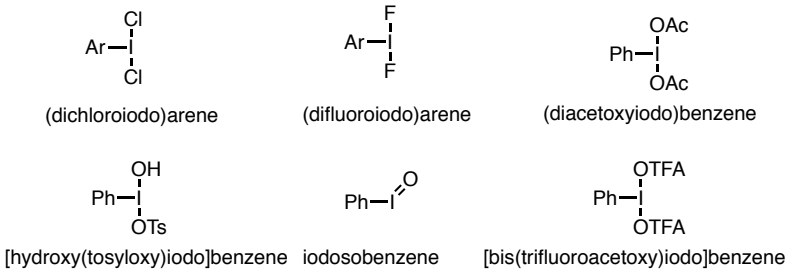
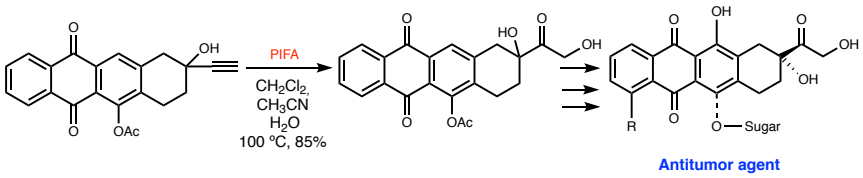


Figure 1: Common iodine(III) reagents in organic synthesis.

Despite all these progresses, thorough attention from the synthetic organic community regarding advanced synthetic application was initially small, and it was necessary to wait for one century to see the first time use of an iodine(III) reagent in the synthesis of a natural product[4] such as an antitumor agent, which is shown in Scheme 1. Here, PIFA was used to enable a one-step oxidative conversion of the terminal acetylene into the corresponding hydroxyketone.



Scheme 1: Synthesis of an antitumor agent.

Previously, iodine(III) compounds were named as iodinanes, while iodine(V) compounds were referred to periodinanes. Nowadays, IUPAC has replaced these names by λ^3-iodanes and λ^5-iodanes (Figure 2), respectively.

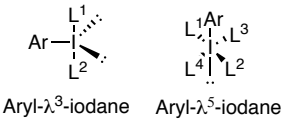


Figure 2: General structures of I(III) and I(V) compounds.

Aryl- λ^3-iodanes have a pseudotrigonal bypiramid geometry, where the lone pairs and the aryl are displaying to the equatorial positions (T-shaped structure). Iodine(III) compounds can be described by molecular orbital (MO) theory as a three-centre-four-electron (3c-4e) arrangement. The theory combines one empty orbital from iodine and one filled orbital from each of the ligands to generate 3 MOs: one bonding, one non-bonding and another one anti-bonding. Of the two pairs of electrons, one resides in the bonding molecular and the other pair in the nonbonding molecular orbital. As depicted in Figure 3, the two bonding electrons reside across the Donor-Acceptor (D-A) and the Acceptor-Ligands (A-L) bonds, and the two non-bonding what are at the terminal atoms (D and L). As a result, the acceptor A is associated with positive charge, and D and L with negative charge. This electronic distribution causes the polarization of the electron cloud towards the terminal atoms.[5] The halogen-bonding interaction between the ligand and the electrophilic iodine atom increases the electrophilicity of the central iodine atom. For example, the distance observed in the crystal structure of $PhICl_2$ is 2.45Å,[6] which is longer than the one observed in the crystal of iodine monochloride

(2.32Å).[7] This obvious weakness of the hypervalent bond dominates the reactivity of hypervalent iodine.

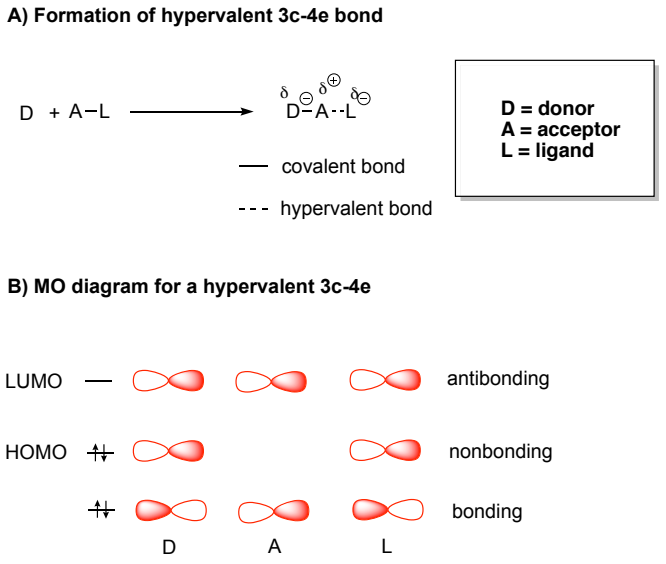


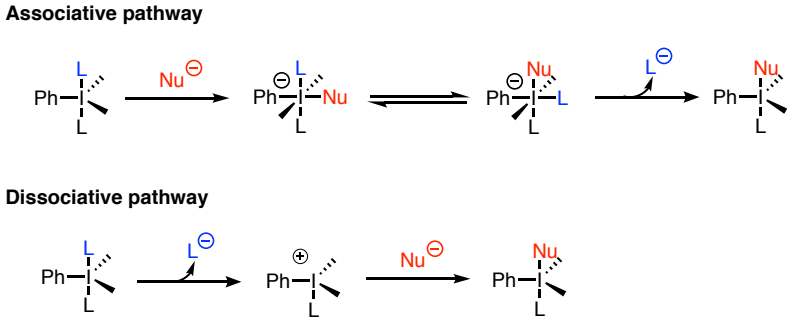
Figure 3: A) Formation of hypervalent 3c-4e bonds between iodine and two ligands. B) General molecular orbital for 3c-4e bonds.

1.1.2. General reactivity

Hypervalent iodine compounds have become useful and routinely employed reagents in the development of novel transformations in organic synthesis.[8] The main reactivity of these reagents originates from ligand exchange at the iodine centre followed by reductive elimination, electrophilic activation by the iodine(III) reagent, radical reactivity from I-X bond homolysis and from single-electron transfer chemistry.

1.1.2.1. Ligand exchange and reductive elimination

It is well known that nucleophiles can easily exchange the ionic ligands in iodine(III) compounds.[3] The exchange of a ligand by a nucleophile can be carried out through two possible mechanistic scenarios, which are best described as associative or dissociative exchanges, respectively (Scheme 2).



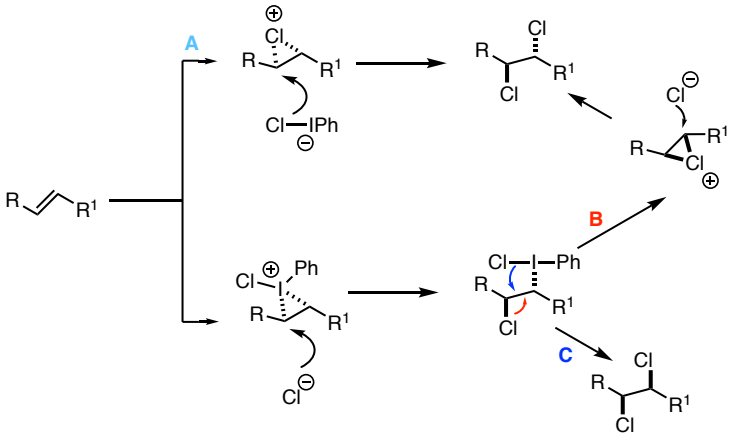
Scheme 2: Associative and dissociative pathways for ligands exchange in iodine(III) compounds.

The associative mechanistic scenario is described as the nucleophilic attack at the electrophilic iodine center, following by the loss of one former ligand of the iodine coordination sphere. In the case of a dissociative pathway, one of the ligand dissociates from the coordination sphere and the resulting positive charge on the iodine atom will be neutralized by the incoming nucleophile.

1.1.2.2. Electrophilic activation by the iodine(III) reagent

The electrophilic capacity of the iodine(III) is influenced by the ligand. When the distance ligand-iodine is short, the interaction between them is higher and as a consequence major stability and less electrophilicity.[9]

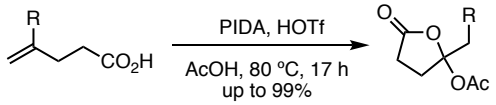
Vicinal dichlorination of alkenes can be carried out with $PhICl_2$. This reaction is usually *anti*-selective.[10] The selectivity can be explained through a direct opening of the initial chloronium ion as is shown in the Scheme 3A or through an anchimeric assistance of a solvent molecule or of neighbouring chlorine in the reductive elimination of the hypernucleofuge iodine(III) (Scheme 3B).[11] *Syn*-addition can be rationalised by the chloride direct S_N2 reaction on the carbon bearing the iodine(III) (Scheme 3C).



Scheme 3: Ionic vicinal dichlorination mechanism.

However, the electrophilicity of the iodine nucleus in PIDA reagent is lower and does not react with alkenes. In 2011, Gade and Kang

described that the alkene diacetoxylation mediated by PIDA can be accelerated using a strong Brønsted acid.[12] The presence of only 5% triflic acid in the reaction promotes the diacetoxylation. The protonolysis of one of the acetates arrives at a cationic, thus more pronounced electrophilic character at the I(III) core, whose electrophilicity is strongly enhanced (Scheme 4).

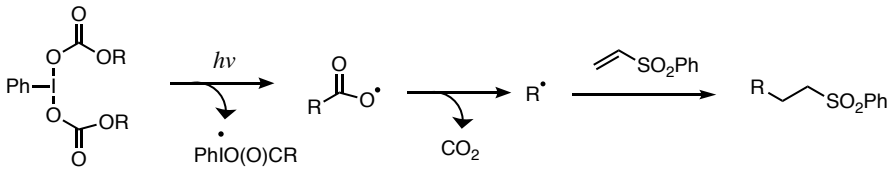


Scheme 4: Kang's and Gade´s Brønsted acid-mediated dioxygenation.

1.1.2.3. Radical reactivity

The radical mechanism is frequently observed during a reaction using an iodine(III) reagent containing chlorine or an oxygenated or nitrogenated group as ligand. This pathway can either be initiated through light or via thermal induction.

As to an illustrative example, (diacetoxyiodo)arenes undergo homolytic cleavage under thermal or photochemical conditions. In Scheme 5, the light induced pathway to an acyloxy radical is shown, which can be trapped through radical combination by other radical molecule,[13] or alternatively can liberate CO_2 leading to the formation of a carbon-centered radical, which as a highly reactive species can add to unsaturated bonds, as the depicted Michael acceptor, ultimately furnishing a C-C bond formation event.

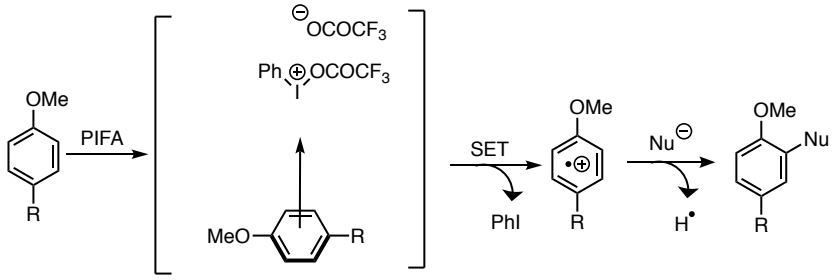


Scheme 5: Example of iodine(III) reagents in a radical reaction under photochemical conditions.

1.1.2.3. Single-electron transfer reaction

A single electron transfer reaction (SET) in iodine(III) chemistry is usually the consequence of an electron donor-acceptor-complex (EDA), which originates from interaction between an electron-demanding and an electron-donating compound, with subsequent formation of radical intermediates formed by a single electron transfer.[14]

In 1991, Kita *et al.* discovered that *o*- and *p*-substituted phenol ethers react with PIFA within built-up of an EDA complex. The aromatic radical cation resulting from single electron transfer pathway can be attacked by suitable nucleophiles to afford the nucleophilic aromatic substitution product upon final H atom abstraction (Scheme 6).[14]



Scheme 6: Nucleophilic aromatic substitution through a SET.

1.2. IODINE(I): A POWERFUL REAGENT

Hypervalent iodine(III) chemistry has been extensively studied, nevertheless, until now, the knowledge about iodine(I) chemistry is limited. In this section, we have been focused in the background about iodine(I) reagents, but due to the similitude of iodine and bromine in organic chemistry, reagents based on both of these halogens will be discussed in this chapter.

In general, a coordinatively saturated halogen(I) reagent can be considered as a three-centre-four-electron system. The halogen is stabilized by simultaneous coordination of two electron-donating ligands. The three atoms of the system [L-X-L]* may either form a static, symmetric geometry [L--X--L]*, or two rapid structures in rapid equilibrium [L-X--L]* ↔ [L--X-L]* (Figure 4). In the symmetric geometry state, the halogen forms two L-X bonds of equal distance and strength. However, in the case of non-symmetric and dynamic systems, the halogen forms one stronger and shorter covalent bond L-X and one weaker and longer halogen bond L--X in each of the isomers. The definition of halogen bond, according to IUPAC, is as an attractive interaction between an electrophile region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity.[15]

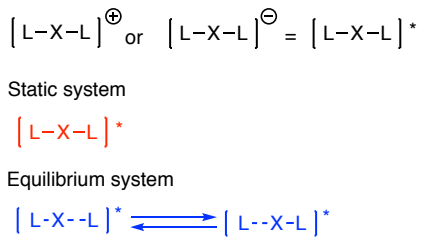


Figure 4: Static or dynamic three-centre-four-electron coordination in halogen(I) complexes.

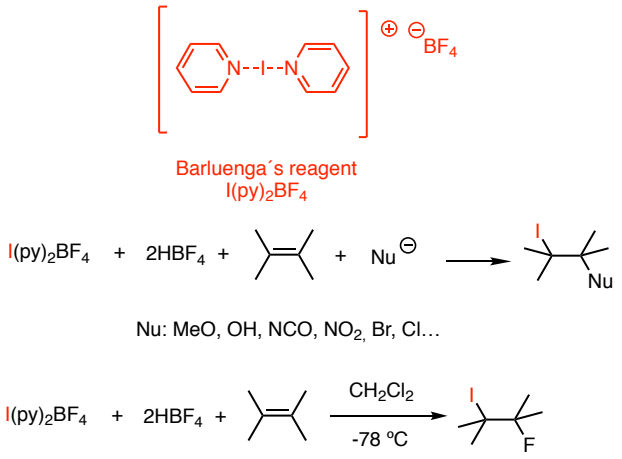
Depending on the nature of the ligands present in the halogen(I) complex, compounds can be divided in two classes: those derived from neutral ligands and those from charged ligands.

1.2.1. Neutral ligands: state of the art

In this section, several organic transformations carried out with halogen(I) compounds containing neutral ligands are discussed.

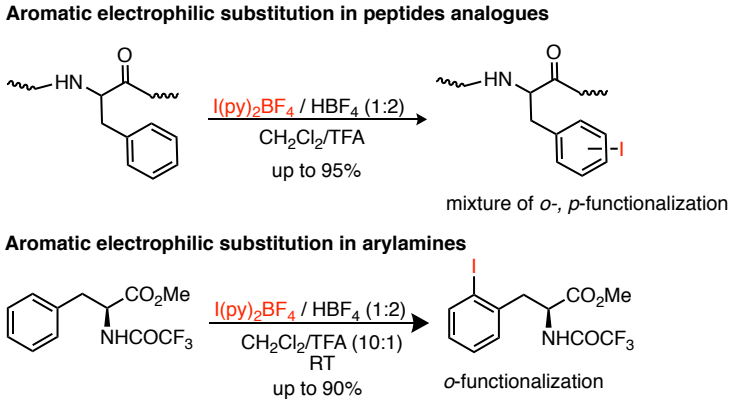
In 1985, bis(pyridine)iodonium(I) tetrafluoroborate ($I(py)_2BF_4$, IPy) was discovered by Barluenga[16] and ever since has been employed in a significant number of reactions as iodonium source and oxidant.[17]

When IPy is employed for olefin derivatization in presence of an external nucleophile, 1,2-iodofunctionalization takes place. However, in the absence of any additional nucleophile, the corresponding 1,2-iodofluorination product is formed, in which the fluorine nucleophile is provided by the BF_4 counterion.[18] In both cases, a stoichiometric amount of tetrafluoroboric acid or boron trifluoride is necessary to acidify the pyridine (Scheme 7).[16],[19]



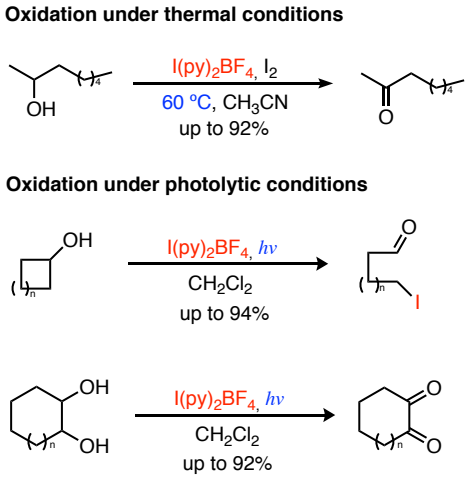
Scheme 7: Barluenga´s reagent in representative olefin difunctionalization.

The synthesis of iodinated aromatic compounds was reported using IPy.[20] The iodination of the *o*- or *p*-position of peptides analogues,[21] phenylamine, *β*- and *γ*-arylamines[22] was effected with $I(py)_2BF_4$ (Scheme 8).



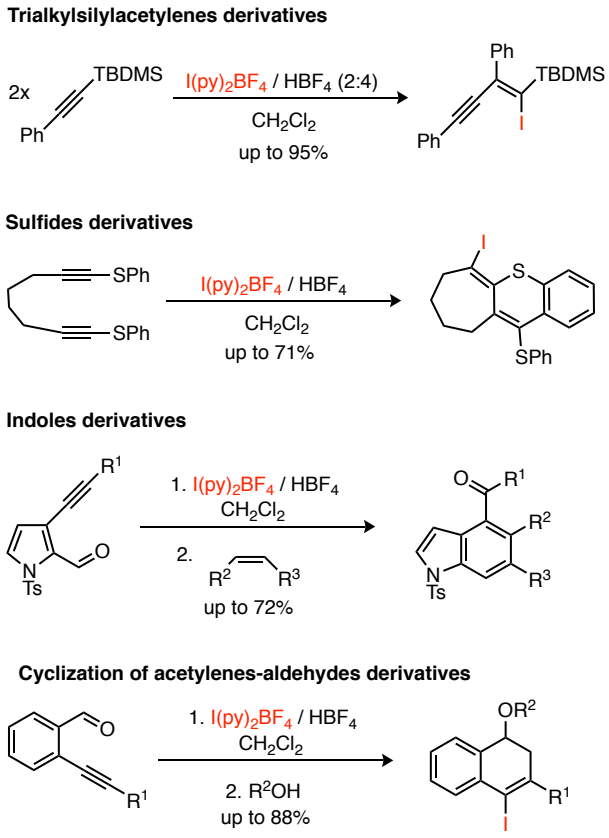
Scheme 8: Barluenga´s reagent: iodination of aromatic compounds.

Barluenga´s reagent can be used as a powerful oxidant outside the incorporation of iodine into the hydrocarbon scaffold. For example, secondary alcohols can be oxidized to ketones under thermal conditions.[23] Cycloalkanols are oxidatively cleaved to the corresponding ω-iodocarbonyls and 1,2-diols are converted to the respective dicarbonyls[17] under photolytic conditions[24] (Scheme 9).



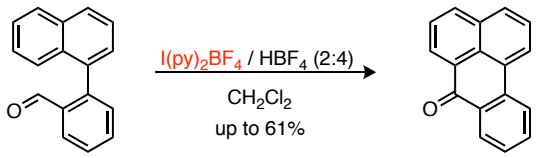
Scheme 9: Barluenga´s reagent as a powerful oxidant.

An interesting reactivity with Barluenga´s reagent and alkynes has been described. Barluenga *et al.* described an unprecedented coupling of (trialkylsilyl)acetylenes derivatives with IPy providing regio- and diastereoisomerically pure enynes derivatives.[25] Further notable transformations include *exo-endo*-cyclizations of α-ω-diynes,[26] the synthesis of different 2,3-unsubstituted indoles from pyrrole derivatives,[27] the cyclization of 2-acetylenyl-benzaldehyde derivatives by reaction with $I(py)_2BF_4$ and several silyl protected alcohols (Scheme 10).[28]



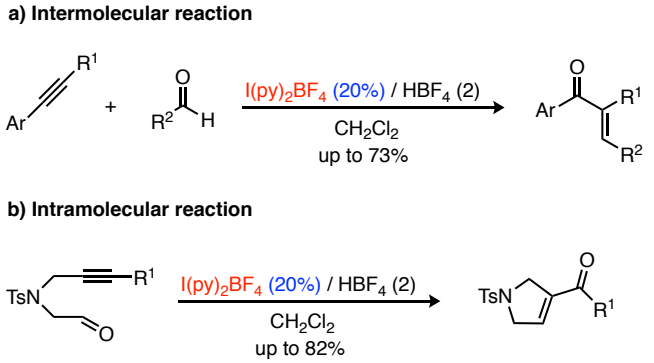
Scheme 10: IPy as an efficient reagent for the transformation of alkyne derivatives.

Iodonium ions have been used to promote the reaction of aldehydes as acylating agent for arenes in a simple synthesis of diarylketones (Scheme 11).[29]



Scheme 11: IPy as an efficient reagent to promote the intramolecular acylation of arenes.

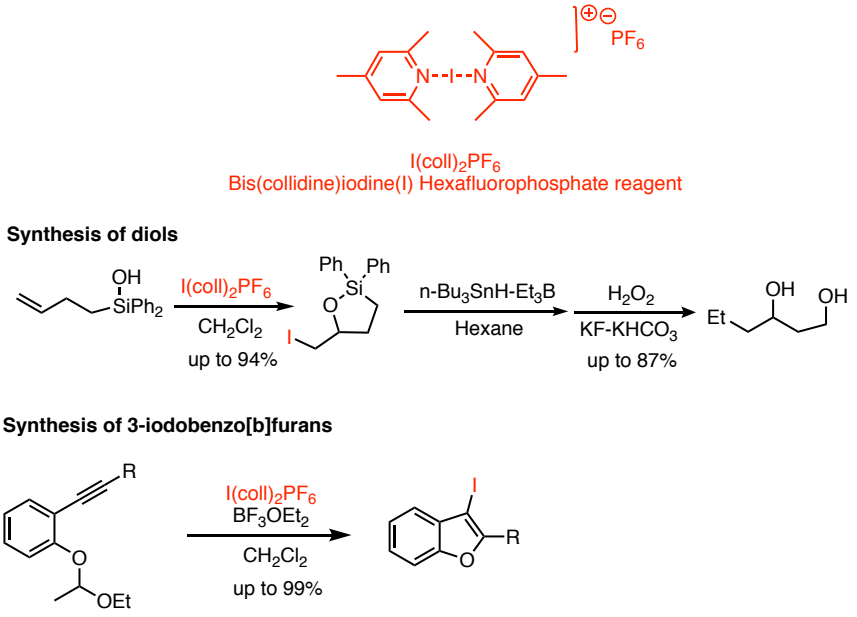
Recently, Murai *et al.* developed the catalytic inter- and intramolecular alkyne-carbonyl metathesis of alkynes with ketones or aldehydes using a catalytic amount of IPy (Scheme 12).[30]



Scheme 12: Catalytic amounts of IPy promote the alkyne-carbonyl metathesis.

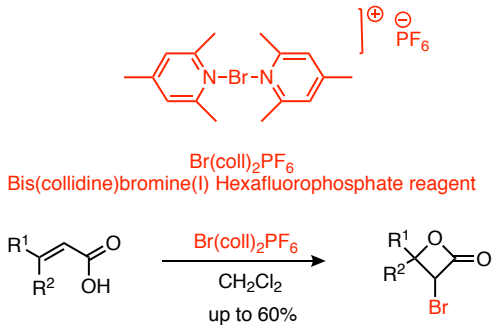
It is known that other ligands can also coordinate to iodonium ions, concretely 2,4,6-collidine (2,4,6-trimethylpyridine), to afford bis(collidine)iodine(I) hexafluorophosphate.[31] This reagent can be used as an iodonium source. Intramolecular iodosilyletherization is an effective procedure for preparing diols from the corresponding ω-alkenylsilanols. The primary cyclic silyl ether products were further derivatized by oxidative cleavage of the carbon-silicon bond to form 1,3-diols as products from sequential dual oxidation.[32] Another example is reported in which $I(coll)_2PF_6$ is employed for the

synthesis of 3-iodobenzo[b]furans by iodocyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes (Scheme 13). Okitsu *et al*. examined the possibility to use $I(py)_2BF_4$ as an iodinating reagent instead of $I(coll)_2PF_6$ and the yield was similar, but this reagent is more economic than IPy.[33]



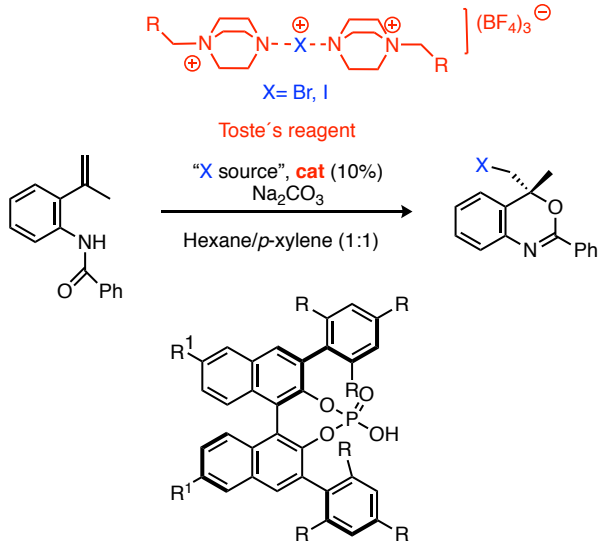
Scheme 13: $I(coll)_2PF_6$ as an iodonium source in organic transformations.

Bromonium ions are also reported to coordinate with two collidines to provide highly reactive bromonium ion precursors.[34] The reactivity of a α,β-unsaturated acid with $Br(coll)_2PF_6$ was studied to afford 2-oxetanones through 4-*endo* cyclization (Scheme 14).[35]



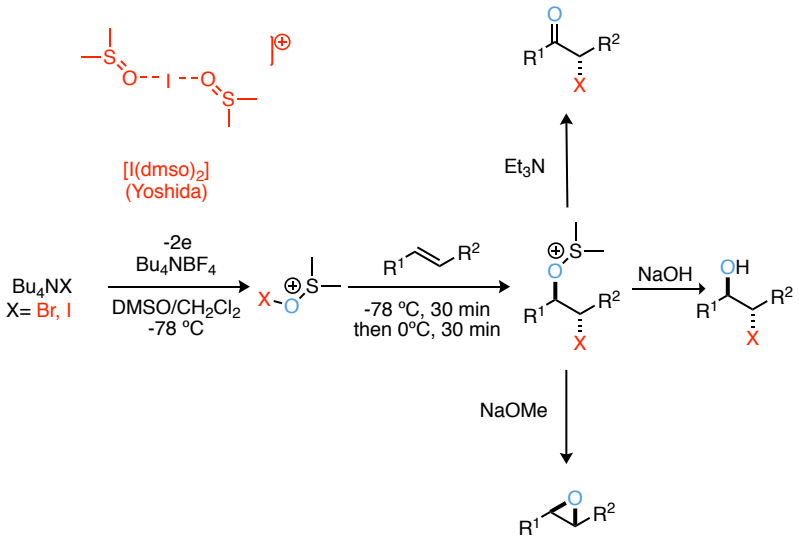
Scheme 14: $Br(coll)_2PF_6$ as a reagent for the synthesis of 2-oxetanones.

Enantioselective halogenation with a chiral anion phase-transfer system was described by Toste *et al.* developing highly insoluble, ionic reagent as electrophilic bromide and iodine sources.[36] Phosphoric acid was used as the source of an anionic phase-transfer catalyst to achieve the enantioselective reaction of *o*-anilidostyrenes to yield 4-H-3,1-benzoxazines (Scheme 15).



Scheme 15: Toste´s reagent in an enantioselective halogenation reaction.

On the other hand, Yoshida *et al.* provided an elegant electrochemical approach to generate iodine and bromine cations in solution, using dimethyl sulfoxide (DMSO) as a stabilizing agent. The resulting stabilized halogen cations served as powerful reagents for alkene difunctionalization. The authors reported that *β*-haloalkoxysulfonium ions treated with triethylamine gave *α*-halocarbonyl compounds.[37] Later, they discovered that changing the nature of the base led to the formation of different products. Triethylamine is a bulky base therefore reacts with the oxygen, but other bases, as NaOMe or NaOH, attack the sulfur atom and cleave the S-O bond under formation of an alkoxide ion and as the consequence give different products (Scheme 16).[38]



Scheme 16: Synthesis of halohydrins, halocarbonyls and epoxides from olefins through DMSO-stabilized halogen cation.

1.2.2. State of the art with charged ligands

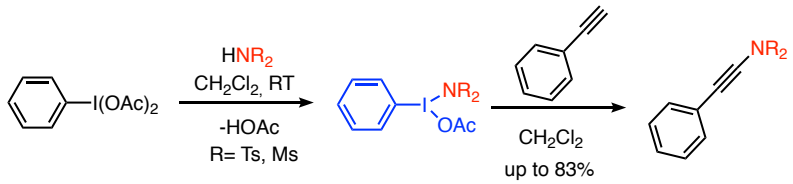
Halogen(I) reagents with charged ligands can be generated in situ or isolated as salts.[39] The main reactivity of these types of compounds has been explored in their behaviour towards olefins. At the outset, the electrophilic halide will be formed in solution and will react with olefins. Two different pathways could then proceed both depending on the role of the active ligand: 1) it can behave as nucleophile leading to the 1,2-difunctionalized products; 2) it can realize a nucleophilic substitution of the halide to afford a new monofunctionalized product. These reagents also can display the required radical-based reactivity due to the possibility to react as an electrophilic halide or nucleophilic source.[40]

1.2.2.1. General synthesis.

As discussed at the outset, several pathways exist to generate iodine(III) compounds, which in turn can be employed in the synthesis of different halogen(I) compounds. Two accessible routes to generate the hypervalent reagents are described here. PIDA or PIFA are used as precursors due to the fact that they display a different reactivity and are commercially available.

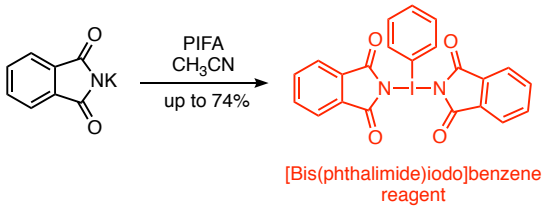
The acetate moiety in PIDA has a conjugated pKa of 4.75.[41] Consequently, it can easily exchange ligands with stronger acids, which display pKa value smaller than acetic acid. In 2011, Muñiz *et al.* developed two new iodine(III) reagents. The combination of PIDA with bistosylamide or bismesylamide promotes the desired ligand exchange to afford the new I^{III}-N covalent bond,[42] creating a novel class of hypervalent iodine(III) reagents of the general formula $ArI(OAc)N(SO_2R)_2$. The development of new metal free amination reactions with these iodine(III) reagents is due to the acidic nature of the bissulfonylimide with a pKa of 1.9.[43] In 2012, the same group

used this reagent to carry out the synthesis of ynamines from acetylenes establishing a C-H to C-N bond conversion (Scheme 17). In this project, they tried to synthesize other iodine(III) reagents with another nitrogen source such as phthalimide. Unfortunately, the C-N bond formation was not found possible under this condition. This outcome could be explained by the low acidity of phthalimide,[41] which does not promote the required protonolysis.[44]



Scheme 17: A novel iodine(III) reagent promotes the synthesis of ynamines.

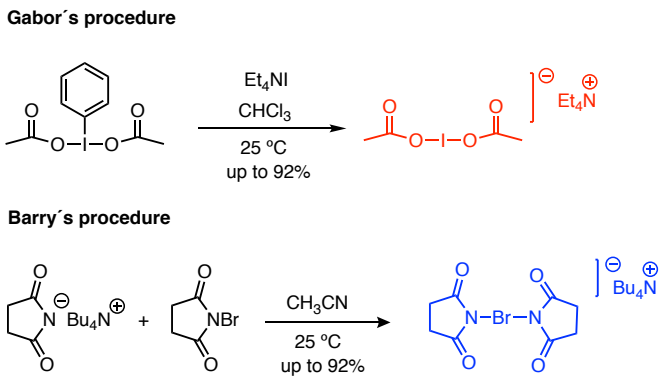
In the case of PIFA, protolytic ligand exchange cannot be performed as in the case of PIDA due to the strong acidity of the trifluoroacetic acid (pKa = 0.23). However, due to the strong electron-withdrawing nature of its carboxylate ligands, PIFA might easily undergo bond exchange through nucleophilic addition. In 1983, Varvoglis *et al*. reported a stable iodine(III) compound, [bis(phthalimide)iodo]benzene, which is prepared by the reaction of PIFA with potassium phthalimide in acetonitrile (Scheme 18).[45]a



Scheme 18: Synthesis of Varvoglis' reagent.

As it was explained above, different halide(I) reagents can be generated from iodine(III) reagents. Gabor *et al.* in 1980, carried out the synthesis of the first iodine(I) salt by mixing PIDA with

tetraethylammonium iodide.[46] This route can be called the classical pathway due to the fact that the majority of the authors form these types of reagents using iodine(III) compounds in presence of ammonium iodide or bromide. Another route, which is less common and, as a consequence, can be referenced as the non-classical pathway, was described by Barry, Eberson *et al*. in 1984. They formed halide(I) reagents by mixing ammonium salts containing the anion, in presence of *N*-halogenated amides (Scheme 19).[47]

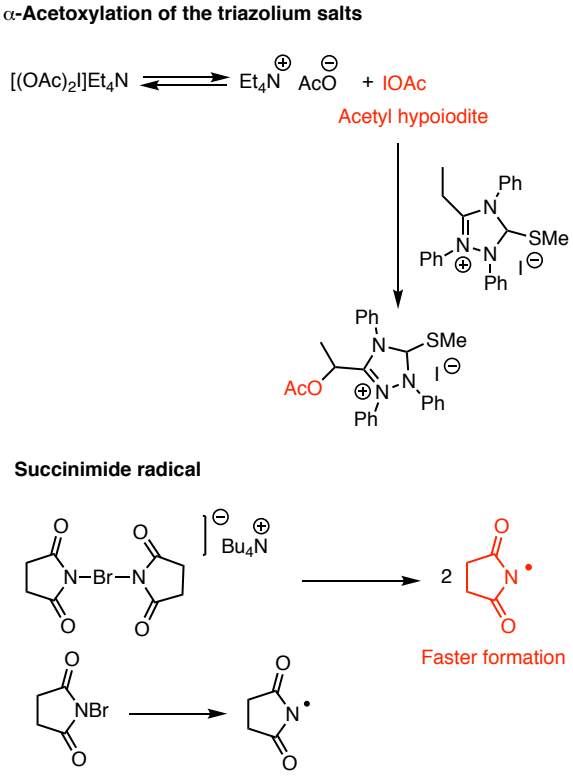


Scheme 19: Synthesis of halide(I) reagents using the classical or non-classical pathway.

1.2.2.2. The most representative halogen(I) reagent

The first contributions in the synthesis of halide(I) reagents were achieved by Gabor, Barry and Eberson in the 1980's. Gabor *et al.* synthesized tetraethylammonium [diacetoxyiodate(I)] using the classical pathway. They reported that this reagent is an efficient source of acetyl hypoiodite, which proved to be an excellent α-acetoxylating agent of the triazolium salts.[46] Later Barry, Eberson *et al*. developed, through the non-classical pathway, different bromide(I) reagents[47] using succinimide derivatives as ligands.[48] They studied the rate of formation of succinimide radicals, and they

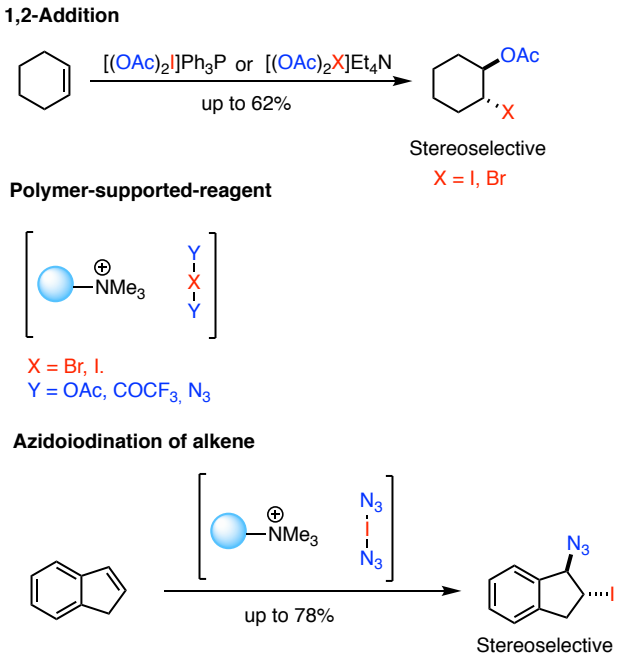
discovered a relatively faster homogeneous reaction when the succinimide source comes from complex tetrabutylammonium [disuccinimidebromide(I)], instead of N-bromosuccinimide (Scheme 20).[49]



Scheme 20: First contributions of halogen(I) reagents.

One of the main contributions to the synthesis of halogen(I) compounds has been made by Kirschning. The main research interest was the 1,2-addition to double bonds due to the high importance of this transformation in organic synthesis. At the beginning, they synthetized different halogen(I) reagents to provide iodine-[50] or bromine-[51] promoted haloacetoxylation.

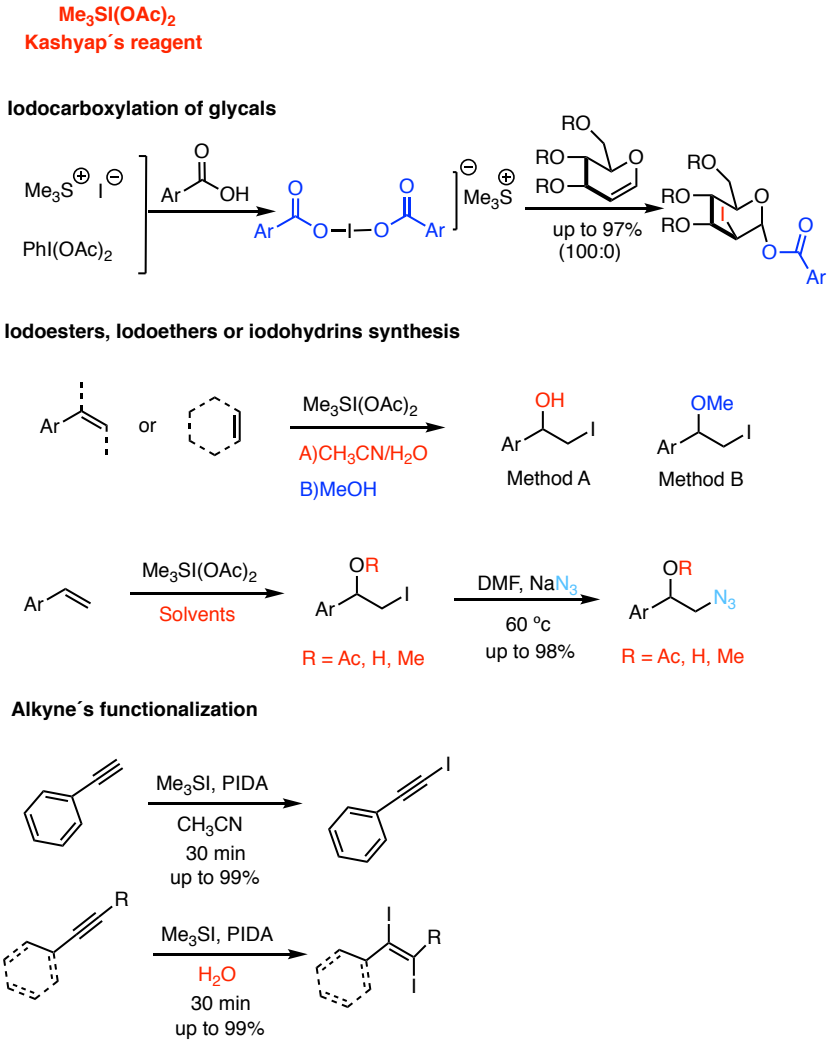
Later, a number of polymer-bound reagents has been reported for the synthesis of organic molecules, as before, for the difunctionalization of double bond of different substrates.[52],[53] In this field, they developed the first polymer-supported iodine azide source, which promotes azidoiodination of alkenes.[54] Carbohydrate derivatives can be accessed with this type of polymer-supported reagents (Scheme 21).[55]



Scheme 21: Kirschning´s reagents promote the difunctionalization of alkenes.

The most recent contribution in the iodine(I) reagent field has been made by Kashyap *et al*. In 2016, they prepared a new iodine(I)-based sulfonium salt. They carried out the iodoacetoxylation of glycal derivatives with trimethylsulfonium bis(acetoxy)iodate(I). During the screening of the reaction, they discovered that better results were obtained when the iodine(I) was generated in situ. After that,

Kashyap´s group developed a robust method for iodocarboxylation using PIDA, sulfonium salt and carboxylic acid derivatives with glycals. The desired products were obtained with good yields, but sometimes with low regioselectivity. This result was explained due to the competitive nucleophilic attack by acetate.[39] Later on, they employed the sulfonium bis(acetoxy)iodate(I) complex in a successfully intramolecular regio- and stereoselective vicinal iodo-functionalization of alkenes to afford iodoethers, iodohydrins and iodoesters in a one-pot process, depending on the selected solvent.[56] In 2018, Kashyap *et al*. developed the iodination of alkynes, again using a solvent-controlled process. The characteristic reactivity of this iodine(I) reagent with alkyne derivatives can be controlled by the nature of the solvent, leading to 1-iodoalkynes and vicinal (*E*)-diiodoalkene products (Scheme 22).[57]



Scheme 22: Iodoester, iodoether or iodohydrine synthesis and alkyne functionalization.

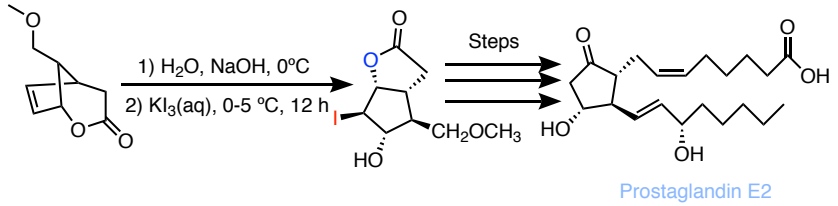
CHAPTER 2: A NOVEL IODINE(I) REAGENT FOR IODO-OXIGENATION

2.1. INTRODUCTION: IODINE REAGENTS IN ALKENE VICINAL DIFUNCTIONALIZATION

Recently, iodine reagents have been recognized as powerful tools for the oxidative transformation of hydrocarbons.[58],[59] The benefits of this modern functionalization by use of iodine allows to avoid the use of transition metals. Despite the fascinating application and significant advances of transition metals in organic chemistry,[60] the use of metal catalyzed reactions is limited for the production of pharmaceutical ingredients and can be prohibitively expensive at large scale applications.[61] Stereoselective bisfunctionalization of alkenes is a highly important transformation[62] to access bioactive molecules and natural products in organic chemistry. Concretely, halofunctionalization has been extensively studied due to the selective and easy addition of two new chemical entities in a single step. The process involves the electrophilic halide addition, such as iodine (I^+), to the double bond. Subsequently, a suitable nucleophile opens the cyclic iodonium intermediate to provide the 1,2-iodofunctionalized product. This type of reaction generates two new stereocenters with highly *anti*-selectivity to incorporate vicinal hydroxy (*β*-iodohydrins), ester (*β*-iodoesters) or alkoxy (*β*-iodoethers) moieties.[56]

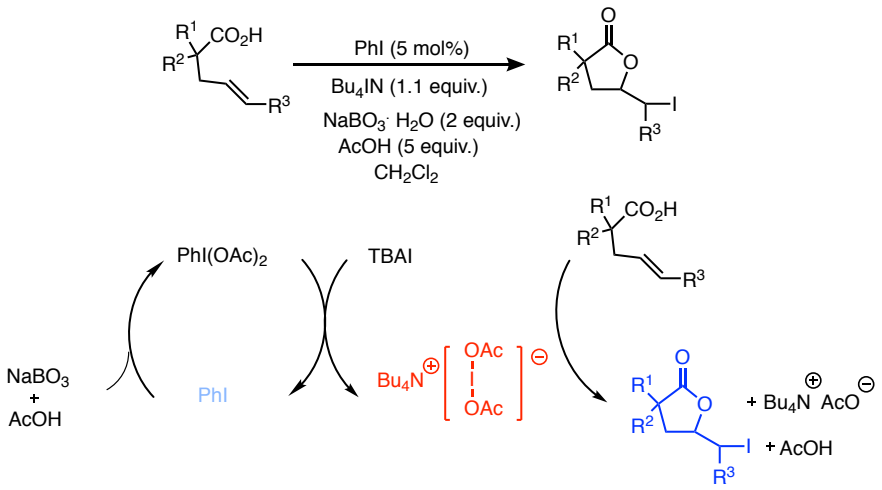
A noteworthy transformation using an electrophilic iodine was carried out by Corey *et al.* in 1969. The authors developed an effective pathway to synthesize lactones by the combined addition of oxygen and iodine across a carbon-carbon bond. This reaction is conducted under mild conditions and incorporation of the versatile

iodine atom into the product. This powerful generation of lactones was used to synthesize numerous prostaglandins (Scheme 23).[63]



Scheme 23: Corey´s lactonization.

A new approach to halolactonization was developed by Tan *et al*. to construct iodolactones from olefinic carboxylic acids. It was found that tetrabutylammonium [diacetoxyiodate(I)] was able to promote the iodolactonization in yields of up to 98%. As depicted in the previous chapter (1.2.2.1), the iodine salt was prepared using PIDA and tetrabutylammonium iodide (TBAI) in a 1:1 molar ratio. Tan´s group investigated the catalytic version of the lactonization reaction regenerating PIDA in situ. To do that, catalytic amounts of iodobenzene and sodium perborate as terminal oxidant were used to give the iodine(I) reagent, which afforded the iodolactonization product (Scheme 24).[64]

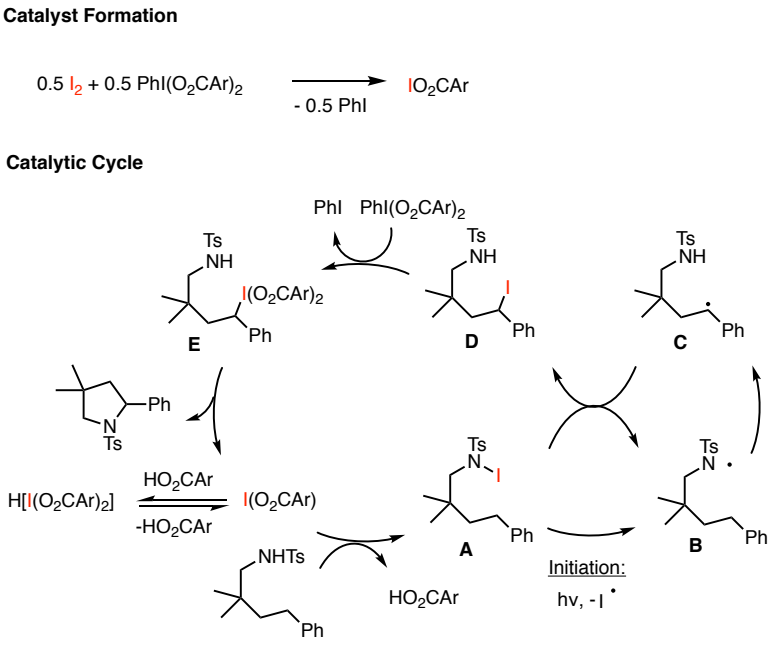


Scheme 24: Tetrabutylammonium [diacetoxyiodate(I)] promoted iodolactonization.

As highlighted in the introduction, the groups of Kirschning[50] and Kashyap[39],[56] developed a number of iodine(I) salts as precursors of electrophilic iodine reagents. The applicability in organic synthesis has been demonstrated by numerous chemo- and regioselective iodooxygenation reactions of olefins.

One of multiple reactions to synthesize pyrrolidines by the generation of *N*-centered radicals is known as the Hofmann-Löffler reaction.[65] In this scenario, the *N*-centered radical is formed by photochemical or thermal decomposition of a *N*-halogenated bond in presence of a strong acid to promote the intramolecular amination reaction. Although this reaction has a huge potential, the required reaction conditions are very harsh. Our group developed the first example of a Hofmann-Löffler-type amination reaction, which used a catalytic amount of halogen to build up the pyrrolidine's core under extremely mild conditions.[65] The initial reaction between hypervalent

iodine(III) reagent PhI(*m*CBA)$_2$ and molecular iodine allows the formation of I(*m*CBA), which is the active catalyst (Scheme 25). Once the catalyst is generated, it leads to N-I bond formation to afford the intermediate **A**. Under light irradiation, the resulting nitrogen-centered radical **B,** engages in a 1,5-hydrogen atom transfer from the benzylic position, forms the carbon-centered radical **C**. This intermediate abstracts an iodine atom from another molecule of **A** in a radical chain reaction to lead to the intermediate **D**. Here, iodine(I) is oxidized to iodine(III) increasing the iodine's ability to act as a good leaving group. After that, the nucleophilic amination proceeds with regeneration of the active catalyst I(*m*CBA). Muñiz´s group discovered that the regeneration of the catalyst is possible due to the stabilization of I(*m*CBA) by the formation of an adduct with the carboxylic acid. To confirm this hypothesis, the salt of the ammonium derivative Bu$_4$N[I(*m*CBA)$_2$] was prepared. Under stoichiometric use of this model compound, pyrrolidine formation took place in comparable yields as in the catalytic cycloamination.



Scheme 25: An iodine(I/III)-catalyzed Hofmann-Löffler.

2.1.1 General objectives

As an iodine(I) compound was recognized as the active species leading to N-I bond formation, we were interested in further exploring iodine(I) reagents in electrophilic halide promoted reactions. It was envisioned to synthesize powerful electrophilic halide reagents of the general formula $R_4N[I(O_2CAr)_2]$ and subsequently employ these reagents in alkene functionalization.

2.2. RESULTS AND DISCUSSION

2.2.1. Synthesis and study of stability of iodine(I) reagents

We started our studies with the synthesis of dioxoiodanes using different benzoates as ligands. The general synthesis of reagents **3** can be accomplished by reaction between an ammonium salt **1** and a hypervalent iodine(III) compound **2** (Figure 5). The thus obtained iodine(I) reagents **3** were isolated as white to yellow solids which display high stability against moisture and air.

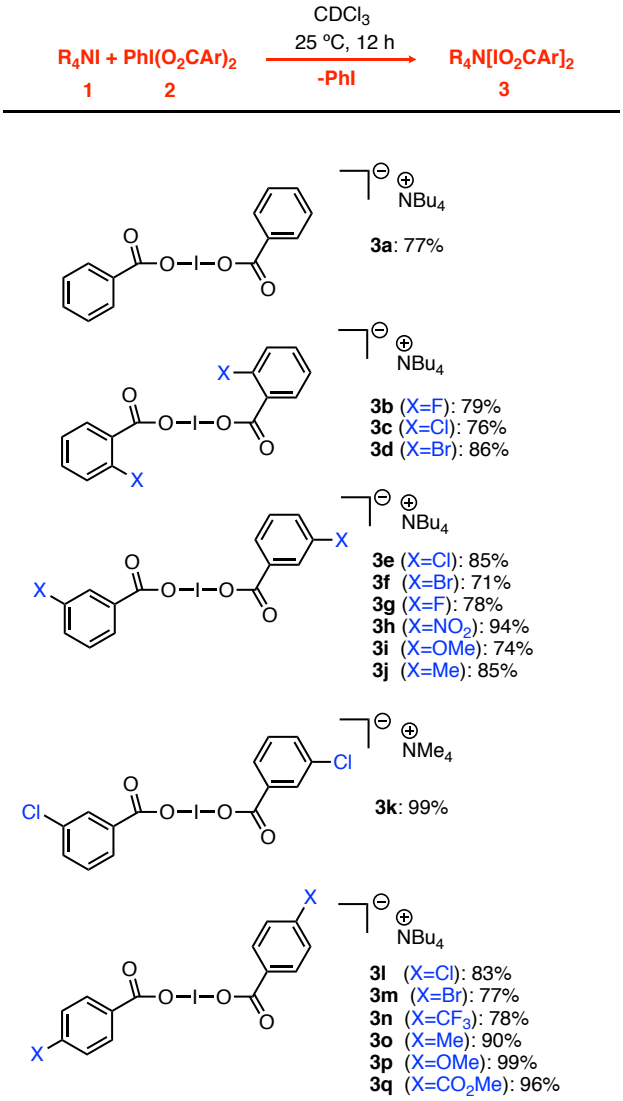


Figure 5: Synthesis of iodine(I) reagents of the general formula $R_4N[I(O_2CAr)_2]$.

The high stability of this type of compounds can be rationalized by examining the X-ray structures. Four of the new compounds **3f**, **3g**, **3i** and **3k** were submitted to analysis by X-ray diffraction of suitable

crystals as it is shown in Figure 6.[65] These compounds display the expected linear coordination mode at the central iodine atom by the anionic carboxylates, and the iodine-oxygen distance is comprised between 2.16 and 2.20 Å. The bond length between the iodine center and the ligands is shorter compared to the interaction for the neutral ligands of Barluenga's reagent (2.255-2.261 Å)[66],[67] or Yoshida´s reagent (2.27 Å).[37] The shorter bond lengths that are observed for anionic ligands is a proof of more pronounced iodine-ligand interaction and as a consequence, higher stability.

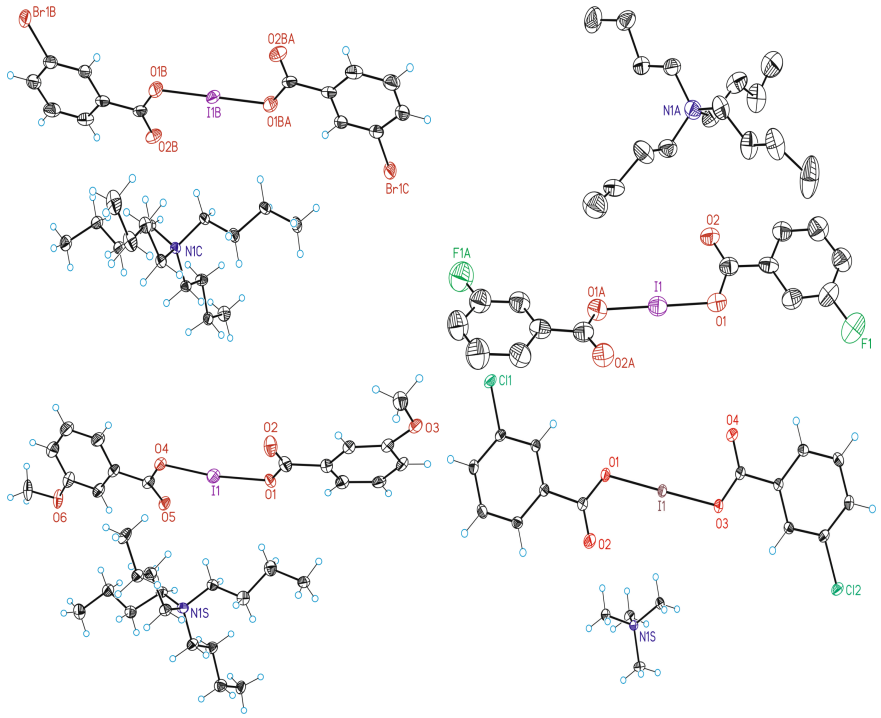
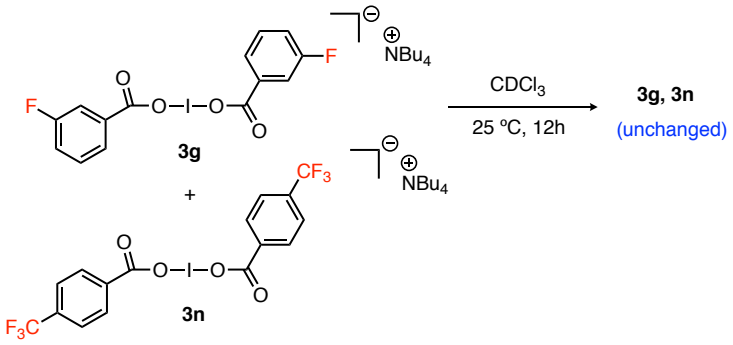


Figure 6: From top to bottom, right to left: Solid-state structures of compound **3f**, **3g**, **3i** and **3k**.

Although these reagents appeared to be air- and moisture-stable in their solid form, we were interested to study the stability of these

reagents with regard to ligand exchange in solution. Hence fluorinated compounds **3g** and **3n** were dissolved in deuterated chloroform (Scheme 26). This experiment continued repeated monitoring by ^{19}F-NMR spectroscopy. The spectra showed no cross-over between the benzoates from the iodine coordination sphere of the two differently fluorinated reagents, thereby confirming that the two anionic iodine units remained stable at 25°C in $CDCl_3$ solvent.



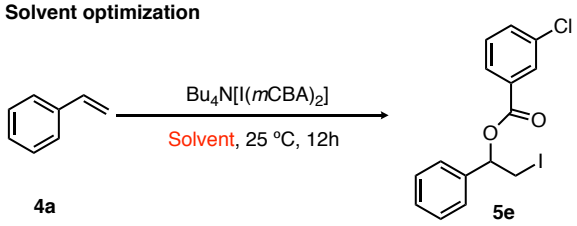
Scheme 26: Proof of stability of two iodine(I) compounds against dissociation in solution.

2.2.2. Reagent performance in alkene oxidation

We have investigated the reaction of styrene with these iodine(I) reagents. In the previous chapter was shown how some iodine(I) compounds induce iodooxygenation reactions, due to this fact, we were interested to explore this particular reaction for the present case. We started our exploration by mixing $Bu_4N[I(mCBA)_2]$ with styrene in different solvents at 25 ºC (Table 1, Scheme 27). Using Et_2O, acetonitrile or toluene, the desired iodooxygenation reaction did not proceed (entries 1, 2 and 3), whereas the expected product was observed using THF and DMF with an average of 15% yield (entries

4 and 5). However, in THF and DMF, a significant amount of by-products were observed. Finally, DCM was found to be the best solvent leading to a cleaner reaction and a better isolated yield (25%, entry 6). Then, we observed that the temperature is not an important factor for the efficiency of the reaction (Table 2, Scheme 27). In fact, increasing the temperature to 30 °C, 40 °C or 60 °C led to the same range of yield (32%, 28% and 31% respectively) and it also led to the formation of multiple impurities along with unreacted starting material. To avoid the formation of too many by-products, we decided to work at 30°C.

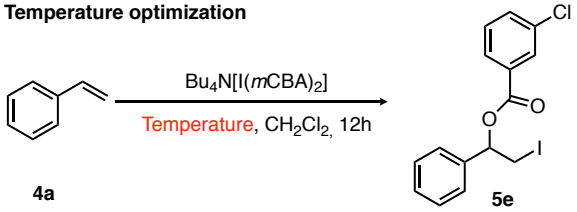
Solvent optimization



4a **5e**

Entry	Solvent	Isolated yield (%)
1	Et_2O	0
2	ACN	0
3	Toluene	0
4	THF	10
5	DMF	15
6	CH_2Cl_2	25

Temperature optimization



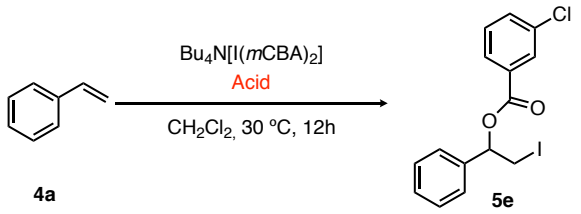
4a **5e**

Entry	T (°C)	Isolated yield (%)
1	25	25
2	30	32
3	40	28
4	60	31

Scheme 27: Temperature and solvent optimizations.

Due to these informations, we thought that the addition of an acid might be beneficial to accelerate the reaction (Scheme 28). Our

investigation of different acid promoters started with the use of a solution of 4M HCl and we observed a slight improvement of the yield (37%, entry 1). Acetic acid (43%, entry 2), formic acid (46%, entry 3), citric acid (40%, entry 4), pivalic acid (50%, entry 5) and TFA (54%, entry 6) gave better results than 4M HCl but still left room for improvement. Finally, the use of the *m*-chlorobenzoic acid, which is present as carboxylate ligand in the iodine(I) reagent, gave the best result with 94% isolated yield (entry 7).

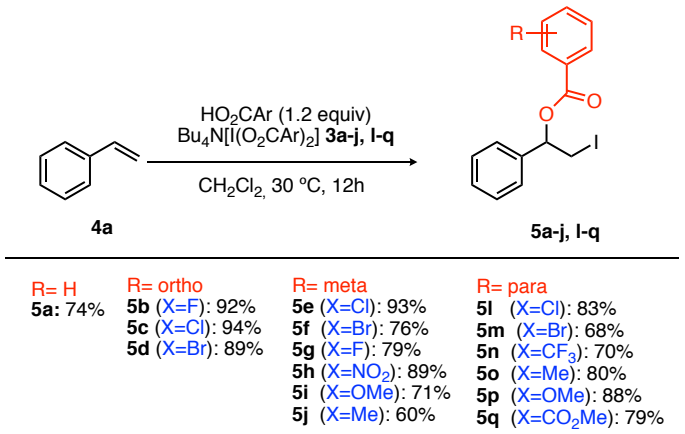


Entry	Acid	Isolated yield (%)
1	HCl (4M)	37
2	Acetic acid	43
3	Formic acid	46
4	Citric acid	40
5	Pivalic acid	50
6	TFA	54
7	*m*-CBA	94

Scheme 28: Effect of the addition of an acid to the iodooxygenation reaction.

This proved that the iodine(I) reagent is activated by the addition of an equimolar amount of free carboxylic acid, which accelerated the reaction.

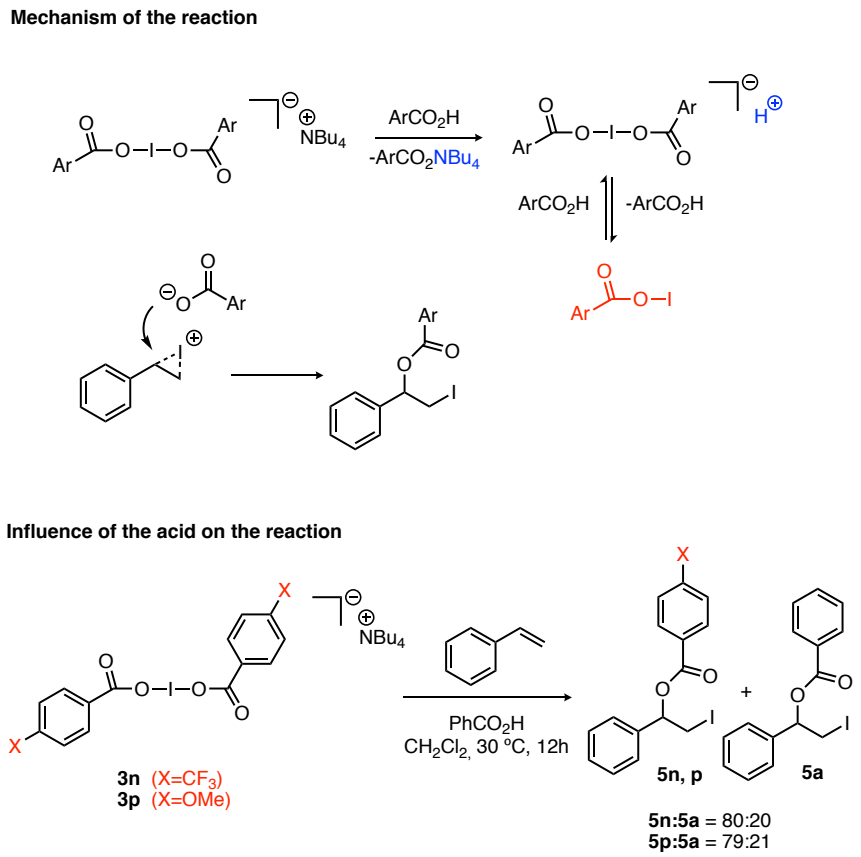
As observed for the complete set of 16 examples, all reagents **3** provided the corresponding 1,2-difunctionalized products in 60-94% isolated yield regardless of the position of the electron-donating or electron-withdrawing group in the iodine(I) reagent (Scheme 29).



Scheme 29: Iodooxygenation of styrene **4a** with the set of reagents **3**.

Mechanistic studies of the transformation revealed (Scheme 30, top), that the iodine(I) reagent in presence of the benzoic acid derivative gives the protonated iodine derivative and the corresponding tetrabutylammonium benzoate. One of the two carboxylate ligands dissociates from the central iodine and the resulting active species I-O_2CAr reacts with styrene, forming an intermediate iodonium, which undergoes nucleophilic attack by the carboxylate to afford the iodooxygenated product. To study the influence of the free acid in the coordination sphere of the iodine center, two experiments were carried out with two different *para*-substituted iodine(I) reagents, one with an electron-withdrawing CF_3-group, **3n**, and another with an electron-donating OMe-group, **3p**, in presence of benzoic acid. In both cases a mixture of two products with a ratio 4:1 of **5n/5a** and

5p/**5a** was formed, respectively, regardless of the electronic substitution, leading to an identical outcome (Scheme 30, bottom). Finally, it is also noteworthy that the use of a catalytic amount of free acid (10 mol%) results in a significant reduction of the reactivity.



Scheme 30: Exploration into the mechanism of the I(I) promoted iodooxygenation.

Furthermore, we studied potential substitution effects on the initial rate of the iodooxygenation. As represented at the top of Figure 7,

such electronic influences are indeed present in the oxidation of styrene **4a** with different iodine(I) reagents. In order to avoid the steric influence on the reaction rate, we selected four reagents with a *para*-substitution (**3n-3q** and **3a).** As it can be observed in Figure 7, electron-withdrawing substituents enhance the initial rate of the reaction, which represents a logical result due to the lower stability of the ligand at the iodine(I)-center, enabling the fastest liberation of the active species I-O_2CAr and also, the electrophilic character is more pronounced.

Moreover, this observation was confirmed by the corresponding Hammett plot. Based on the initial rate of the individual reactions, a linear relationship is obtained between the logarithm of the rate fractions versus the Hammett σ values (Figure 7, bottom). The graphical correlation yields a corresponding *p* value of 0.78, which is characteristic of a built-up of electrophilicity in the slow step of the reaction as discussed before.

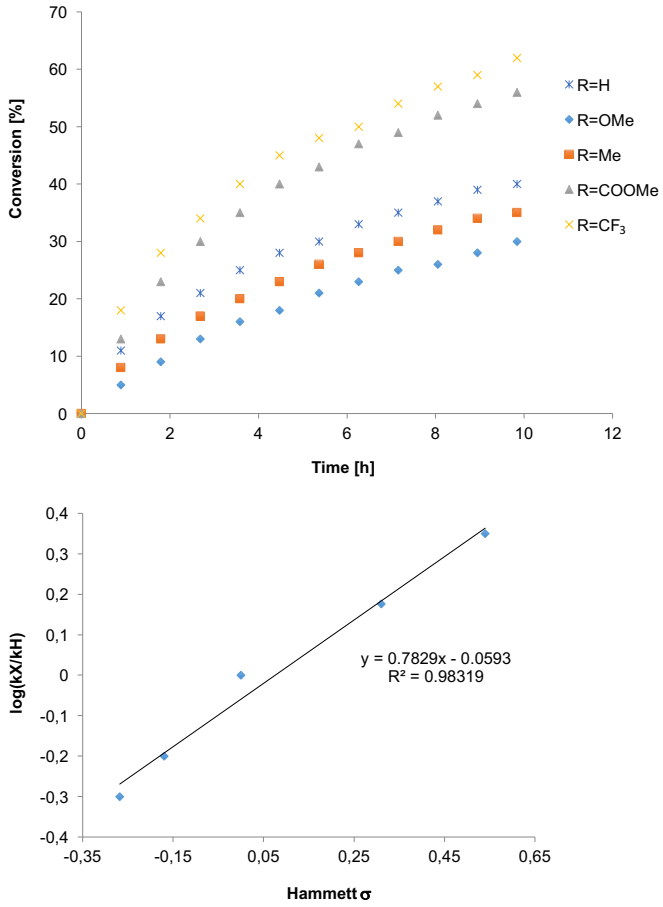
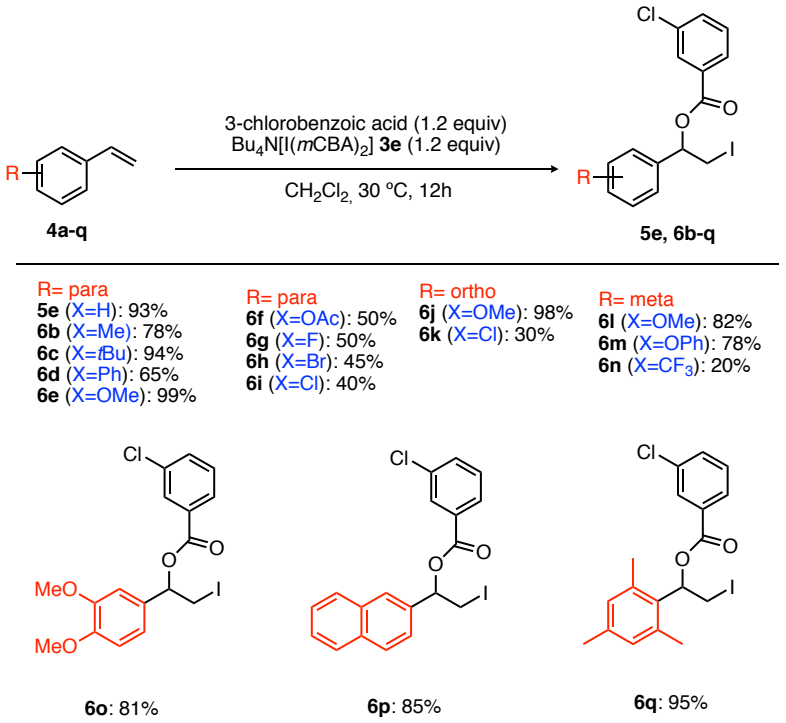


Figure 7: Effect of the 4-substitution on the initial rate of the iodooxygenation of styrene with different iodine(I) reagents (top) and Hammett correlation (bottom).

Due to the best result of the iodooxygenation obtained with the iodine(I) containing *m*CBA as ligands, we decided to use this reagent with different arene derivatives to increase the scope of the reaction. As demonstrated in Scheme 31 for 17 examples, the corresponding vicinal difunctionalization reaction proceeds well for a serie of different substitution patterns at the arene core. Good results were

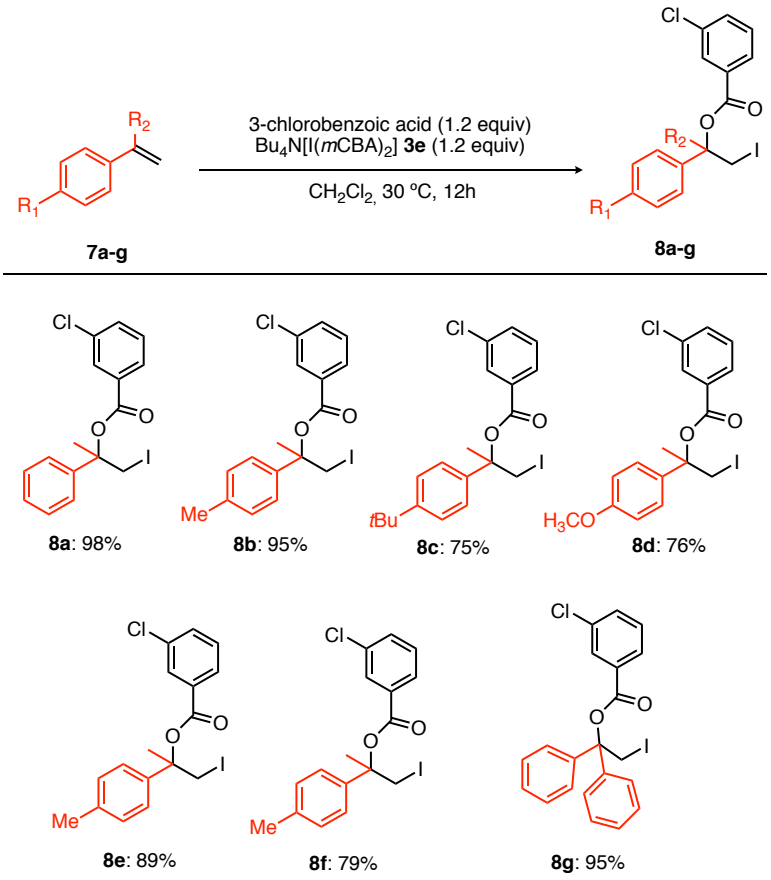
obtained with individual 2-, 3- and 4-substitutions as demonstrated for products **6b-n** with 20-99% isolated yield. Moreover, the reaction allowed higher substitution at the aromatic ring as it is shown for products **6 o-q** with 81-95% isolated yield.



Scheme 31: Iodooxygenation of styrenes **4a-q** with reagent **3e**.

Furthermore, we observed that the reaction gives the desired iodooxygenated products **8 a-g** in 55-98% isolated yield, with α-substituted styrenes as substrates (Scheme 32). As in the case of previous examples, all the reactions proceeded with complete regio- and chemoselectivity, which is in favor of the carboxylate incorporation at the benzylic position. This is logical because the

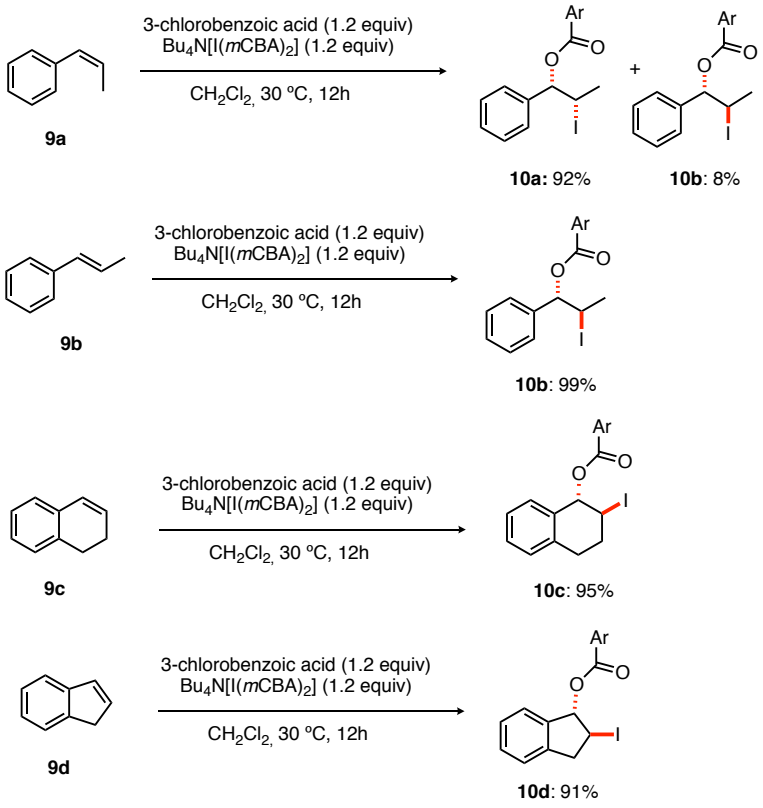
benzylic position is the most reactive for nucleophilic attack at the stage of the iodonium intermediate, resulting from alkene addition to the electrophilic iodine center.



Scheme 32: Iodooxygenation of α-substituted styrenes **7a-g** with reagent **3**.

Furthermore, we investigated the stereospecificity of the reaction with *β*-styrene **9a** and **9b**. We observed that in the case of *cis*-*β*-styrene, the reaction is stereoselective as the *cis*-product **10a** was obtained as the major stereoisomer (*cis/trans* = 92/8). In the case of

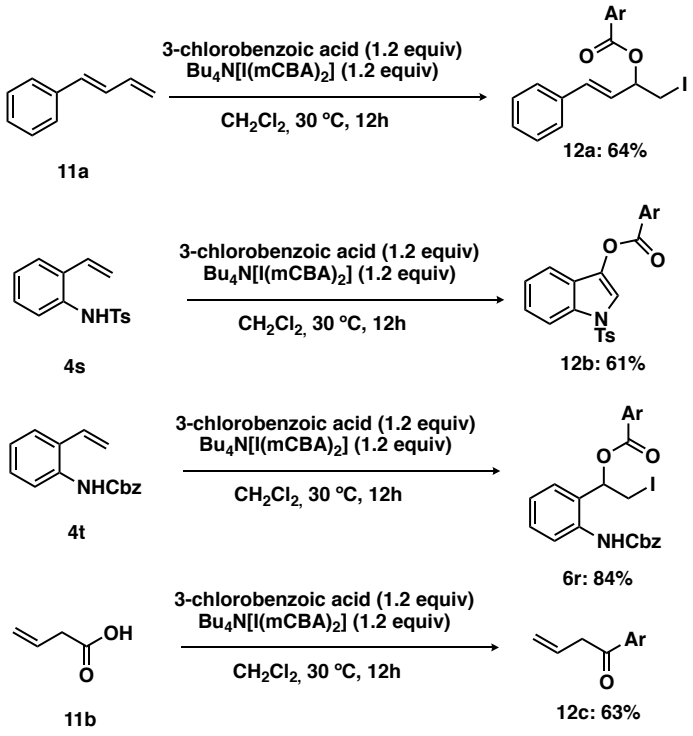
trans-*β*-styrene, the reaction is stereospecific with formation of the *trans*-product **10b** in 99% isolated yield. Cyclic alkenes such as **9c** and **9d** gave the corresponding regiospecific products **10c** and **10d** in a 95-91% isolated yield. This means that the vicinal iodooxygenation reaction proceeds with stereospecificity regarding the geometry of internal double bond (Scheme 33).



Scheme 33: Iodooxygenation of internal alkenes **9a-d** with reagent **3e**.

Further studies were focused on the exploration of additional substrates. In previous work, Muñiz´s group studied the diamination of butadiene derivatives such as **11a** with hypervalent iodine reagents

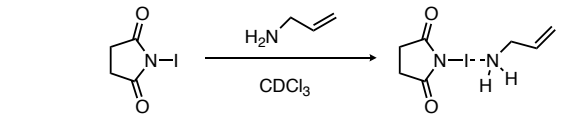
and observed the selective formation of vicinal diamines. As expected, the reaction with **3e** led to the formation of a single regioisomer **12a**, due to the formation of the thermodynamic product (maintenance of styrene conjugation).[68] Two examples of amino styrenes with different protecting groups were studied. We observed that the tosylamide derivative **4s** promotes an aminooxygenation to the 3-oxygenated indoline. Instance of that is provided by the observation that the Cbz derivative undergoes clean iodooxygenation to **6r**.[69] In the case of substrate **11b**, we obtained a similar result as Minakata in the study of the decarboxylative acetoxylation of unsaturated carboxylic acid.[70] Here, the iodine reagent promotes the decarboxylation of the compound, followed by oxygenation to give the allylic product (Scheme 34).

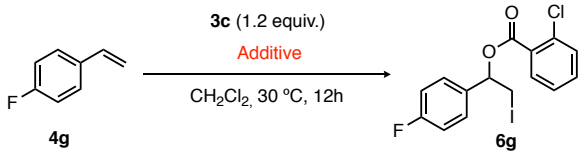


Scheme 34: Further examples on the oxidation of alkenes **4s-t, 11a-b** with reagent **3e**.

To conclude our research, it was interesting to find a general additive that could replace the benzoic acid derivative in each reaction in order to activate the intermediate I-O_2CAr to promote the iodooxygenated product. In the beginning of the project, we tried to optimize the reaction with several acids but we observed that none of them provided the iodooxygenated product with a good yield. On the other hand, in 2015, Hayashi *et al*. reported the activation of *N*-iodosuccinimide with allylamine.[38] In our case, allylamine was not compatible with iodine(I) reagent **3c**, however, acetamide derivatives promoted the iodooxygenated product of 4-fluorostyrene **4g** to the corresponding product **6g** (66-100%, conversion yield) in a way that is comparable with 2-chlorobenzoic acid. Due to its instability in solution, no structural data has become yet; an activation of iodine(I) by acetamide, similar to the case of Hayashi, is proposed to be involved in this case (Scheme 35).

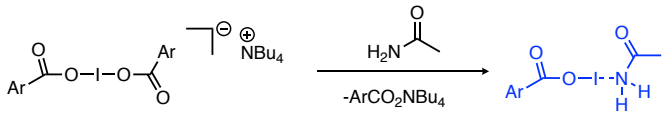
Hayashi (2015)





4g **6g**

Additive	Equivalents	Conversion (%)[a]
2-Chlorobenzoic acid	1.2	96
Allylamine	1.2	-
Acetamide	1.2	75
Acetamide	2	90
Acetamide	3	100 (83)[b]
Trifluoroacetamide	1.2	72
2-Phenylacetamide	1.2	66



Scheme 35: Iodooxydation upon activation of reagent **3c** with amides. [a] Conversion by ^{19}F-NMR spectroscopy with fluorobenzene as internal standard. [b] Isolated yield purification.

This outcome demonstrated that there are further possible activation modes for compounds **3** in metal-free oxidation reactions.

2.3. CONCLUSION

In this section, we have presented the general synthesis, isolation and characterization of several important iodine(I) reagents with the general formula $R_4N[I(O_2CAr)_2]$. These compounds are air- and moisture-stable and also survive upon exposure in solution. They represent conceptually new iodine(I) compounds with anions as stabilizers. These compounds display the expected performance as electrophilic reagents upon interaction with electron-rich substrates such as styrene derivatives. This iodine(I) compounds are powerful reagents for the vicinal iodooxygenation of alkenes with a total of 47 different examples obtained. In this versatile application, the reaction mechanism was studied in detail. Furthermore, the initial rates of the individual reactions and the chemo- and regioselectivity of the transformation were investigated. Finally, we discovered acetamide as general additive, which can be added to the reaction in order to activate the intermediate $I\text{-}O_2CAr$ to promote the reaction.

2.4. EXPERIMENTAL SECTION

2.4.1. General procedures

General procedure for the synthesis of iodine derivatives

A Schlenk tube equipped with a magnetic stirrer was charged with the corresponding iodine(III) compound (1.0 equiv) and ammonium iodide (2.17 mmol, 1.0 equiv), evacuated and backfilled with argon. At this point, 4 mL of $CDCl_3$ were added. The solution was stirred for 12 h at 25ºC. Et_2O was then added to induce the precipitation of a solid which was filtered and washed with Et_2O. The solid was dried under reduced pressure to obtain the pure title compound.

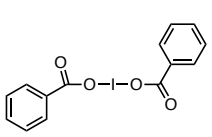
General procedure for the difunctionalization reaction

A Schlenk tube equipped with a magnetic stirrer was charged with benzoic acid derivative (1.2 equiv), iodine(I) reagent **3** (1.2 equiv) and 3 mL of dry dichloromethane. The corresponding styrene (0.2 mmol, 1 equiv) was added and the reaction was stirred overnight at 30ºC. Then, DCM was added and the solution was washed with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc, 9/1, v/v) to provide the correspond-ding iodooxygenated product.

2.4.2. Compound characterization

Iodine(I) reagent

Tetrabutylammonium 1,3-benzoyldioxiodane 3a



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 12H), 1.42 (h, *J* = 7.4 Hz, 8H), 1.63-1.77 (m, 8H), 3.34-3.44 (m, 8H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.98 (d, *J* = 7.3 Hz, 4H).

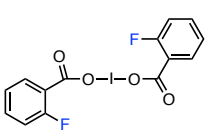
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.1, 127.8, 129.9, 130.8, 133.2, 171.5.

IR ν(cm^{-1}): 3066, 2960, 2931, 2873, 1607, 1574, 1320, 1292, 1124, 1023, 707, 678.

HRMS (MALDI-TOF): cald. for $C_{14}H_{10}IO_4$-(M-Bu_4N): 368.9629; found: 368.9640.

mp: 142-143 ºC.

Tetrabutylammonium 1,2-bis(2-fluorobenzoyl) dioxiodane 3b



^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.00 (t, *J* = 7.4 Hz, 12H), 1.48 (h, *J* = 7.4 Hz, 8H), 1.73-1.83 (m, 8H), 3.44-3.49 (m, 8H), 6.97-7.04 (m, 2H), 7.05-7.12 (m, 2H), 7.30-7.36 (m, 2H), 7.75-7.84 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 19.7, 24.0, 60.0, 115.9, 116.1, 123.4 (d, *J* = 3.7 Hz), 131.5 (d, *J* = 8.6 Hz), 132.0 (d, *J* = 2.3 Hz), 161.0 (d, *J* = 253.8 Hz), 169.0.

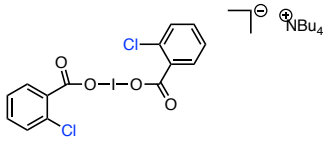
^{19}F NMR (376 MHz, $CDCl_3$): δ = -112.7.

IR ν(cm^{-1}): 2962, 2933, 2875, 1648, 1304, 759, 653.

HRMS (MALDI-TOF): cald. for $C_{14}H_8F_2IO_4$-(M-NBu_4):404.9441; found: 404.9449.

mp: 124-126 ºC.

Tetrabutylammonium 1,2-bis(2-chlorobenzoyl) dioxiodane 3c



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 12H), 1.45 (h, *J* = 7.3 Hz, 8H), 1.68-1.78 (m, 8H), 3.38-3.44 (m, 8H), 7.15-7.23 (m, 4H), 7.27-7.33 (m, 2H), 7.55-7.67 (m, 2H).

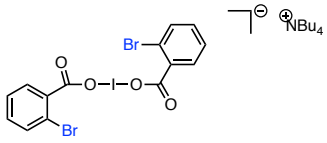
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 19.8, 24.1, 59.1, 126.3, 129.8, 129.9, 130.3, 131.6, 134.2, 171.0.

IR ν(cm^{-1}): 2961, 2932, 2874, 1656,1635, 1290, 1256, 750, 648.

HRMS (MALDI-TOF): cald. for $C_{14}H_8Cl_2IO_4$-(M-NBu_4): 436.8850; found: 436.8869.

mp: 98-100 ºC.

Tetrabutylammonium 1,2-bis(2-bromobenzoyl) dioxiodane 3d



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92-1.00 (m, 12H), 1.36-1.50 (m, 8H), 1.65-1.79 (m, 8H), 3.33-3.44 (m, 8H), 7.03-7.14 (m, 2H), 7.19-7.25 (m, 2H), 7.43-7.50 (m, 2H), 7.03-7.14 (m, 2H).

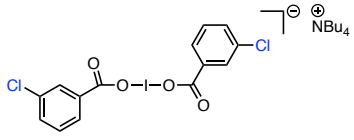
^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 20.0, 24.3, 59.1, 120.2, 127.1, 130.2, 130.3, 133.2, 136.8, 171.8.

IR ν(cm^{-1}): 2960, 2931, 2874, 1656, 1295, 1256, 1137, 748, 693, 432.

HRMS (MALDI-TOF): cald. for $C_{14}H_8Br_2IO_4$-(M-NBu_4): 524.8850; found: 524.8840.

mp: 104-106 ºC.

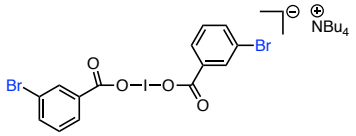
Tetrabutylammonium 1,3-bis(3-chlorobenzoyl)dioxiodane 3e



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (s, 12H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.37 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 2H), 7.83 (dt,

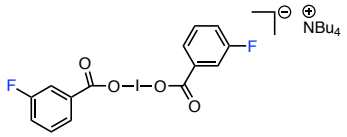
J = 7.7, 1.3 Hz, 2H), 7.93 (t, *J* = 1.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.5, 128.0, 129.3, 129.9, 131.1, 133.9, 170.7.
IR ν(cm^{-1}): 3084, 3056, 3033, 2954, 1623, 1563, 1483, 1292, 1256, 736.
HRMS (MALDI-TOF): cald. for $C_{14}H_8Cl_2IO_4$-(M-Me_4N): 436.8850; found: 436.8843.
mp: 118-119 ºC.

Tetrabutylammonium 1,3-bis(3-bromobenzoyl)dioxiodane 3f



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 12H), 1.41-1.43 (m, 8H), 1.64-1.78 (m, 8H), 3.33-3.44 (m, 8H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.53 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H), 8.12 (brs, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.1, 121.9, 128.6, 129.5, 133.0, 138.6, 170.0.
IR ν(cm^{-1}): 2960, 2931, 2872, 1609, 1561, 1293, 1258, 750, 717.
HRMS (MALDI-TOF): cald. for $C_{14}H_8Br_2IO_4$-(M-Bu_4N): 524.7839; found: 524.7819.
mp: 118-119 ºC.

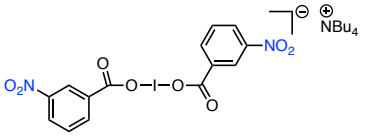
Tetrabutylammonium 1,3-bis(3-fluorobenzoyl)dioxiodane 3g



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.4 Hz, 12H), 1.45 (h, *J* = 7.4 Hz, 8H), 1.64-1.79 (m, 8H), 3.36-3.45 (m, 8H), 7.09 (tdd, *J* = 8.4, 2.7, 1.0 Hz, 2H), 7.24-7.34 (m, 2H), 7.65 (d, *J* = 9.9 Hz, 2H), 7.77 (d, *J* = 7.7 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.2, 116.7 (d, *J* = 21.9 Hz), 117.6 (d, *J* = 21.4 Hz), 125.7, 125.6, 129.2 (d, *J* = 7.7 Hz), 162.5 (d, *J* = 245.1 Hz), 170.3.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -114.5.

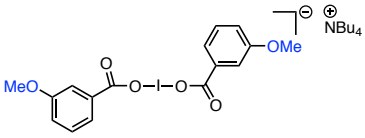
IR ν(cm^{-1}): 3075, 2960, 2934, 2874, 1617, 1582, 1297, 1288, 1214, 760.
HRMS (MALDI-TOF): cald. for $C_{14}H_8F_2IO_4$-(M-Bu_4N): 404.9441; found: 404.9475.
mp: 107-108 ºC.

Tetrabutylammonium 1,3-bis(3-nitrobenzoyl)dioxiodane 3h



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 12H), 1.45 (h, *J* = 7.5 Hz, 8H), 1.72-1.80 (m, 8H), 3.25-3.66 (m, 8H), 7.50 (t, *J* = 7.9 Hz, 2H), 8.13 (ddd, *J* = 8.2, 2.5, 1.2 Hz, 2H), 8.30 (dt, *J* = 7.7, 1.5 Hz, 2H), 8.72-8.79 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.2, 124.8, 125.4, 128.9, 134.8, 135.9, 148.0, 169.0.
IR ν(cm^{-1}): 2959, 2932, 2874, 1654, 1628, 1527, 1347, 1296, 1257, 716.
HRMS (MALDI-TOF): cald. for $C_{14}H_8IN_2O_8$-(M-Bu_4N): 458.9331; found: 458.9377.
mp: 129-130 ºC.

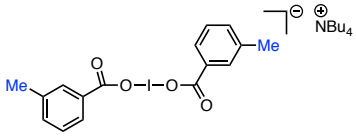
Tetrabutylammonium 1,3-bis(3-methoxybenzoyl)dioxiodane 3i



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 12H), 1.41 (h, *J* = 7.4 Hz, 8H), 1.64-1.73 (m, 8H), 3.34-3.43 (m, 8H), 3.81 (s, 6H), 6.93 (ddd, *J* = 8.2, 2.8, 1.1 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.51 (dd, *J* = 2.7, 1.4 Hz, 2H), 7.55 (dt, *J* = 7.7, 1.2 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 55.5, 59.1, 114.5, 117.3, 122.5, 128.7, 134.8, 159.3, 171.2.
IR ν(cm^{-1}): 2960, 2932, 2872, 2837, 1605, 1578, 1432, 1289, 1278, 1230, 1100, 1043, 758.

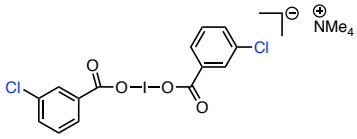
HRMS (MALDI-TOF): cald. for $C_{16}H_{14}IO_6$-(M-Bu_4N): 428.9841; found: 428.9822.
mp: 112-113 ºC.

Tetrabutylammonium 1,3-bis(3-methylbenzoyl)dioxiodane 3j



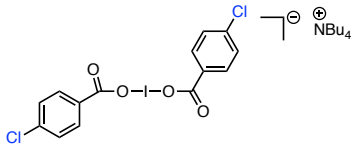
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 12H), 1.38 (h, *J* = 7.4 Hz, 8H), 1.60-1.65 (m, 8H), 2.32 (s, 6H), 3.20-3.39 (m, 8H), 7.20-7.26 (m, 4H), 7.72-7.74 (m, 2H), 7.77 (s, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 21.4, 24.1, 58.9, 127.0, 127.7, 130.6, 131.5, 133.1, 137.3, 171.5.
IR ν(cm^{-1}): 2959, 2931, 2872, 1613, 1601, 1583, 1295, 1279, 1210, 749, 673.
HRMS (MALDI-TOF): cald. for $C_{16}H_{14}IO_4$-(M-Bu_4N): 396.9942; found: 396.9995.
mp: 143-144 ºC.

Tetramethylammonium1,3-bis(3-chlorobenzoyl)dioxiodane 3k



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (s, 12H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.37 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 2H), 7.83 (dt, *J* = 7.7, 1.3 Hz, 2H), 7.93 (t, *J* = 1.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.5, 128.0, 129.3, 129.9, 131.1, 133.9, 170.7.
IR ν(cm^{-1}): 3084, 3056, 3033, 2954, 1623, 1563, 1483, 1292, 1256, 736.
HRMS (MALDI-TOF): cald. for $C_{14}H_8Cl_2IO_4$-(M-Me_4N): 436.8850; found: 436.8843.
mp: 118-119 ºC.

Tetrabutylammonium 1,4-bis(4-chlorobenzoyl)dioxiodane 3l



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 12H), 1.40 (h, *J* = 7.4 Hz, 12H), 1.64-1.72 (m, 8H), 3.20-3.47 (m, 8H), 7.27 8d, *J* = 8.4 Hz, 4H), 7.88 (d, *J* = 8.4 Hz, 4H).

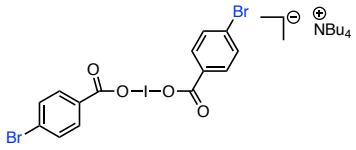
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.1, 128.0, 131.4, 131.7, 136.9, 170.4.

IR ν(cm^{-1}): 2960, 2933, 2874, 1618, 1608, 1285, 1275, 1123, 1013, 765, 552.

HRMS (MALDI-TOF): cald. for $C_{14}H_8Cl_2IO_4$-(M-Bu_4N): 436.8850; found: 436.8768.

mp: 152-153 ºC.

Tetrabutylammonium 1,4-bis(4-bromobenzoyl)dioxiodane 3m



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 12H), 1.41 (h, *J* = 7.4 Hz, 8H), 1.55-1.77 (m, 8H), 3.24-3.46 (m, 8H), 7.44 (d, *J* = 8.3 Hz, 4H), 7.83 (d, *J* = 8.2 Hz, 4H).

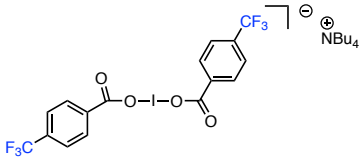
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 19.8, 24.1, 59.0, 125.4, 130.9, 131.5, 131.9, 170.5.

IR ν(cm^{-1}): 2957, 2930, 2871, 1646, 1585, 1284, 1118, 1011, 832, 761.

HRMS (MALDI-TOF): cald. for $C_{14}H_8Br_2IO_4$-(M-Bu_4N): 524.7840; found: 524.7587.

mp: 164-165 ºC.

Tetrabutylammonium 1,4-bis(4-(trifluoromethyl)benzoyl) dioxiodane 3n



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 12H), 1.41 (h, *J* = 7.4 Hz, 8H), 1.63-1.76 (m, 8H), 3.32-3.43 (m, 8H), 7.56 (d, *J* = 8.2 Hz, 4H), 8.05 (d, *J* = 8.0 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 59.2, 124.2 (q, *J* = 272.3 Hz), 124.8 (q, *J* = 3.8 Hz), 130.2, 132.5 (q, *J* = 32.7 Hz), 136.3, 170.0.

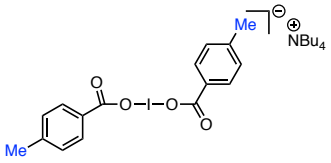
^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.8.

IR ν(cm^{-1}): 2962, 2935, 2876, 1654, 1630, 1329, 1307, 1289, 1162, 1117, 1061, 863, 781, 703.

HRMS (MALDI-TOF): cald. for $C_{16}H_8F_6IO_4$-(M-Bu_4N): 504.9377; found: 504.9323.

mp: 171-172 ºC.

Tetrabutylammonium 1,4-bis(4-methylbenzoyl)dioxiodane 3o



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 12H), 1.38 (h, *J* = 7.4 Hz, 8H), 1.60-1.69 (m, 8H), 2.33 (s, 6H), 3.26-3.40 (m, 8H), 7.09 (d, *J* = 7.9 Hz, 4H), 7.83 (d, *J* = 7.9 Hz, 4H).

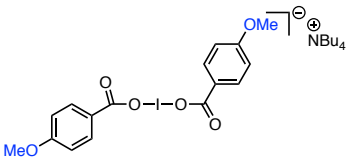
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 21.5, 24.1, 58.9, 128.5, 129.9, 130.5, 140.9, 171.4.

IR ν(cm^{-1}): 2961, 2932, 2873, 1645, 1609, 1282, 1170, 1119, 1020, 759, 616.

HRMS (MALDI-TOF): cald. for $C_{16}H_{14}IO_4$-(M-Bu_4N): 396.9942; found: 396.9898.

mp: 170-171 ºC.

Tetrabutylammonium 1,4-bis(4-methoxybenzoyl)dioxiodane 3p



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 12H), 1.42 (h, *J* = 7.3 Hz, 8H), 1.60-1.79 (m, 8H), 3.27-3.48 (m, 8H), 3.82 (s, 6H), 6.82 (d, *J* = 8.8 Hz, 4H), 7.93 (d, *J* = 8.8 Hz, 4H).

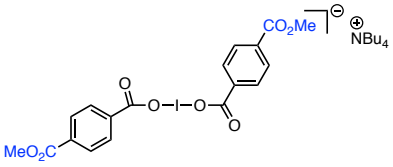
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.9, 24.2, 55.4, 59.1, 112.9, 125.8, 131.7, 161.7, 171.2.

IR ν(cm^{-1}): 2999, 2951, 2930, 2872, 2840, 1634, 1601, 1505, 1280, 1239, 1157, 1022, 773, 616.

HRMS (MALDI-TOF): cald. for $C_{16}H_{14}IO_6$-(M-Bu_4N): 428.9841; found: 428.9867.

mp: 145-146 ºC.

Tetrabutylammonium 1,4-bis(methylesterbenzoyl) dioxiodane 3q



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92-1.04 (m, 12H), 1.36-1.41 (m, 8H), 1.58-1.71 (m, 8H), 3.30-3.42 (m, 8H), 3.92 (s, 6H), 7.94-8.17 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 20.1, 24.4, 52.5, 59.2, 129.3, 130.0, 132.1, 137.3, 167.2, 170.7.

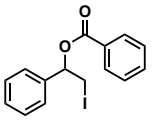
IR ν(cm^{-1}): 2957, 2928, 2872, 1710, 1646, 1278, 731.

HRMS (MALDI-TOF): cald. for $C_{18}H_{14}IO_8$-(M-NBu_4): 484.9739; found: 484.9734.

m.p.: 129-130 ºC.

Iodooxygenated products.

2-Iodo-1-phenylethylbenzoate 5a



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.67 (dd, *J* = 10.7, 7.7 Hz, 1H), 6.12 (dd, *J* = 7.7, 5.2 Hz, 1H), 7.36-7.52 (m, 7H), 7.59-7.65 (m, 1H), 8.13-8.18 (m, 2H).

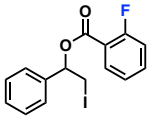
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 75.5, 126.3, 128.5, 128.6, 128.8, 129.8, 129.9, 133.3, 138.6, 165.3.

IR ν(cm^{-1}): 3031, 2054, 1710, 1260, 1098, 1026, 699, 684.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{13}INaO_2$ 374.9852, found; 374.9866.

m.p: 44-47 ºC.

2-Iodo-1-phenylethyl-2-fluorobenzoate 5b



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.66 (dd, *J* = 10.6, 7.7 Hz, 1H), 6.16 (dd, *J* = 7.7, 5.2 Hz, 1H), 7.15-7.21 (m, 2H), 7.33-7.51 (m, 5H), 7.53-7.63 (m, 1H), 8.05 (td, *J* = 7.5, 1.9 Hz, 1H).

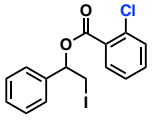
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.7, 76.1, 117.3 (d, *J* = 22.2 Hz), 118.3 (d, *J* = 9.4 Hz), 124.0 (d, *J* = 4.1 Hz), 126.5, 128.7, 128.8, 132.3, 134.9 (d, *J* = 9.1 Hz), 138.3, 160.0 (d, *J* = 3.7 Hz), 162.2 (d, *J* = 261.2 Hz).

^{19}F NMR (376 MHz,$CDCl_3$): δ = -108.5.

IR ν(cm^{-1}): 3030, 2921, 1727, 1612, 1246, 1073, 750.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}FINaO_2$ 392.9758, found; 392.9765.

2-Iodo-1-phenylethyl-2-chlorobenzoate 5c



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.67 (dd, *J* = 10.6, 7.8 Hz, 1H), 6.16 (dd,

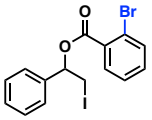
J = 7.8, 5.2 Hz, 1H), 7.35-7.52 (m, 8H), 8.00 (dd, *J* = 7.7, 1.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 76.4, 126.6, 126.7, 128.8, 128.9, 129.5, 131.2, 131.8, 132.9, 134.1, 138.1, 164.2.0.

IR ν(cm^{-1}): 3032, 2963, 1729, 1283, 1213, 1109, 1043, 743.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}ClINaO_2$ 408.9463, found; 408.9462.

2-Iodo-1-phenylethyl-2-bromobenzoate 5d



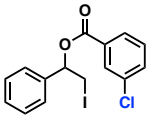
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.68 (dd, *J* = 10.6, 7.7 Hz, 1H), 6.15 (dd, *J* = 7.7, 5.3 Hz, 1H), 7.34-7.51 (m, 7H), 7.67-7.73 (m, 1H), 7.94-7.99 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.4, 76.6, 122.0, 126.6, 127.2, 128.8, 128.9, 131.5, 131.7, 132.9, 134.5, 138.0, 164.7.

IR ν(cm^{-1}): 3063, 3031, 1731, 1241, 1099, 1026, 740, 696.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}BrINaO_2$ 452.8958, found; 452.8954.

2-Iodo-1-phenylethyl-3-chlorobenzoate 5e



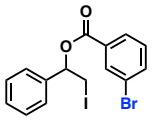
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.67 (dd, *J* = 10.7, 7.9 Hz, 1H), 6.13 (dd, *J* = 7.9, 5.1 Hz, 1H), 7.36-7.49 (m, 6H), 7.59 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 8.03 (dt, *J* = 7.9, 1.2 Hz, 1H), 8.12 (t, *J* = 2.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6. 76.1, 126.3, 128.0, 128.8, 128.9, 129.8, 129.8, 131.5, 133.3, 134.7, 138.2, 164.1.

IR ν(cm^{-1}): 3066, 3032, 1722, 1248, 1120, 1070, 742.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}ClINaO_2$ 408.9463, found; 408.9466.

2-Iodo-1-phenylethyl-3-bromobenzoate 5f



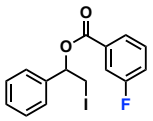
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.67 (dd, *J* = 10.7, 7.9 Hz, 1H), 6.13 (dd, *J* = 7.9, 5.1 Hz, 1H), 7.34-7.49 (m, 6H), 7.74 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 8.06-8.10 (m, 1H), 8.27 (t, *J* = 2.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6, 76.1, 122.6, 126.4, 128.5, 128.8, 128.9, 130.1, 131.7, 132.8, 136.3, 138.2, 164.0.

IR ν(cm^{-1}): 2956, 2924, 1722, 1235, 1114, 742, 769.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}BrINaO_2$ 452.8958, found; 452.8949.

2-Iodo-1-phenylethyl-3-fluorobenzoate 5g



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.66 (dd, *J* = 10.7, 7.8 Hz, 1H), 6.12 (dd, *J* = 7.8, 5.1 Hz, 1H), 7.32 (tdd, *J* = 8.3, 2.7, 1.1 Hz, 1H), 7.36-7.52 (m, 6H), 7.82 (ddd, *J* = 9.2, 2.7, 1.4 Hz, 1H), 7.94 (dt, *J* = 7.8, 1.4 Hz, 1H).

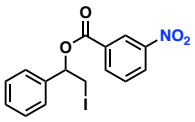
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6, 76.0, 116.7 (d, *J* = 23.1 Hz), 120.4 (d, *J* = 21.3 Hz), 125.6 (d, *J* = 3.1 Hz), 126.3, 128.9, 129.0, 130.2 (d, *J* = 7.7 Hz), 131.9 (d, *J* = 7.4 Hz), 138.3, 162.6 (d, *J* = 247.3 Hz), 164.2 (d, *J* = 3.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -111.8.

IR ν(cm^{-1}): 3069, 3033, 1721, 1445, 1266, 1195, 1091, 749.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}FINaO_2$ 392.9758, found; 392.9764.

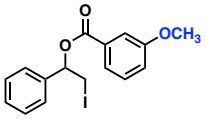
2-Iodo-1-phenylethyl-3-nitrobenzoate 5h



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.70 (dd, *J* = 10.8, 8.2 Hz, 1H), 6.17 (dd, *J* = 8.2, 4.9 Hz, 1H), 7.38-7.50 (m, 5H), 7.71 (t, *J* = 8.0 Hz, 1H), 8.44-8.49 (m, 2H), 8.94-8.96 (m, 1H).

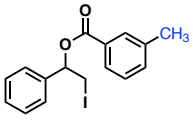
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.1, 76.8, 124.8, 126.4, 127.7, 128.9, 129.1, 129.8, 131.6, 135.5, 137.9, 148.4, 163.3.
IR ν(cm^{-1}): 2923, 2852, 1727, 1526, 1349, 1250, 1061, 694.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}INNaO_4$ 419.9703, found; 419.9705.
m.p: 108-109 ºC.

2-Iodo-1-phenylethyl-3-methoxybenzoate 5i



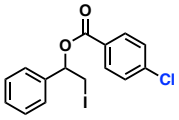
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.66 (dd, *J* = 10.7, 7.7 Hz, 1H), 3.89 (s, 3H), 6.11 (dd, *J* = 7.7, 5.1 Hz, 1H), 7.14-7.18 (m, 1H), 7.35-7.43 (m, 4H), 7.44-7.48 (m, 2H), 7.66 (dd, J = 2.7, 1.4 Hz, 1H), 7.76 (dt, *J* = 7.6, 1.4 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 55.5, 75.6, 114.5, 119.7, 122.3, 126.3, 128.8, 128.9, 129.5, 131.1, 138.5, 159.6, 165.2.
IR ν(cm^{-1}): 2960, 2835, 1715, 1269, 1209, 1033, 750.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{15}INaO_3$ 404.9958, found; 404.9976.

2-Iodo-1-phenylethyl-3-methylbenzoate 5j



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 3.43-2.71 (m, 2H), 6.12 (dd, *J* = 7.5, 5.2 Hz, 1H), 7.27-7.33 (m, 2H), 7.43 (s, 3H), 7.43-7.50 (m, 2H), 8.03-8.08 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 21.3, 75.5, 126.4, 127.0, 128.4, 128.7, 129.7, 130.3, 134.1, 138.3, 138.6, 165.5.
IR ν(cm^{-1}): 3033, 2922, 1719, 1270, 1194, 741.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{15}INaO_2$ 389.0009, found; 389.0011.

2-Iodo-1-phenylethyl-4-chlorobenzoate 5l



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59-3.69 (m, 2H), 6.11 (dd, *J* = 7.7, 5.2 Hz, 1H), 8.06-8.11 (m, 2H), 7.37-7.50 (m, 7H).

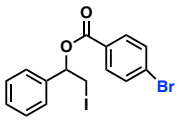
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8, 75.8, 126.3, 128.2, 128.8, 128.9, 129.0, 131.2, 138.3, 139.8, 164.5.

IR ν(cm^{-1}): 2924, 1720, 1592, 1261, 1088, 754, 697.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}ClINaO_2$ 408.9463, found; 408.9461.

m.p: 67-69 ºC.

2-Iodo-1-phenylethyl-4-bromobenzoate 5m



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.65 (dd, *J* = 10.7, 7.8 Hz, 1H), 6.10 (dd, *J* = 7.8, 5.1 Hz, 1H), 7.37-7.46 (m, 5H), 7.62-7.66 (m, 2H), 7.98-8.02 (m, 2H).

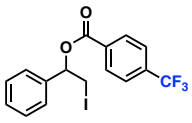
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8, 75.9, 126.3, 128.5, 128.7, 128.8, 128.9, 131.4, 131.9, 138.3, 164.6.

IR ν(cm^{-1}): 3033, 2924, 1719, 1588, 1261, 1095, 1010, 751.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{12}BrINaO_2$ 452.8958, found; 452.8940.

m.p: 53-54 ºC.

2-Iodo-1-phenylethyl-4-trifluoromethylbenzoate 5n



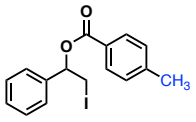
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.68 (dd, *J* = 10.7, 8.0 Hz, 1H), 6.14 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.35-7.49 (m, 5H), 7.77 (d, *J* = 8.2 Hz, 2H), 8.23-8.30 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 76.2, 123.6 (q, *J* = 272.9 Hz), 125.5 (q, *J* = 3.8 Hz), 126.3, 128.9, 130.3, 132.9, 134.8 (q, *J* = 32.7 Hz), 138.1, 164.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.3.

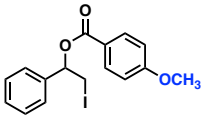
IR ν(cm^{-1}): 2925, 2853, 1722, 1324, 1265, 1094, 698.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{12}F3INaO_2$ 442.9726, found; 442.9721.

2-Iodo-1-phenylethyl-4-methylbenzoate 5o



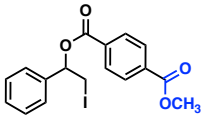
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 3.60-3.69 (m, 2H), 6.12 (dd, *J* = 7.5, 5.2 Hz, 1H), 7.27-7.32 (m, 2H), 7.37-7.49 (m, 5H), 8.02-8.08 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.2, 21.7, 75.3, 126.3, 127.0, 128.7, 128.8, 129.2, 129.9, 138.7, 144.1, 165.4.
IR ν(cm^{-1}): 3033, 2921, 1717, 1263, 1092, 748.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{15}INaO_2$ 389.0009, found; 389.0003.

2-Iodo-1-phenylethyl-4-methoxybenzoate 5p



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60-3.67 (m, 2H), 3.90 (s, 3H), 6.09 (dd, *J* = 7.5, 5.2 Hz, 1H), 6.95-7.00 (m, 2H), 7.35-7.42 (m, 3H), 7.43-7.47 (m, 2H), 8.09-8.13 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.3, 55.5, 75.1, 113.8, 122.1, 126.3, 128.7, 128.7, 131.9, 138.8, 163.7, 165.0.
IR ν(cm^{-1}): 2959, 2933, 1710, 1604, 1250, 1164, 695.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{15}INaO_3$ 404.9958, found; 404.9960.

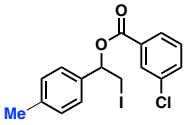
2-Iodo-1-phenylethyl-4-terephthalatebenzoate 5q



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.68 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.98 (s, 3H), 6.13 (dd, *J* = 7.8, 5.1 Hz, 1H), 7.35-7.49 (m, 5H), 8.13-8.24 (m, 4H).

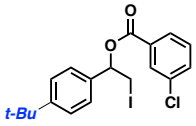
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6, 52.5, 76.1, 126.4, 128.8, 128.9, 129.7, 129.8, 133.5, 134.3, 138.2, 164.5, 166.2.
IR ν(cm^{-1}): 2953, 2925, 1714, 1270, 1235, 1083, 726, 700.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{15}INaO_4$ 432.9907, found; 432.9908.
m.p: 112-114 ºC.

2-Iodo-1-(*p*-tolyl)ethyl 3-chlorobenzoate 6b



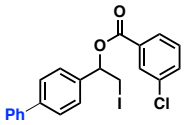
^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.60 (qd, *J* = 10.6, 6.6 Hz, 2H), 6.07 (dd, *J* = 7.9, 5.1 Hz, 1H), 7.18-7.22 (m, 2H), 7.29-7.34 (m, 2H), 7.38-7.43 (m, 1H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.99 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.07 (t, *J* = 1.9 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8, 21.4, 76.2, 126.4, 126.7, 128.1, 129.6, 129.9, 131.7, 133.4, 134.7, 135.4, 138.9, 164.3.
IR ν(cm^{-1}): 3067, 3029, 2958, 2922, 2860, 1725, 1721, 1274, 1247, 1121, 744.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_2$ 422.9619, found; 422.9630.

1-(4-(*tert*-Butyl)phenyl)-2-iodoethyl 3-chlorobenzoate 6c



^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 3.58 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.64 (dd, *J* = 10.7, 8.4 Hz, 1H), 6.10 (dd, *J* = 8.4, 4.7 Hz, 1H), 7.34-7.37 (m, 2H), 7.39-7.43 (m, 3H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 8.09 (t, *J* = 1.8 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.8, 31.4, 34.8, 76.2, 125.9, 126.2, 128.1, 129.9, 129.9, 131.8, 133.4, 134.8, 135.3, 152.1, 164.4.
IR ν(cm^{-1}): 2967, 2919, 2866, 1721, 1610, 1574, 1425, 1289, 1277, 1250, 1120, 1070, 852, 745, 673, 613, 590.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{19}H_{20}ClINaO_2$ 465.0089, found; 465.0081.

1-([1,1'-Biphenyl]-4-yl)-2-iodoethyl 3-chlorobenzoate 6d



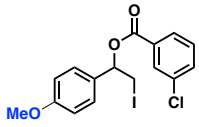
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.63 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.68 (dd, *J* = 10.7, 8.1 Hz, 1H), 6.15 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.34-7.39 (m, 1H), 7.41-7.47 (m, 3H), 7.49-7.52 (m, 2H), 7.56-7.59 (m, 2H), 7.60-7.63 (m, 2H), 8.03 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.11 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6, 76.1, 125.5, 126.9, 127.3, 127.7, 127.8, 128.2, 128.9, 130.0, 131.6, 133.5, 134.8, 137.3, 140.5, 142.0, 164.3.

IR ν(cm^{-1}): 3063, 3029, 2960, 2922, 1721, 1574, 1486, 1425, 1286, 1247, 1120, 1070, 764, 744, 732, 695, 672, 590, 503.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{16}ClINaO_2$ 484.9776, found; 484.9768.

2-Iodo-1-(4-methoxyphenyl)ethyl 3-chlorobenzoate 6e



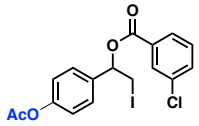
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49-3.70 (m, 2H), 3.80 (s, 3H), 6.06 (dd, *J* = 8.1, 5.2 Hz, 1H), 6.88-6.94 (m, 2H), 7.34-7.43 (m, 3H), 7.55 (ddt, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.98 (dt, *J* = 7.7, 1.8 Hz, 1H), 8.06 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.8, 55.4, 76.1, 114.3, 127.9, 128.1, 129.8, 129.9, 130.4, 131.7, 133.4, 134.7, 160.1, 164.3.

IR ν(cm^{-1}): 3074, 2996, 2958, 2925, 2833, 2652, 2959, 2546, 1690, 1509, 1417, 1290, 1244, 1029, 746.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_3$ 438.9568, found; 438.9572.

1-(4-Acetoxyphenyl)-2-iodoethyl 3-chlorobenzoate 6f



^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.52-3.67 (m, 2H), 6.09 (dd, *J* = 7.7, 5.3 Hz, 1H), 7.08-7.15 (m, 2H), 7.37-7.47 (m, 3H), 7.56 (ddt, *J*

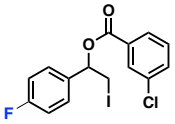
= 8.1, 2.2, 1.1 Hz, 1H), 7.99 (dq, *J* = 7.8, 1.2 Hz, 1H), 8.07 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4, 21.2, 75.7, 122.1, 127.7, 128.1, 129.9, 131.5, 133.6, 134.8, 135.8, 151.1, 164.2, 169.4.

IR ν(cm^{-1}): 3076, 2955, 2919, 2850, 1757, 1714, 1695, 1574, 1509, 1464, 1427, 1417, 1369, 1261, 1216, 1197, 1168, 1197, 1168, 1127, 912, 896, 748, 719, 668, 526.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{14}ClINaO_4$ 466.9518, found; 466.9510.

1-(4-Fluorophenyl)-2-iodoethyl 3-chlorobenzoate 6g



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (ddd, *J* = 16.0, 10.7, 6.5 Hz, 2H), 6.07 (dd, *J* = 7.6, 5.3 Hz, 1H), 7.03-7.14 (m, 2H), 7.37-7.47 (m, 3H), 7.57 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.98 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 8.06 (t, *J* = 1.7 Hz, 1H).

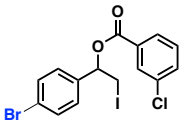
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 75.6, 115.9 (d, *J* = 21.7 Hz), 128.1, 128.4 (d, *J* = 8.4 Hz), 129.8, 129.9, 131.5, 133.6, 134.2 (d, *J* = 3.3 Hz), 134.8, 162.9 (d, *J* = 248.1 Hz), 164.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -112.4.

IR ν(cm^{-1}): 3070, 2959, 2925, 2853, 1721, 1605, 1574, 1510, 1425, 1286, 1248, 1225, 1158, 1121, 1084, 1070, 949, 834, 744, 672, 567, 503.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{11}ClFINaO_2$ 426.9369, found; 426.9364.

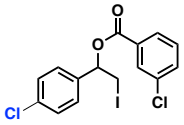
1-(4-Bromophenyl)-2-iodoethyl 3-chlorobenzoate 6h



^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46-3.68 (m, 2H), 5.95-6.10 (m, 1H), 7.23-7.34 (m, 3H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 13.7, 8.2 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 1.9 Hz, 1H).

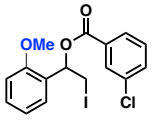
^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.1, 75.5, 123.1, 128.1, 128.2, 129.9, 130.0, 131.4, 132.2, 133.6, 134.9, 137.3, 164.2.
IR ν(cm^{-1}): 3069, 2958, 2924, 2851, 1722, 1574, 1487, 1426, 1277, 1247, 1121, 1070, 1011, 954, 817, 744, 673, 587, 554, 506.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{11}BrClINaO_2$ 486.8568, found; 486.8560.

1-(4-Chlorophenyl)-2-iodoethyl 3-chlorobenzoate 6i



^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.52-3.66 (m, 2H), 6.04 (dd, *J* = 7.5, 5.3 Hz, 1H), 7.36-7.38 (m, 4H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.57 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 7.98 (dt, *J* = 7.9, 1.3 Hz, 1H), 8.06 (t, *J* = 1.8 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.2, 75.5, 127.9, 128.1, 129.2, 129.9, 130.0, 131.4, 133.6, 134.9, 134.9, 136.8, 164.2.
IR ν(cm^{-1}): 3070, 2927, 2852, 1725, 1575, 1490, 1456, 1426, 1278, 1249, 1230, 1120, 1070, 947, 896, 743, 672, 518, 492.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{11}Cl_2INaO_2$ 442.9073, found; 442.9069.

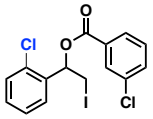
2-Iodo-1-(2-methoxyphenyl)ethyl 3-chlorobenzoate 6j



^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.58 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.71 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.90 (s, 3H), 6.41 (dd, *J* = 7.8, 3.8 Hz, 1H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.36-7.40 (m, 1H), 7.41-7.45 (m, 1H), 7.57 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 8.05 (ddd, *J* = 7.8, 2.2, 1.1 Hz, 1H), 8.13 (t, *J* = 1.6 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0, 55.7, 71.0, 110.9, 120.8, 126.4, 126.8, 128.1, 129.8, 129.9, 130.0, 131.8, 133.4, 134.8, 156.2, 164.1.
IR ν(cm^{-1}): 3069, 3006, 2936, 2837, 1723, 1601, 1574, 1491, 1463, 1425, 1352, 1287, 1241, 1122, 1085, 1027, 957, 895, 745, 673, 587.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_3$ 438.9568, found; 438.9572.

1-(2-Chlorophenyl)-2-iodoethyl 3-chlorobenzoate 6k



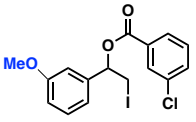
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (dd, *J* = 10.9, 7.7 Hz, 1H), 3.73 (dd, *J* = 10.9, 4.1 Hz, 1H), 6.39 (dd, *J* = 7.7, 4.1 Hz, 1H), 7.21-7.35 (m, 2H), 7.35-7.52 (m, 3H), 7.59 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.97-8.08 (m, 1H), 8.11 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.4, 72.7, 127.3, 127.4, 128.2, 129.9, 130.0, 130.1, 131.4, 132.4, 133.7, 134.9, 136.2, 163.9.

IR ν(cm^{-1}): 3069, 2959, 2924, 2852, 1725, 1574, 1473, 1426, 1279, 1248, 1120, 1051, 1039, 744, 457.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{15}H_{11}Cl_2INaO_2$ 442.9073, found; 442.9072.

2-Iodo-1-(3-methoxyphenyl)ethyl 3-chlorobenzoate 6l



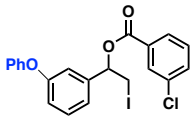
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51-3.68 (m, 2H), 3.82 (s, 3H), 6.06 (dd, *J* = 7.7, 5.3 Hz, 1H), 6.86-7.04 (m, 3H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.56 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 8.02 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.08 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.6, 55.4, 76.1, 112.4, 114.1, 118.7, 128.1, 129.8, 129.9, 130.1, 131.6, 133.5, 134.8, 139.9, 159.9, 164.3.

IR ν(cm^{-1}): 3069, 2957, 2835, 1722, 1600, 1586, 1575, 1488, 1455, 1426, 1285, 1247, 1122, 1043, 957, 879, 744, 698.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_3$ 438.9568, found; 438.9569.

2-Iodo-1-(3-phenoxyphenyl)ethyl 3-chlorobenzoate 6m



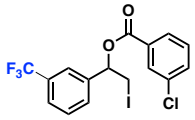
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.55-3.62 (m, 2H), 6.05 (dd, *J* = 7.4, 5.4 Hz, 1H), 6.97 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.00-7.04 (m, 2H), 7.07 (t, *J* = 2.1 Hz, 1H), 7.12-7.16 (m, 2H), 7.31-7.37 (m, 3H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.57 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.98 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.06 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6, 75.7, 116.5, 118.9, 119.4, 121.1, 123.9, 128.1, 129.9, 130.0, 130.3, 131.5, 133.5, 134.8, 140.3, 156.7, 157.9, 164.2.

IR ν(cm^{-1}): 3071, 3003, 2957, 2933, 2835, 1721, 1595, 1574, 1517, 1463, 1422, 1246, 1122, 1071, 1025, 884, 807, 744, 650, 545.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{16}ClINaO_3$ 500.9725, found; 500.9719.

2-Iodo-1-(3-(trifluoromethyl)phenyl)ethyl 3-chlorobenzoate 6n



^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50-3.74 (m, 2H), 6.12 (dd, *J* = 7.3, 5.5 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.49-7.70 (m, 5H), 7.97-8.04 (m, 1H), 8.08 (t, *J* = 1.8 Hz, 1H).

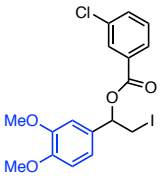
^{13}C NMR (125 MHz, $CDCl_3$): δ = 6.9, 75.4, 123.4 (q, *J* = 3.9 Hz), 125.9 (q, *J* = 3.7 Hz), 128.2, 129.6, 129.8, 129.9, 130.1 (q, *J* = 2.9 Hz), 131.2, 133.8, 134.9, 139.4, 164.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.8.

IR ν(cm^{-1}): 3071, 2960, 2927, 2854, 1724, 1575, 1426, 1328, 1286, 1248, 1165, 1120, 1070, 956, 899, 869, 801, 744, 701, 672, 657, 460.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{11}ClF_3INaO_2$ 476.9337, found; 476.9335.

1-(3,4-Dimethoxyphenyl)-2-iodoethyl 3-chlorobenzoate 6o



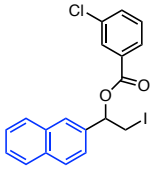
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.56 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.64 (dd, *J* = 10.6, 8.3 Hz, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 6.04 (dd, *J* = 8.3, 5.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 1H), 7.98 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.07 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.7, 56.1, 76.3, 109.8, 111.3, 119.1, 128.1, 129.9, 130.8, 131.7, 133.4, 134.8, 149.3, 149.6, 164.3.

IR ν(cm^{-1}): 3003, 2957, 2933, 2835, 1721, 1595, 1574, 1517, 1463, 1422, 1246, 1122, 1071, 1025, 884, 807, 744, 650, 545.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{16}ClINaO_4$ 468.9674, found; 468.9670.

2-Iodo-1-(naphthalen-2-yl)ethyl 3-chlorobenzoate 6p



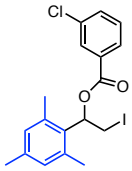
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.74 (dd, *J* = 10.3, 8.6 Hz, 1H), 6.27 (dd, *J* = 8.1, 5.1 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.49-7.55 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.82-7.93 (m, 4H), 8.03 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 76.5, 123.6, 126.2, 126.7, 126.8, 127.9, 128.2, 128.3, 128.9, 129.9, 130.0, 131.6, 133.2, 133.5, 133.6, 134.8, 135.6, 164.3.

IR ν(cm^{-1}): 3057, 2921, 2850, 1721, 1574, 1425, 1286, 1277, 1248, 1121, 1084, 1070, 815, 742, 666, 476.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{19}H_{14}ClINaO_2$ 458.9619, found; 458.9609.

2-Iodo-1-mesitylethyl 3-chlorobenzoate 6q



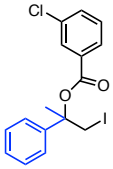
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3H), 2.50 (s, 6H), 3.55 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.84 (t, *J* = 10.6 Hz, 1H), 6.52 (dd, *J* = 10.4, 4.9 Hz, 1H), 6.85 (s, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.98 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.06 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 4.6, 20.8, 20.9, 74.4, 128.1, 129.9, 130.5, 131.1, 131.7, 133.3, 134.8, 136.5, 138.4, 164.3.

IR ν(cm^{-1}): 3069, 2967, 2919, 2866, 1721, 1610, 1574, 1473, 1425, 1373, 1289, 1277, 1250, 1120, 1084, 1070, 927, 886, 852, 804, 673, 745, 613, 590, 497.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{18}H_{18}ClINaO_2$ 450.9932, found; 450.9920.

1-Iodo-2-phenylpropan-2-yl 3-chlorobenzoate 8a



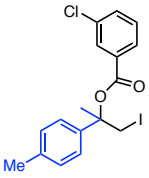
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3H), *J* = 10.7 Hz, 1H), 3.98 (d, *J* = 10.7 Hz, 7.28-7.46 (m, 6H), 7.59 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.97-8.03 (m, 1H), 8.09 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 26.0, 81.9, 124.8, 128.1, 128.2, 128.8, 129.9, 130.0, 132.7, 133.3, 134.7, 141.4, 163.6.

IR ν(cm^{-1}): 3065, 3028, 2984, 2933, 1721, 1574, 1447, 1424, 1375, 1282, 1254, 1193, 1158, 1122, 1070, 1030, 889, 744, 672, 696, 574, 501.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_2$ 422.9619, found; 422.9610.

1-Iodo-2-(*p*-tolyl)propan-2-yl 3-chlorobenzoate 8b



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 2.35 (s, 3H), 3.75 (d, *J* = 10.7 Hz, 1H), 3.94 (d, *J* = 10.7 Hz, 1H), 7.16-7.20 (m, 2H), 7.27-7.31 (m, 2H), 7.39-7.43

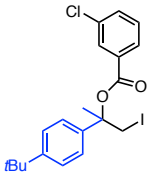
(m, 1H), 7.56 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 7.99 (dt, J = 7.8, 1.3 Hz, 1H), 8.09 (t, J = 1.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8, 21.2, 25.9, 81.8, 124.7, 128.1, 129.5, 129.9, 129.9, 132.8, 133.2, 134.7, 137.9, 138.4, 163.6.

IR ν(cm^{-1}): 3067, 3026, 2982, 2922, 1721, 1574, 1513, 1452, 1424, 1374, 1294, 1282, 1254, 1186, 1158, 1122, 1070, 1027, 889, 876, 814, 744, 721, 673, 608, 499.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{16}ClINaO_2$ 436.9776, found; 436.9771.

2-(4-(*tert*-Butyl)phenyl)-1-iodopropan-2-yl 3-chlorobenzoate 8c



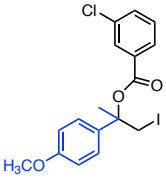
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 9H), 2.11 (s, 3H), 3.75 (d, J = 10.7 Hz, 1H), 3.96 (d, J = 10.7 Hz, 1H), 7.28-7.44 (m, 5H), 7.56 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 7.98-8.02 (m, 1H), 8.09 (t, J = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 26.1, 31.4, 34.7, 81.9, 124.5, 125.7, 128.1, 129.9, 130.0, 132.8, 133.2, 134.7, 138.2, 150.9, 163.7.

IR ν(cm^{-1}): 3034, 2962, 2868, 1722, 1574, 1463, 1425, 1282, 1257, 1192, 1159, 1123, 1070, 1016, 831, 746, 672, 605, 579.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{20}H_{22}ClINaO_2$ 479.0245, found; 479.0232.

1-Iodo-2-(4-methoxyphenyl)propan-2-yl 3-chlorobenzoate 8d

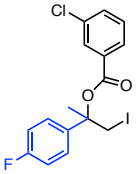


^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 3.73 (d, J = 10.6 Hz, 1H), 3.80 (s, 3H), 3.93 (d, J = 10.6 Hz, 1H), 6.86-6.93 (m, 2H), 7.29-7.36 (m, 2H), 7.39-7.43 (m, 1H), 7.55 (ddd, J = 8.0, 2.2, 1.1 Hz, 1H), 7.98 (dt, J = 7.8, 1.4 Hz, 1H), 8.07 (t, J = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 25.8, 55.4, 81.7, 114.1, 126.2, 128.1, 129.9, 129.9, 132.8, 133.2, 133.3, 134.7, 159.3, 163.7.

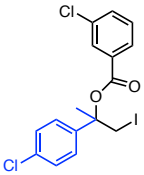
IR ν(cm^{-1}): 3071, 2953, 2926, 2833, 2651, 2591, 2544, 1690, 1596, 1573, 1509, 1459, 1426, 1415, 1288, 1244, 1158, 1030, 896, 828, 805, 746, 718, 667, 544.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{16}ClINaO_3$ 452.9725, found; 452.9718.

2-(4-Fluorophenyl)-1-iodopropan-2-yl 3-chlorobenzoate 8e



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.91 (d, *J* = 10.7 Hz, 1H), 7.00-7.10 (m, 2H), 7.34-7.46 (m, 3H), 7.57 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.95-8.01 (m, 1H), 8.07 (t, *J* = 1.8 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 25.9, 81.5, 115.7 (d, *J* = 21.6 Hz), 126.8 (d, *J* = 8.2 Hz), 128.1, 129.9 (d, *J* = 4.3 Hz), 132.5, 133.4, 134.8, 137.3 (d, *J* = 3.3 Hz), 162.4 (d, *J* = 247.5 Hz), 163.6.
^{19}F NMR (376 MHz, $CDCl_3$): δ = -114.1.
IR ν(cm^{-1}): 3067, 3041, 2960, 2926, 2879, 1725, 1698, 1597, 1507, 1473, 1417, 1225, 1158, 1014, 832, 747, 544.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{13}ClFINaO_2$ 440.9525, found; 440.9526.

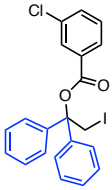
2-(4-Chlorophenyl)-1-iodopropan-2-yl 3-chlorobenzoate 8f



^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 3.77 (d, *J* = 10.7 Hz, 1H), 3.89 (d, *J* = 10.7 Hz, 1H), 7.31-7.37 (m, 4H), 7.40-7.43 (m, 1H), 7.57 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.97 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.06 (t, *J* = 1.8 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.9, 25.9, 81.5, 126.4, 128.1, 129.0, 129.9, 130.0, 132.4, 133.4, 134.1, 134.8, 140.0, 163.6.
IR ν(cm^{-1}): 3068, 2983, 2933, 1720, 1574, 1491, 1423, 1293, 1252, 1193, 1159, 1121, 1094, 1068, 1012, 889, 826, 763, 743, 719, 673, 591, 555, 520.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{13}Cl_2INaO_2$ 456.9230, found; 456.9212.

2-Iodo-1,1-diphenylethyl 3-chlorobenzoate 8g



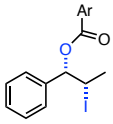
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.72 (s, 2H), 7.27-7.32 (m, 2H), 7.34-7.40 (m, 4H), 7.42-7.49 (m, 5H), 7.59 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 8.05 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.12 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 84.8, 100.1, 126.3, 127.9, 128.1, 128.5, 129.9, 130.0, 132.8, 133.4, 134.9, 142.4, 163.4.

IR ν(cm^{-1}): 3087, 3059, 3024, 2924, 2853, 1725, 1659, 1574, 1491, 1447, 1421, 1294, 1281, 1261, 1233, 1114, 1069, 961, 784, 739, 701, 691, 670, 592.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{16}ClINaO_2$ 484.9776, found; 484.9767.

(1*S*, 2*S*) 2-Iodo-1-phenylpropyl 2-chlorobenzoate 10a



d.e. 84%.

Yellow oil.

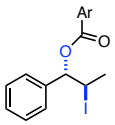
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88 (d, *J* = 7.0 Hz, 3H), 4.54 (p, *J* = 7.0 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 7.41-7.35 (m, 4H), 7.44-7.51 (m, 4H), 8.04-8.07 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.0, 28.6, 81.3, 126.7, 127.1, 128.61, 128.8, 129.4, 131.8, 131.3, 132.9, 134.2, 137.1, 163.9.

IR ν(cm^{-1}): 1924, 1732, 1243, 1074, 1045.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_2$ 422.9627, found; 422.9606.

(1*S*, 2*R*) 2-Iodo-1-phenylpropyl 2-chlorobenzoate 10b



Diastereospecific.

Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (d, *J* = 7.0 Hz, 3H), 4.56-4.64 (m, 1H), 6.15 (d, *J* = 5.4 Hz, 1H), 7.36-7.43 (m, 4H), 7.45-7.52 (m, 4H), 8.03 (dd, *J* = 7.7, 1.7 Hz, 1H).

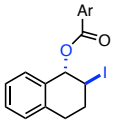
^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.3, 27.8, 80.7, 126.7, 127.2, 128.40, 128.6, 129.5, 131.3, 131.9, 132.9, 134.1, 137.3, 164.1.

IR ν(cm^{-1}): 1924, 1733, 1243, 1111, 1043.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{14}ClINaO_2$ 422.9627, found; 422.9610.

A. Shimizu, R. Hayashi, Y. Ashikan, T. Nokami, j. Yoshida. *J. Org. Chem.* **2015**, *11*, 242-248.

(1*S*, 2*S*)-2-iodo-2,3-dihydro-1H-inden-1-yl-3-chlorobenzoate 10c



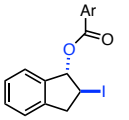
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.44 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.86 (dd, *J* = 17.0, 6.8 Hz, 1H), 4.67 (ddd, *J* = 6.8, 4.6, 3.7 Hz, 1H), 6.67 (d, *J* = 3.7 Hz, 1H), 7.29-7.36 (m, 2H), 7.37-7.47 (m, 2H), 7.48-7.53 (m, 1H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.95 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.02 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8, 43.5, 86.7, 124.8, 125.9, 127.7, 128.0, 129.7, 129.8, 129.9, 131.4, 133.3, 134.6, 138.3, 142.2, 164.8.

IR ν(cm^{-1}): 2962, 1714, 1265, 1087, 749.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{16}H_{12}ClINaO_2$ 420.9463, found; 420.9458.

(1*S*, 2*S*) 2-Iodo-1,2,3,4-tetrahydronaphthalen-1-yl-3-chlorobenzoate 10d



Yellow oil.

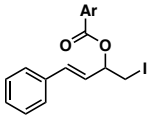
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20-2.51 (m, 2H), 3.91-2.20 (m, 2H), 4.77 (ddd, *J* = 5.8, 4.2, 3.0 Hz, 1H), 6.49 (d, *J* = 4.3 Hz, 1H), 7.20-7.31 (m, 2H), 7.32-7.42 (m, 3H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.96 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.02 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 28.0, 28.8, 75.7, 126.7, 128.0, 129.0, 129.8, 129.9, 130, 131.1, 131.6, 133.3, 134.6, 136.1, 164.5.

IR ν(cm^{-1}): 2925, 1716, 1243, 1243, 1119, 1069, 745.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{14}ClINaO_2$ 434.9619, found; 434.9623.

(*E*)-1-Iodo-4-phenylbut-3-en-2-yl 3-chlorobenzoate 12a



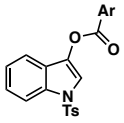
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, *J* = 5.8, 2.6 Hz, 2H), 5.66-5.75 (m, 1H), 6.23 (dd, *J* = 16.2, 7.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 7.28-7.37 (m, 3H), 7.39-7.44 (m, 3H), 7.56 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.99 (dt, *J* = 7.8, 1.3 Hz, 1H), 8.07 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.1, 74.5, 125.3, 126.9, 128.1, 128.7, 128.8, 129.9, 129.9, 131.8, 133.4, 134.8, 135.2, 135.7, 164.3.

IR ν(cm^{-1}): 3063, 3026, 2924, 1719, 1575, 1425, 1285, 1245, 1121, 1084, 1070, 963, 938, 743, 692, 673, 496.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{17}H_{14}ClINaO_2$ 434.9619, found; 434.9627.

1-Tosylindolin-3-yl 3-chlorobenzoate 12b



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 4.10-4.20 (m, 2H), 6.16 (dd, *J* = 5.8, 3.1 Hz, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.32 (t, *J* = 7.9 Hz,

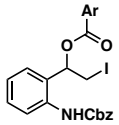
1H), 7.40-7.44 (m, 2H), 7.51 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.65-7.70 (m, 3H), 7.73 (t, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 55.8, 72.6, 115.7, 124.4, 127.0, 127.4, 127.9, 128.8, 129.6, 129.7, 129.8, 131.2, 131.3, 133.5, 133.9, 134.6, 143.3, 144.5, 164.9.

IR ν(cm^{-1}): 3257, 3069, 3030, 2924, 2858, 1718, 1466, 1356, 1248, 1163, 1070, 747, 670.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{22}H_{18}ClNNaO_4S$ 450.0537, found; 450.0543.

1-(2-(((Benzyloxy)carbonyl)amino)phenyl)-2-iodoethyl 3-chlorobenzoate 6r



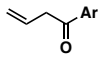
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.80 (t, *J* = 10.7 Hz, 1H), 5.27 (s, 2H), 6.18 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.32-7.48 (m, 8H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.72-7.74 (m, 2H), 7.94 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.03 (t, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.1, 67.4, 73.5, 125.7, 126.9, 128.1, 128.4, 128.5, 128.7, 130.0, 130.2, 130.9, 133.7, 134.9, 135.7, 136.3, 154.5, 165.1.

IR ν(cm^{-1}): 3325, 3067, 3032, 2957, 2930, 1707, 1517, 1453, 1247, 1214, 1041, 744.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{23}H_{19}ClINNaO_4$ 557.9940, found; 557.9945.

Allyl 3-chlorobenzoate 12c

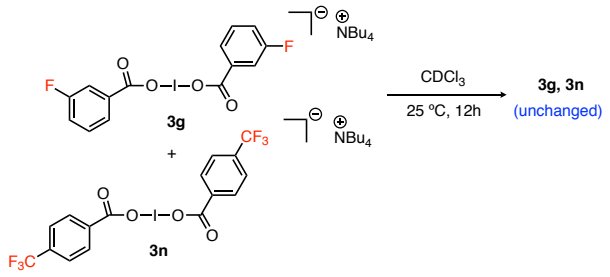


T. A. Strayer, C. C. Culy, M. H. Bunner, A. R. Frank, P. A. Albiniak. *Tetrahedron Lett*. **2015**, 56, 6807.

2.4.3. Control experiments

Cross over experiment.

A Schlenk tube equipped with a magnetic stirrer was charged with tetrabutylammonium 1,2-bis(fluorobenzoyl) dioxiodane (0.15 mmol,1.0 equiv.) and tetrabutylammonium 1,3-bis(fluorobenzoyl) dioxiodane (0.15 mmol, 1.0 equiv.) in 1 mL of $CDCl_3$ and the reaction was stirred 12 h at 25 ºC. Then, the reaction mixture was analyzed by ^{19}F-NMR without additional treatment.



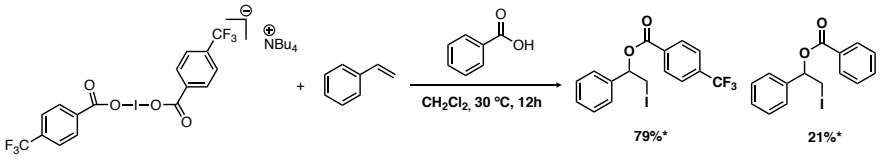
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 24H), 1.41 (h, *J* = 7.3 Hz, 16H), 1.62-1.76 (m, 16H), 3.28-3.46 (m, 16H), 6.95-7.02 (m, 2H), 7.03-7.12 (m, 4H), 7.23-7.36 (m, 4H), 7.58-7.67 (m, 2H), 7.70-7.79 (m, 4H).
^{19}F(H) NMR (376 MHz, $CDCl_3$): δ = -112.4, -114.3.

Reactions of iodine(I) derivatives with styrene in presence of benzoic acid

A Schlenk tube equipped with a magnetic stirrer was charged with benzoic acid (1.2 equiv.), the corresponding iodine(I) (1.2 equiv.) and 3 mL of dry DCM. The styrene (0.19 mmol, 1.0 equiv.) was added and the reaction was stirred 12 h at 30ºC. Then DCM was added and the solution was washed with a saturated aqueous solution of

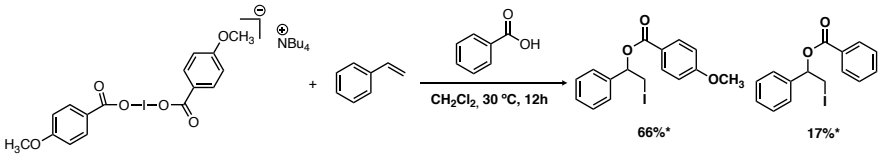
$Na_2S_2O_3$. The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 90/10, v/v).

2-Iodo-1-phenylethyl-4-trifluoromethylbenzoate and 2-iodo-1-phenylethylbenzoate



The products have the same R_f and they could not be separated by column chromatography.
*Conversion calculated by ^{1}H-NMR.

2-Iodo-1-phenylethylbenzoate and 2-iodo-1-phenylethyl-4-methoxybenzoate

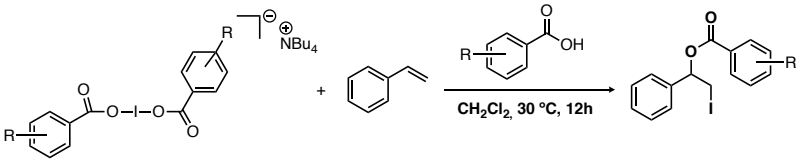


*Yield obtained after column chromatography.
2-Iodo-1-phenylethyl-4-methoxybenzoate
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59-3.68 (m, 2H) 3.90 (s, 3H), 6.09 (dd, *J* = 7.4, 5.3 Hz, 1H), 6.94-7.00 (m, 2H), 7.33-7.49 (m, 5H), 8.08-8.14 (m, 2H).

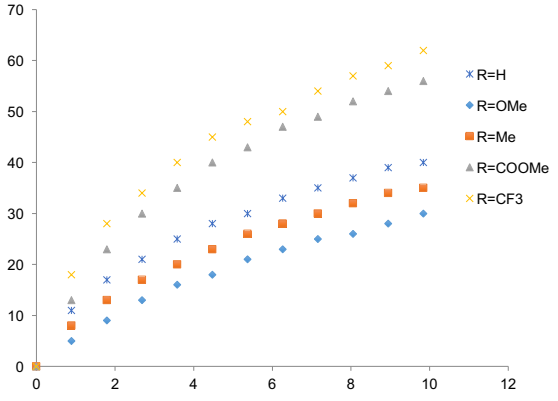
2-Iodo-1-phenylethylbenzoate

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 5.2 Hz, 1H) 3.67 (dd, *J* = 10.7, 7.6 Hz, 1H), 6.12 (dd, *J* = 7.6, 5.2 Hz, 1H), 7.34-7.53 (m, 7H), 7.59-7.65 (m, 1H), 8.13-8.18 (m, 2H).

Kinetic studies on 4-fluorostyrene with iodine(I) derivatives in presence of the corresponding acid derivatives.



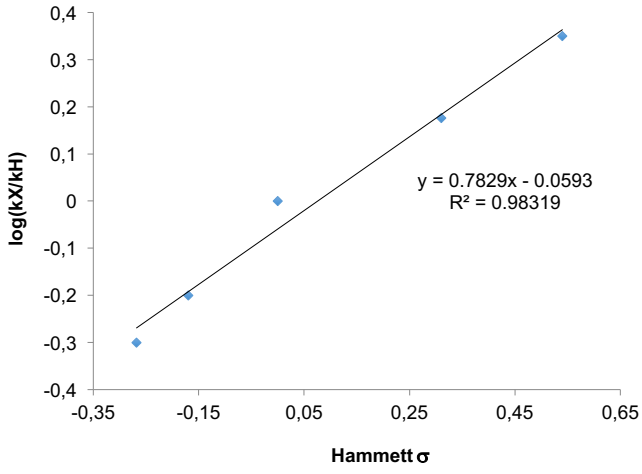
General procedure. The iodine(I) derivative (1.2 equiv.) and the benzoic acid derivative (1.2 equiv.) were charged in a NMR tube, followed by addition of CD_2Cl_2 (0.75 mL). After all solids were dissolved, styrene (0.05 mmol, 1 equiv.) was added and the reaction monitored by acquisition of a ^{1}H-NMR experiment every 5.37 min. All datas were collected in 500 MHz ^{1}H-NMR. In the following plot conversion [%] vs time [h] is represented.



Kinetic profiles for iodooxigenation with iodine(I) derivatives in presence of the corresponding benzoic acid derivatives. Hammett Plot:

With the slopes of these initial rates obtained in the previous plot, a Hammett correlation plot could be generated:

Entry	X	$\log(K_X/K_H)$	Hammett constant $\sigma_{p\text{-}X}$
1	OCH_3	-0.30	-0.27
2	Me	-0.20	-0.17
3	H	0.00	0.00
4	COOMe	0.18	0.31
5	CF_3	0.35	0.54



Hammett correlation studies show that the nature of the group in *p*-position has a clear effect on the reaction rate. In the case of compounds containing electron-withdrawing groups, the reaction was noticed faster than with electron-donor groups.

2.4.4. X-Ray analytical data

Tetramethylammonium 1,3-bis(3-chlorobenzoyl)dioxiodane

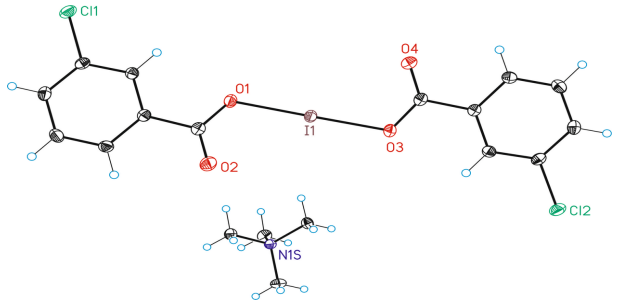


Table S1. Crystal data and structure refinement for compound **3k**.

Empirical formula	C18 H20 Cl2 I N O4
Formula weight	512.15
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 10.7553(7)Å. α= 90°. b = 12.5457(8)Å β = 90°. c = 30.0421(18)Å γ = 90°.
Volume	4053.7(4) $Å^3$
Z	8
Density (calculated)	1.678 Mg/m^3
Absorption coefficient	1.866 mm^{-1}

F(000)	2032
Crystal size	0.20 x 0.20 x 0.20 mm^3
Theta range for data collection	2.329 to 30.446°.
Index ranges	-15<=h<=10,-17<=k<=17,-39<=l<=42
Reflections collected	25746
Independent reflections	5514[R(int) = 0.0317]
Completeness to theta =30.446°	89.600006%
Absorption correction	Multi-scan
Max. and min. transmission	0.835 and 0.642
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5514/ 0/ 239
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0191, wR2 = 0.0477
R indices (all data)	R1 = 0.0216, wR2 = 0.0484
Largest diff. peak and hole	0.874 and -0.509 e.$Å^{-3}$

Tetrabutylammonium 1,3-bis(3-bromobenzoyl)dioxiodane 3f

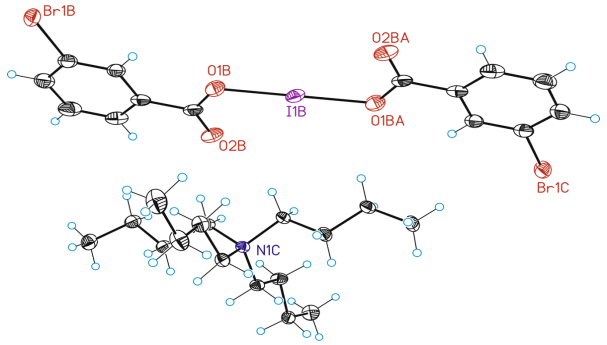


Table S2. Crystal data and structure refinement for compound **3f**.

Empirical formula	C15.50 H22.50 Br Cl1.50

I0.50 N0.50 O2	
Formula weight	444.37
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.309(2) α=85.338(10)°.
	b = 13.407(3)Å β=79.825(10)°.
	c = 15.224(4)Å γ = 78.116(8)°.
Volume	1828.1(8) $Å^3$
Z	4
Density (calculated)	1.615 Mg/m^3
Absorption coefficient	3.315 mm^{-1}
F(000)	888
Crystal size	0.20 x 0.20 x 0.20 mm^3
Theta range for data collection	2.266 to 36.452°.
Index ranges	-15<=h<=15,-22<=k<=22,-
25<=l<=25	
Reflections collected	59113
Independent reflections	17672[R(int) = 0.0619]
Completeness to theta =36.452°	98.7%
Absorption correction	Multi-scan

Max. and min. transmission	0.733 and 0.564
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	17672/ 102/ 431
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0499, wR2 = 0.1411
R indices (all data)	R1 = 0.0773, wR2 = 0.1540
Largest diff. peak and hole	3.358 and -2.545 e.Å^{-3}

Tetrabutylammonium 1,3-bis(3-fluorobenzoyl)dioxiodane 3g

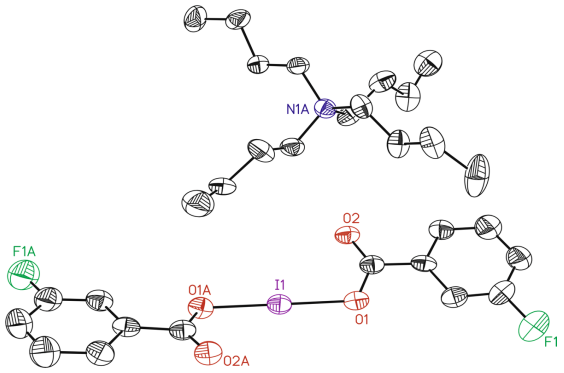


Table S3. Crystal data and structure refinement for compound **3g**.

Empirical formula	C30 H44 F2 I N O4
Formula weight	647.56
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Orthorhombic
Space group	Pccn
Unit cell dimensions	a = 24.9785(14)Å. α = 90°.
	b = 9.4157(5)Å. β = 90°.
	c = 13.1047(6)Å. γ = 90°.
Volume	3082.1(3) $Å^3$
Z	4
Density (calculated)	1.396 Mg/m^3
Absorption coefficient	1.084 mm^{-1}
F(000)	1336
Crystal size	0.40 x 0.15 x 0.02 mm^3
Theta range for data collection	2.786 to 29.635°.
Index ranges	-23<=h<=34,-7<=k<=7,-18<=l<=17
Reflections collected	19450
Independent reflections	2888[R(int) = 0.0736]
Completeness to theta =29.635°	86.4%
Absorption correction	Multi-scan
Max. and min. transmission	0.979 and 0.753
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2888/ 4/ 176

Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1454
R indices (all data)	R1 = 0.1117, wR2 = 0.1672
Largest diff. peak and hole	2.302 and -1.301 e.Å^{-3}

Tetrabutylammonium 1,3-bis(3-methoxybenzoyl)dioxiodane 3i

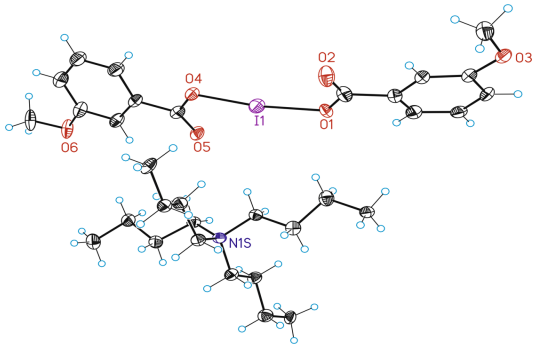


Table S4. Crystal data and structure refinement for compound **3i**.

Empirical formula	C32 H50 I N O6	
Formula weight	671.63	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 24.499(5)Å.	α = 90°.
	b = 18.058(4)Å	β= 94.37(3)°.

c = 14.723(3)Å γ = 90°.

Volume	6495(2) $Å^3$
Z	8
Density (calculated)	1.374 Mg/m^3
Absorption coefficient	1.028 mm^{-1}
F(000)	2800
Crystal size	0.20 x 0.20 x 0.20 mm^3
Theta range for data collection	1.927 to 27.533°.
Index ranges	-31<=h<=22,-23<=k<=23,-19<=l<=17
Reflections collected	26062
Independent reflections	7397[R(int) = 0.1142]
Completeness to theta =27.533°	98.799995%
Absorption correction	Multi-scan
Max. and min. transmission	0.970 and 0.746
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7397/ 1209/ 709
Goodness-of-fit on F^2	1.204
Final R indices [I>2sigma(I)]	R1 = 0.0939, wR2 = 0.2428
R indices (all data)	R1 = 0.1154, wR2 = 0.2487
Largest diff. peak and hole	1.821 and -3.180 $e.Å^{-3}$

CHAPTER 3: OXIDATIVE AMINATION OF C-(sp^3) IN DERIVATIVES OF TETRAHYDROCARBAZOLE

3.1. INTRODUCTION: BACKGROUND OF HYPERVALENT IODINE(III) REAGENT PhI(NPhth)$_2$ IN ORGANIC CHEMISTRY. STRATEGIES FOR THE DIRECT α-FUNCTIONALIZATION OF THE SIDE CHAIN OF 2,3-DISUBTITUTED INDOLES.

Hypervalent iodine(III) reagents with I-N bonds are generally less common than those with I-O bonds. Most of these compounds lack stability and are sensitive to moisture.[71] Except for few examples, these reagents cannot be isolated.[72] The chemistry of aryliodine(III) reagents with phthalimide, saccharine, succinimide, and glutarimide as ligands was reported by Varvoglis and co-workers (Figure 8).[45]

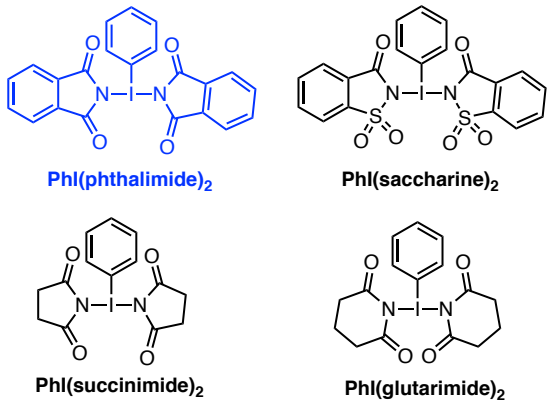
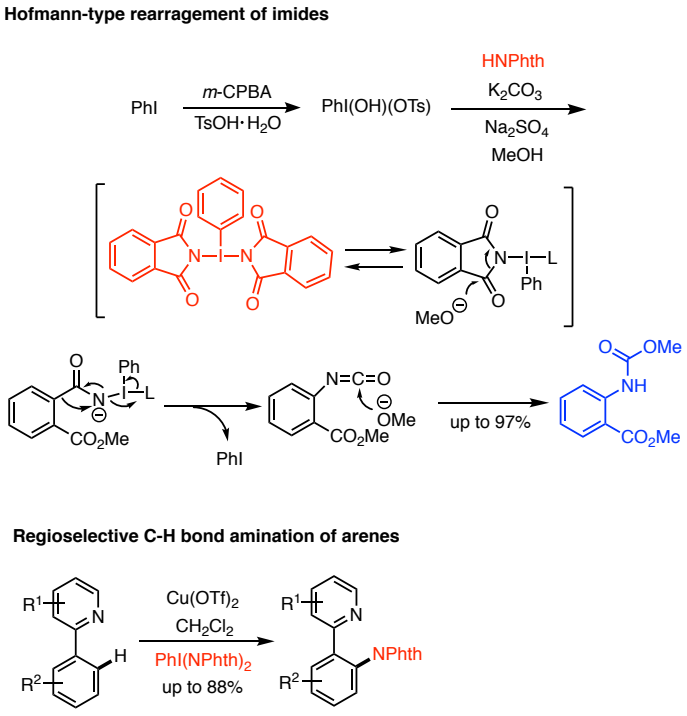


Figure 8: Varvoglis´ reagents.

Varvoglis *et al*. described PhI(NPhth)$_2$ as a thermally stable reagent which is slowly hydrolyzed to iodobenzene and phthalimide by

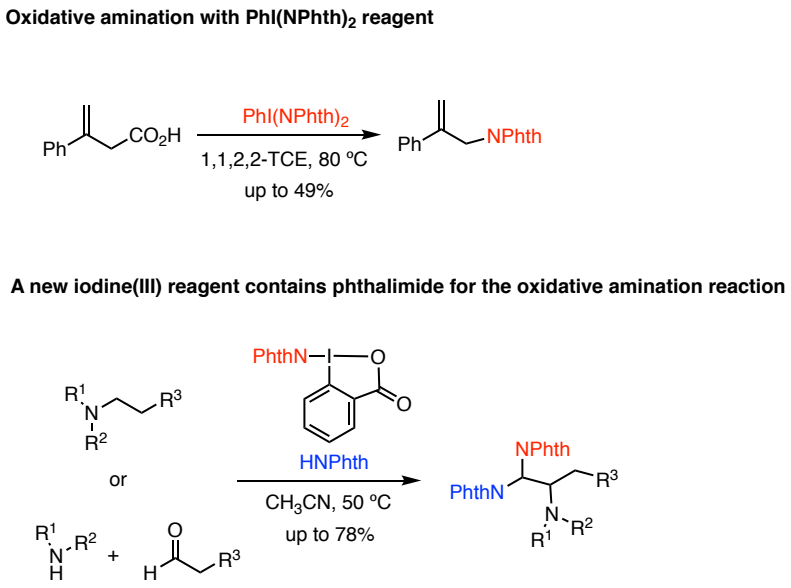
atmospheric moisture and quickly in solvents containing traces of water. This reagent is insoluble in common organic solvents which could explain the fact that it has not been used as a reagent in organic synthesis for many years.

First reports on the use of Varvoglis´ reagents in organic synthesis appeared almost 30 years after their discovery. In 2012, Moriyama *et al*. reported that $PhI(NPhth)_2$ is formed in situ as an intermediate in a Hofmann-type rearrangement of aromatic and aliphatic imides.[73] Two years later, Deboef developed a process for the direct amination of 2-arylpyridine derivatives using $PhI(NPhth)_2$ with copper triflate (Scheme 36).[74]



Scheme 36: Varvoglis´ reagent used in a Hofmann-type rearrangement with imide derivatives and in a regioselective amination of arenes.

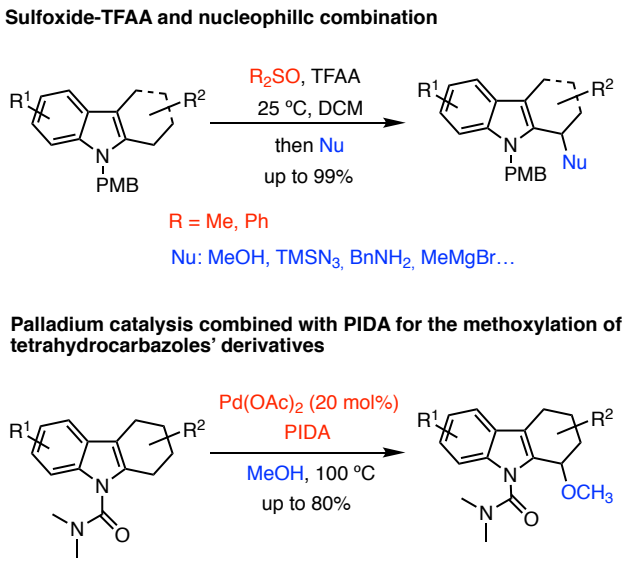
Minakata´s group studied the use of hypervalent iodine reagents containing I-N bond to give rise the decarboxylative amination of unsaturated carboxylic acid.[70] To this end, they examined the use of $PhI(NPhth)_2$ and the decarboxylative amination proceeded with success as shown in Scheme 37, top. Minakata also developed a new class of hypervalent iodine reagents containing phthalimide as ligand. This novel I(III) reagent (depicted in Scheme 37, bottom) was used for the oxidative amination of C(sp^3)-H bond of *N,N*-dimethylanilines. In addition, this reagent was also satisfactory applicable to the oxidative amination with rearrangement of trialkylamines as well as enamines that were prepared in situ from secondary amines and aldehydes.[75]



Scheme 37: Minakata´s oxidative amination using reagents which contain phthalimide as ligand.

Indoles are common structural motives in natural products, bioactive compounds and pharmaceuticals.[76] Hence, considerable efforts have been carried out towards the development of efficient methods for their functionalization and synthesis.[77] In this regard, the functionalization of C-H bonds has been studied extensively, being a powerful and atom economical tool for the formation of C-C and C-heteroatom bonds.[78] Indole derivatives like tetrahydrocarbazoles containing numerous stereogenic centers have significant value in the synthesis of pharmaceutical products, as the exhibit outstanding biological activities.[79] Numerous strategies have been studied towards the synthesis of tetrahydrocarbazole derivatives, involving asymmetric Fischer[80], Diels-Alder[81] and cross-coupling[82] reactions. Despite significant progresses in the synthesis of tetrahydrocarbazoles, strategies involving the direct α-functionalization of the side chain of 2,3-disubstituted indoles are quite limited.

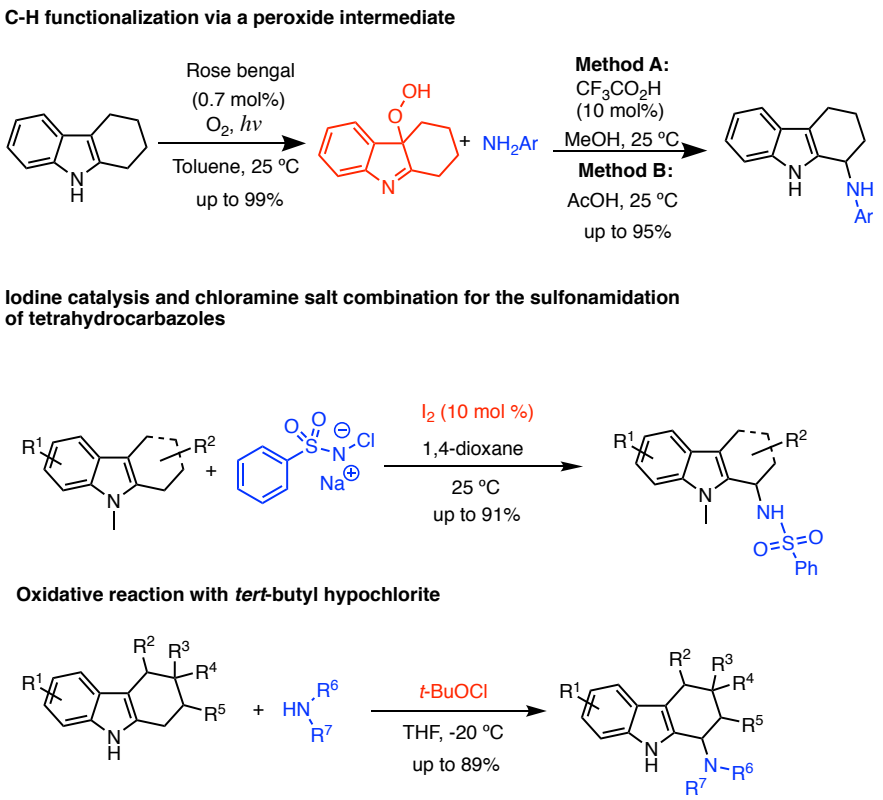
Kawasaki *et al*. were interested in the functionalization of 2α-substituted indole derivatives. In 2011,[83] they developed the acyloxythionium mediated intermolecular C-H functionalization at the 2α-position of the indole ring using a nucleophile from DMSO-TFAA combination. Two years later, they increased the scope of the reaction and to achieve this goal, they discovered that the change of the sulfoxide source allows a higher functionalization, including the formation of C-C bonds.[84] In 2013, Lupton *et al*. studied the C(sp^3)-H oxidation of the carbamoyl protected tetrahydrocarbazole using PIDA in presence of a catalytic amount of $Pd(OAc)_2$ (Scheme 38).[85]



Scheme 38: Different combination of reagents towards the oxidative functionalization of the of 2α-position of tetrahydrocarbazoles.

The following examples are directed towards C-H amination of tetrahydrocarbazoles:

C-H amination of the 1-position of the tetrahydrocarbazole core has been explored by a number of research groups. Klussmann developed a method for the amination of the 1-position of unprotected tetrahydrocarbazole derivatives via a hydroperoxide intermediate using visible light, oxygen, a catalytic amount of Brønsted acid and photosensitizer.[86] Liu *et al*. have reported a general method for iodine-catalyzed regioselective C-H amidation and imination at the 1-position of tetrahydrocarbazole derivatives with chloramine salts.[87] Another interesting research about the C-H amination of tetrahydrocarbazoles was carried out by Zu *et al.* They described a simple protocol for the direct functionalization giving rise to a diastereoselective oxidative coupling process mediated by *tert*-butyl hypochlorite (Scheme 39).[88]

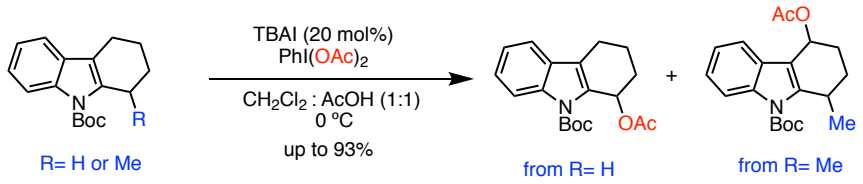


Scheme 39: Different combinations of reagents towards the oxidative amination at the 1-position of tetrahydrocarbazoles.

As decribed above, oxidative C(sp³)-H functionalization at the 4-position of tetrahydrocarbazoles was not reported.

After several approaches for the C-H functionalization of tetrahydrocarbazoles using different reagents, Ishibashi *et al.* studied this type of reaction using PIDA and TBAI, which form tetrabutylammonium [diacetoxyiodate(I)] as reactive species in situ. This transformation is regioselective and is dependent on the substitution of the tetrahydrocarbazole. The thus obtained acetoxylated products can be transformed into different functionalized tetra-

hydrocarbazoles by a substitution reaction using appropriate nucleophiles (Scheme 40).[89]



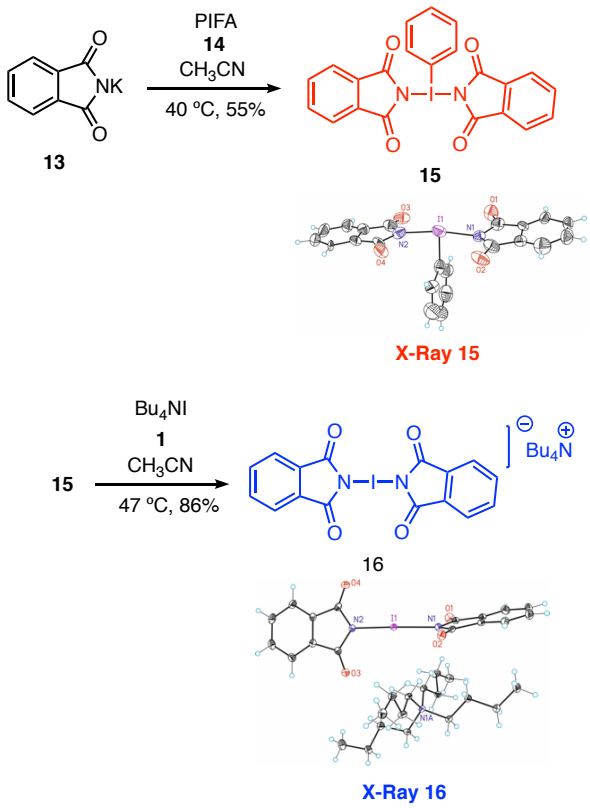
Scheme 40: Iodine-mediated acetoxylation in the 1- and 4-position of tetrahydrocarbazole.

3.1.1. General objectives

As $PhI(NPhth)_2$ has hardly been explored until now but can be considered as a potentially useful oxidative "phthalimide source" and, as a consequence, a useful reagent in organic chemistry, we were interested in the synthesis, characterization and development of a new C-H amination methodology employing this reagent. Since the C-H amination of tetrahydrocarbazoles has been less explored, we thought to develop an innovating methodology to carry out the $C(sp^3)$-H oxidative amination of tetrahydrocarbazole derivatives using $PhI(NPhth)_2$ as reagent.

3.2. RESULTS AND DISCUSSION

We started our exploration with the synthesis of $PhI(NPhth)_2$ **15** following an adaption of the Varvoglis´ procedure. PIFA **14** and potassium phthalimide **13** were added to a flask and the mixture was stirred during 5 hours at 40 ºC. During our previous exploration of the performance of electrophilic iodine(I) reagents upon interaction with electron-rich substrates (Chapter 2, section 2.2.1.), we demonstrated the preparation of reagents of the general formula $R_4N[I(O_2CAr)_2]$ and studied their utility in the iodooxygenation of styrene derivatives.[40] In the present case, we used a similar protocol to form the iodine(I) reagent $R_4N[I(NPhth)_2]$ **16**, which is based on the reaction between tetrabutylammonium iodide with $PhI(NPhth)_2$ at 40°C, using CH_3CN as solvent (Scheme 41).

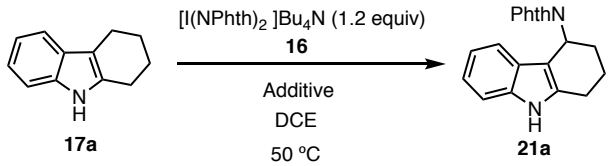


Scheme 41: Synthesis of iodine(III) **15** and iodine(I) **16** reagents.

3.2.1. Reagent performance in oxidative amination of tetrahydrocabazole derivatives. Stoichiometry version.

We began our studies with tetrahydrocarbazole **17a** as the model substrate. In our previous studies of iodooxygenation, iodine(I) reagents were stabilized by the addition of an additive. As a consequence, we started this investigation testing different additives. Initial transformations using iodine(I) reagent **16** were carried out under the following conditions: DCE at 50 ºC (Scheme 42). Using tetrafluoroboric acid or molecular iodine did not lead to the formation

of compound **21a** (entries 1-2), whereas the desired product was observed when phthalimide, acetamide, acetic acid or DBU were used as additives (entries 3-6) with the range of yield 36%, 35%, 20% and 31%, respectively. The addition of previous additives, which possess quite different reactivity such as a base or acid property, gave similar results. This outcome let to the conclusion that the addition of an additive to the reaction was not necessary and the expected product was formed with 50% of yield when no additive was added (entry 7, Scheme 42).

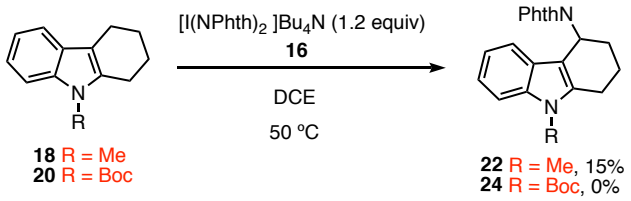


Entry	Additive	^{1}H-NMR Yield (%)
1	BF_4H	0
2	I_2	0
3	HNPhth	36
4	Acetamide	35
5	Acetic acid	20
6	DBU	31
7	Without additive	50

Scheme 42: Different additives tested for the C-N bond formation of tetrahydrocarbazole **21a**.

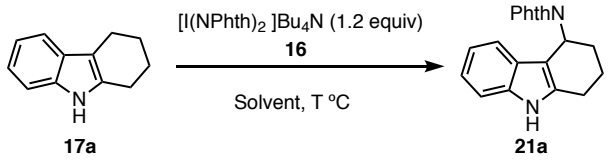
We were interested to check if a *N*-protected tetrahydrocarbazole would lead to a better result, but both, electron-withdrawing and

-donating protecting groups showed that the reaction works better without any nitrogen protection (Scheme 43).



Scheme 43: Acceptor and donor protecting groups tested in the oxidative amination reaction.

We continued our investigation testing different solvents and temperatures. First, we focused on the effect of the solvent on this reaction at 50 ºC. THF was our first test and led to the desired product with 46% yield which is in the same range as the result obtained with DCE (Scheme 44, entry 1). Replacing THF for acetonitrile improved the yield as 56% (entry 2) but toluene and dioxane proved their lack of efficiency (26% and 31% respectively, entries 3-4). The best solvent found during our study was DMF with 61% yield (entry 5). Next, we explored the effect of the temperature on this reaction. We noticed that increasing the temperature of the reaction favored the ^{1}H-NMR yield of the substrate: at 60ºC, the yield was 70% (entry 6), at 70ºC was 87% (entry 7) and finally at 80ºC, 80% (entry 8), which demonstrated the decrease of the yield at elevated temperatures (Scheme 44).



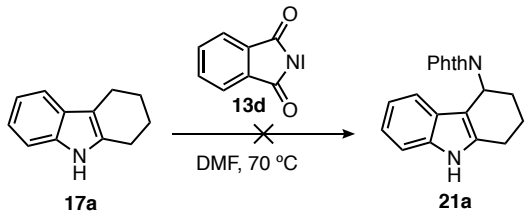
Entry	Solvent	T ºC	^{1}H-NMR yield (%)
1	THF	50	46
2	CH_3CN	50	56
3	Toluene	36	26
4	Dioxane	50	31
5	DMF	50	61
6	DMF	60	70
7	DMF	70	87*
8	DMF	80	80

* Isolated yield 70%

Scheme 44: ^{1}H-NMR yield of product **21a** under different solvents and temperatures conditions.

As a conclusion, the optimized conditions for this kind of transformation are the use of DMF as solvent at 70 ºC which led to 70% isolated yield of **21a**.

To make sure that the iodine(I) compound **16** is necessary to promote the reaction, we conducted a control experiment with *N*-iodophthalimide (Scheme 45). In this case, the reaction did not proceed: in the crude ^{1}H-NMR, we only observed the starting material **17a**. This result proved the importance of $R_4N[I(NPhth)_2]$ to afford the desired product **21a**.



Scheme 45: Control experiment with *N*-iodophthalimide.

In the introduction of this chapter, it is shown that the most reactive part of the tetrahydrocarbazole is 1-position. Only the group of Ishibashi provided the first evidence, that functionalization of the 4-position of tetrahydrocarbazole is possible. In fact, when the 1-position is methylated, the acetoxylation occurs regioselective in the 4-position[89] of the tetrahydrocarbazole. In our case of oxidative C(sp³)-H functionalization, the amination takes place exclusively in the 4-position (Figure 8).

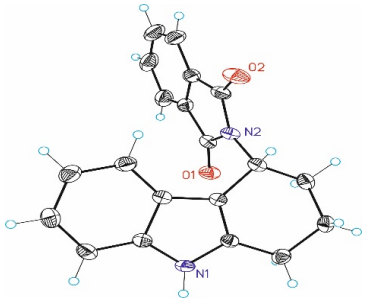
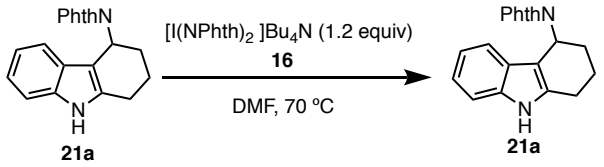


Figure 8: X-ray structure of the compound **21a**.

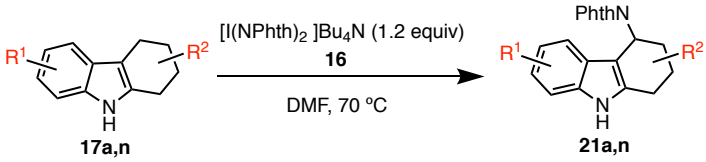
To confirm this outcome, the product **21a** was used as a model substrate in presence of $Bu_4N[I(NPhth)_2]$ (Scheme 46). In the crude ^{1}H-NMR, only the starting material was observed indicating that no alternative amination takes place under these conditions.

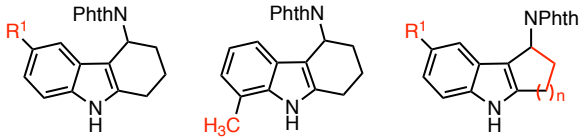


Scheme 46: Study of the regioselectivity of this novel transformation.

As demonstrated in Scheme 47 for 15 examples, the developed amination protocol proceeded for a series of different substitutions at the arene core and at the aliphatic ring. This reaction showed a tolerance for a broad number of functional groups affording good yields and for specific cases, good diastereoselectivities. We explored the influence of the 6-substitution of the arene core of the tetrahydrocarbazole and we noticed that the formation of the product was obtained with the same average of yield with electron-donating and electron-withdrawing groups (**21b-f**, 70-92%), and the best reactivity was observed in the case of chloride (**21c**, 90%) and bromide (**21d**, 92%). Furthermore, the substitution of the 8-position, using a methyl group, gave similar results than a methyl-substitution of the 6-position (**21g**, 65%) and (**21f**, 70%) respectively. The influence of the number of carbons of the ring was studied and it was observed that a decrease in the size of the ring led to an increase of the yield (5C, entry **21h**, 77%), (6C, entry **21a**, 70%), (7C, entry **21i**, 44%). Moreover, it was observed that the substitution of the 6-position with a fluorine improved slightly the isolated yield (entry **21b** and **21j**, 81% and 80% respectively) as the previous results (entry **21a** and **21h**, 70% and 77% respectively). The reaction was explored also with two indoles: with 2,3-dimethylindole **21k**, the reaction proceeded with 38% yield, but in the case of 3-methylindole **21l**, no product formation could be observed.

When the 3-position of the aliphatic ring of the tetrahydrocarbazole is functionalized, the reaction is diastereoselective with formation of the *trans*-product (**21m, 21n**). We studied the influence of the temperature in the ratio of diasteromerisomers for the compound **21n** at low temperature, the *cis*-product (kinetic product) was formed preferably (25ºC, 80:20, *cis*:*trans*), while at high temperature, the *trans*-product (thermodynamic product) is favored (70ºC, 20:80, *cis*:*trans*).

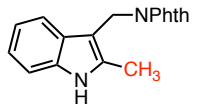




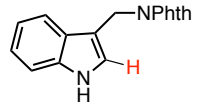
21b (R=F): 81%
21c (R=Cl): 90%
21d (R=Br): 92%
21e (R=OCH_3): 75%
21f (R=CH_3): 70%

21g = 65%

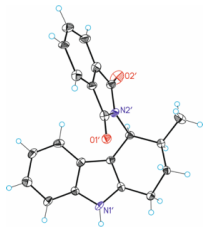
21h (R=H, n=1): 77%
21a (R=H, n=2): 70%
21i (R=H, n=3): 44%
21j (R=F, n=1): 80%



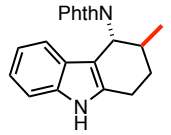
21k = 38%



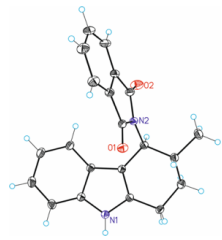
21l = 0%



21m-*cis*

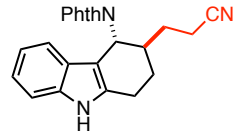


21m (d.e: 54%): 80%



21m-*trans*

T (ºC)	Diastereoisomers **21n** (%) (cis:trans)
25	80:20
40	60:40
70	20:80

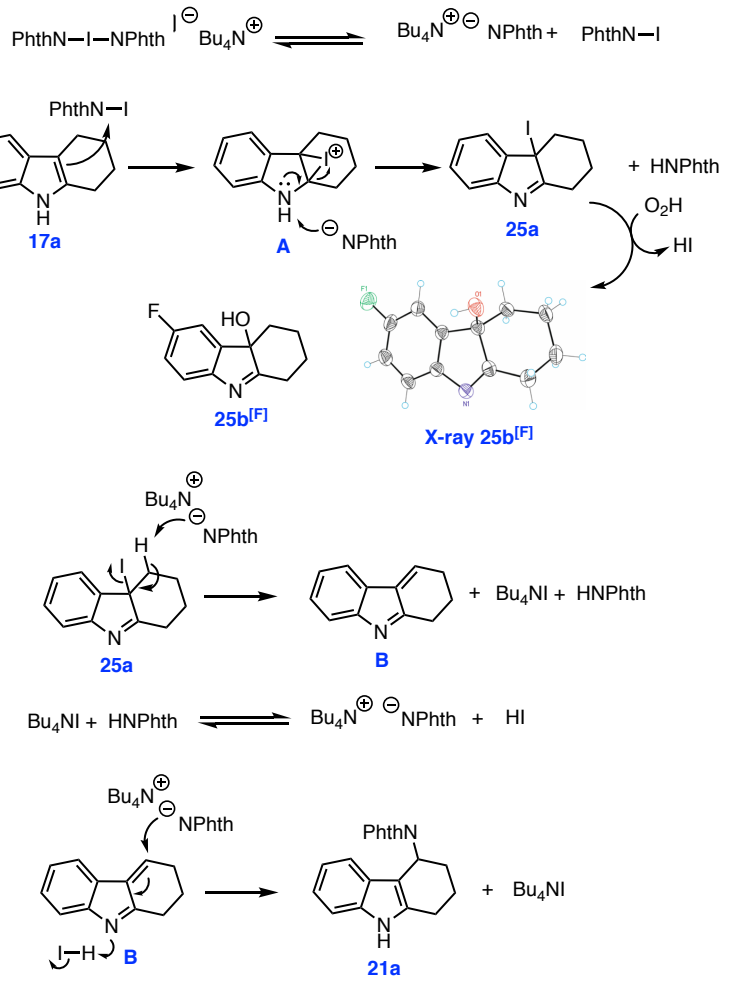


21n (70 ºC, d.e: 60%): 83%

Scheme 47: Scope of the reaction.

The proposed mechanistic pathway is shown in Scheme 48. The double bond of the tetrahydrocarbazole reacts with *N*-

iodophthalimide to form the iodonium intermediate **A**, which leads to compound **25a**. At this stage, one of the phthalimide anions acts as a base to remove the proton on the nitrogen. The other phthalimide anion abstracts a proton of the 4-position of **25a** to afford the intermediate **B**. The equilibrium of tetrabutylammonium iodide and phthalimide could be displaced to the left, giving rise to the formation of hydroiodic acid and the active phthalimide. The intermediate **B** undergoes a nucleophilic attack by the phthalimide and the nitrogen of the indole remained protonated to afford the desired product **21a**.



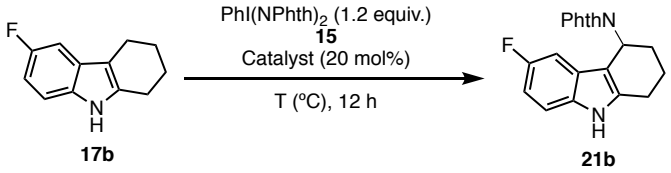
Scheme 48: Proposed mechanistic pathway of the reaction.

When the reaction is carried out in the absence of anhydrous conditions, the intermediate derivative **25b[F]** could be isolated, suggesting that the compound **25a** was formed during the reaction. However, **25a** could not be isolated due to the fact that the iodine is localized on the benzylic position. This position is very reactive and in addition to the good leaving group ability of the iodine under non-

anhydrous conditions, water acts as a nucleophile leading to compound **25b**[F].

3.2.2. Reagent performance in oxidative amination of tetrahydrocabazole derivatives. Catalytic version.

When we proposed the mechanistic pathway, we observed that one of the product of the reaction was Bu_4NI. This fact let us consider that the reaction could be carried out in a catalytic way. We started our approach to develop a catalytic reaction using Bu_4NI as catalyst in DMF at 70ºC, but no product was formed (entry 1, 0%). Furthermore, we wanted to be sure that the reaction cannot only work with iodine(III) reagent which was confirmed by this experiment (entry 2, 0%). The desired product was formed when acetonitrile was used as solvent (entry 3, 60%). Entry 4 showed that when molecular iodine was used as catalyst, the product was not formed and the ^{1}H-NMR yield did not improve when a mixture of I_2 and Bu_4NI was employed (entry 5, 30%). Then, several nitrile solvents were tested as butylonitrile (entry 6, 58%), isotyronitrile (entry 7, 55%) and propionitrile (entry 8, 56%) and gave similar results. Finally, when the influence of the temperature was investigated, we observed that the ^{1}H-NMR yield of the desired product improved with lower temperature (entry 9, 60°C, 63%) and decreased with higher one (entry 10, 90°C, 40%) (Scheme 49).

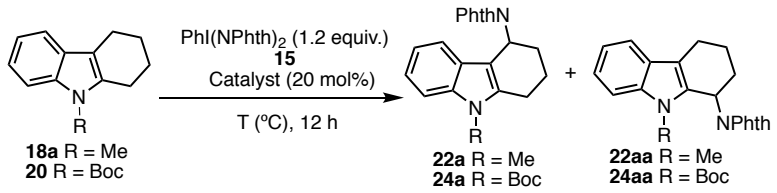


Entry	Solvent	Tº(C)	Catalyst	^{1}H-NMR yield (%)
1	DMF	70	Bu_4NI	0
2	CH_3CN	70	Any catalys	0
3	CH_3CN	70	Bu_4NI	60
4	CH_3CN	70	I_2	0
5	CH_3CN	70	I_2+Bu_4NI	30
6	Butyronitrile	70	Bu_4NI	58
7	Isotyronitrile	70	Bu_4NI	55
8	Propionitrile	70	Bu_4NI	56
9	CH_3CN	60	Bu_4NI	63
10	CH_3CN	90	Bu_4NI	40

Scheme 49: Catalytic version of the oxidative amination reaction.

Several times, the product was isolated in order to check the yield, but the maximum amount of isolated compound was 40%. The major problem of this reaction was the big amount of impurities formed during the reaction, which could be explained by the reactivity of the free nitrogen of the tetrahydrocarbazole towards the iodine(III) reagent. In order to overcome this problem, we decided to protect the nitrogen group. We observed that when the substrate was protected with a methyl group **18a**, the ^{1}H-NMR yield of **22a** was 70% (entry 1) and no side products were formed during the reaction. The issue in this case was the formation of a mixture of regioisomers (75:25).

When the tetrahydrocarbazole was protected with Boc **20**, the reaction did not proceed (entry 2, Scheme 50).

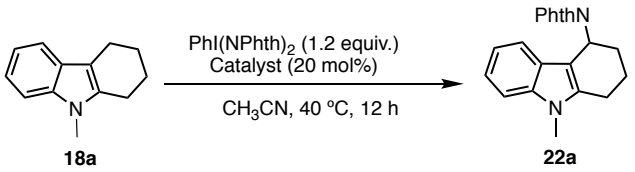


Entry	Protecting group (R)	T°(C)	Catalyst	Conversion (%)	22a:22aa or 24a:24aa
1	Me	70	Bu_4NI	70	75:25
2	Boc	70	Bu_4NI	0	0
3	Me	50	Bu_4NI	65	80:20
4	Me	40	Bu_4NI	55	86:14
5	Me	50	Bu_4NBr	65	100:0
6	Me	40	Bu_4NBr	64	100:0

Scheme 50: Test of different reaction conditions for a catalytic version of the reaction.

We observed that when the temperature was high, the reaction gave better result but is less regioselective with the aminated product at the 4-position (entry 1, 70°C, 75:25), (entry 3, 50°C, 80:20) and (entry 4, 40°C, 86:14). When the catalyst was changed for Bu_4NBr, only one product was formed (entry 5, 50°C, 100:0) and (entry 6, 40°C, 100:0). Once that the problem of regioselectivity was overcome by the use of a bromide salt as catalyst, several sources of bromide sources were tested for this reaction. We observed that with bulky ammonium bromide, the ^{1}H-NMR yield increased significantly and the reaction was optimized when dimethyldioctadecylammonium-

bromide (DDAB) was used as catalyst (entry 1, 91%) and the product was isolated with 80% yield (Scheme 51).



18a **22a**

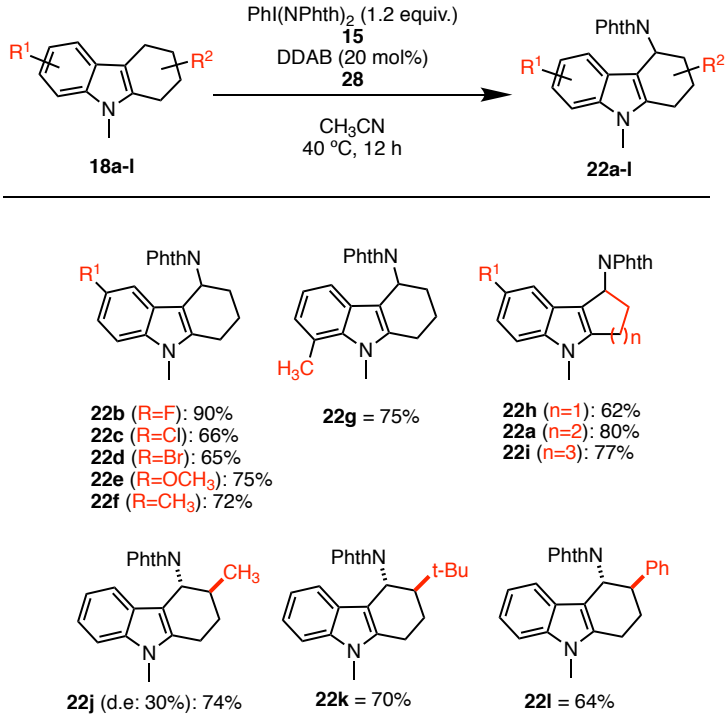
Entry	Catalyst	^{1}H-NMR yield
1	Dimethyldioctadecylammoniumbromide	91*
2	Tetra-*n*-octylammoniumbromide	87
3	Dihexadecyldimethylammonium bromide	85

* Isolated yield 80%

Scheme 51: Screening of bromide salts.

The optimized catalyst (DDAB) and the reaction conditions described before were then employed to explore the scope of the selective C-N bond formation of protected tetrahydrocarbazoles **18a-l**. This reaction also showed a broad functionalization group tolerance with different substrates giving rise to good yields. In the case of aliphatic ring substitution of the tetrahydrocarbazole, the reaction was diastereoselective in favor of the formation of the *trans*-product in the case some compounds. Electron-withdrawing and electron-donating groups at the 6- and 8-postion of the arene core were tolerated and the corresponding products were isolated in good yields (**22b-g**, 65-90%). Studies of the amination of the five-membered ring gave inferior results (**22h**, 62%) than in the stoichiometric reaction (**21h**, 77%) but still better than in the case of the 6-membered ring of tetrahydrocarbazole (**22a** and **21a**, 80% and 70% respectively) and also in the case of 7-membered ring (**22i**, 77%). However, when this

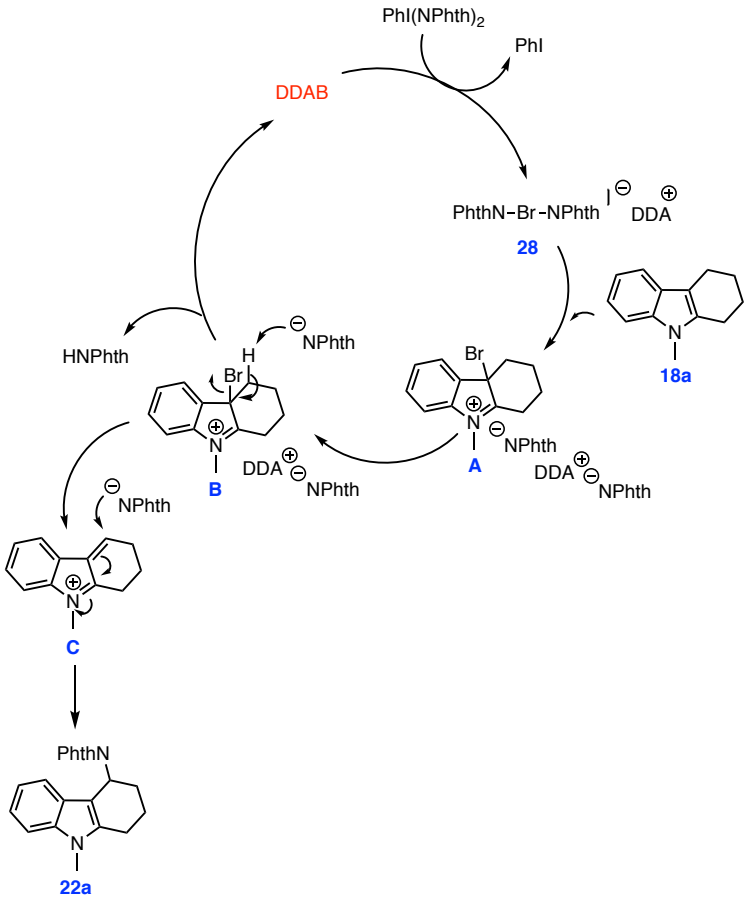
methodology was applied to substituted aliphatic tetrahydrocarbazoles with bulky groups as phenyl and *tert*-butyl, surprisingly only one diastereomer was formed to afford the *trans*-product (*t*-Bu, **22k**, 70%), (Ph, **22l**, 64%). When the substitution in the aliphatic ring was methy group, mixture of diastereomers were formed (**22j, d.e: 30**) (Scheme 52).



Scheme 52: Scope of the oxidative-amination of tetrahydrocarbazole derivatives under catalytic conditions.

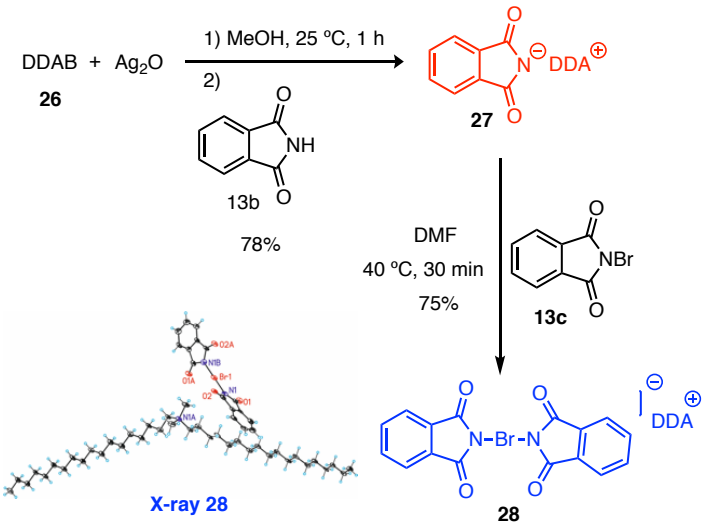
The proposed mechanistic pathway of this reaction starts with the formation of bromine(I) in situ, resulting from the reaction between iodine(III) and the catalytic DDAB. The compound **18a** enters the

catalytic cycle to afford the intermediate **A**. Subsequently, one phthalimide anion abstracts a proton in the 4-position of intermediate **B** to afford **C** by elimination of bromide and at the same time, regeneration of the catalyst. Finally, the second phthalimide anion attacks the double bond of intermediate **C** to give the desired product **22a** (Scheme 53).



Scheme 53: Proposed mechanistic pathway of the catalytic reaction.

In order to confirm the formation of bromine (I) in the catalytic cycle, we were interested in isolating the putative bromine(I) reagent **28**. We tried the classical reaction conditions which we used before to synthesize iodine(I) reagents, however in the present case, the reaction did not take place. Consequently, an adaption of a procedure described by Barry[47] was used: after formation of phthalimide ammonium salt **27**, the precipitate was dissolved in DMF and *N*-bromophthalimide **13c** was added to afford the desired product **28** (Scheme 54).

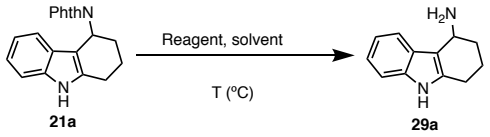


Scheme 54: Synthesis of bromine(I) reagent **28**.

3.2.3. Deprotection of phthalimide

The last step of our study was the deprotection of the phthalimide and we decided to start our investigation with the free tetrahydrocarbazole **21a**. We tried the general protocol with several types of hydrazines, but the free amine was not obtained. We only

noticed decomposition (entry 1). When ammonia was used as a solvent, the semi-deprotection of **30a** was observed (entry 2). When several acids or TBAF was used, we also observed decomposition (entries 3-4, Scheme 55).

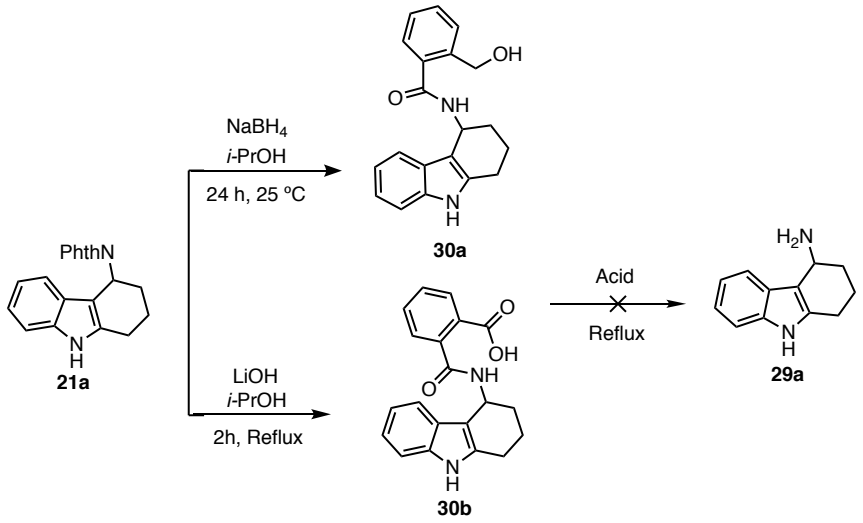


Entry	Reagent	Solvent	T: 25ºC	Reflux
1	NH_2NH_2, NH_2NH_2HCl, CH_3NHNH_2, $BuNHNH_2$, $NH_2CH_2CH_2NH_2$	THF, EtOH, MeOH, IPA	Starting Material and decomposition product	Decomposition products
2	NH_3H_2O, NH_3MeOH	Reagent as solvent	Starting material	Semi-deprotection
3	HCl, H_2SO_4, TFAA, Acetic acid	THF, EtOH, MeOH, IPA	NT*	Decomposition products
4	TBAF	THF	NT*	Decomposition products

* NT = The reaction was not tested

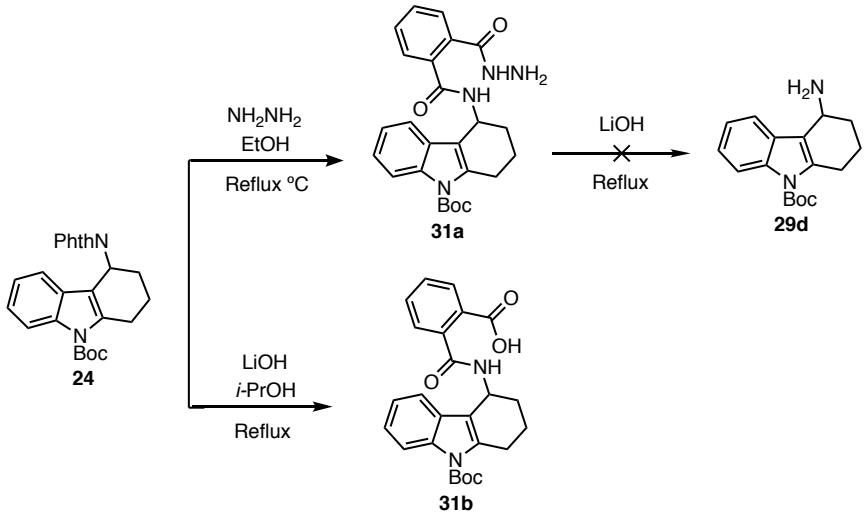
Scheme 55: Screening conditions for the deprotection of phthalimide.

Another attempt to deprotect the phthalimide was the use of $NaBH_4$ as described by John *et al*. in 1984.[90] In this case, the opened phthalimide form **30a** was observed, but the following step with an acid such as TFAA, acetic acid or HCl did not result in cleavage of the amide bond. Semi-deprotected phthalimide was formed also when LiOH was used in the reaction, but when the compound **30b** was in acidic media under reflux, the desired full deprotection did not take place (Scheme 56).



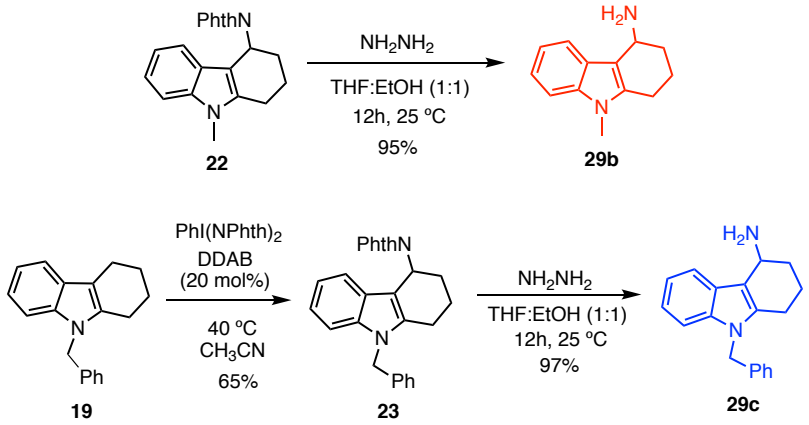
Scheme 56: Different pathways for the deprotection of phthalimide.

Given that the previous procedure did not show any evidence of the deprotection, we decided to protect the free nitrogen of the tetrahydrocarbazole. We started to protect the tetrahydrocarbazole with an electron-withdrawing group like Boc. When the substrate **24** was treated with hydrazine, opened phthalimide **31a** was observed. In order to get the free amine, the compound **24** was setting up in presence of LiOH but no evidence of the free amine was shown in this reaction. When LiOH was directly used with **24**, only the opened phthalimide **31b** was formed. As the free amine was not obtained from **24**, we decided to change the nature of the protecting group in the next step. (Scheme 57).



Scheme 57: Different pathways for the deprotection of phthalimide from *N*-protected tetrahydrocarbazole.

The last strategy was the deprotection of the tetrahydrocarbazole with a donor-group such as methyl **22**. When the substrate was in a mixture with hydrazine in THF:MeOH (1:1), the free amine formed in 95% of yield. Although the methyl protecting group is found in a lot of natural and pharmaceutical compounds, tetrahydrocarbazoles with free N-H are far more common. We tried the same methodology with benzyl protected tetrahydrocarbazole and the free amine was obtained in excellent yield (Scheme 58).



Scheme 58: Deprotection of the phthalimide with different protecting groups on the nitrogen of tetrahydrocarbazole.

3.3. CONCLUSION

In this section, we have presented syntheses, isolations and characterizations including X-ray analyses of iodine(I) $R_4N[I(NPhth)_2]$ and bromine(I) $DDA[Br(NPhth)_2]$ reagents, using Varvoglis' reagent $PhI(NPhth)_2$, which was also characterized by X-ray analysis. We have developed an unprecedented oxidative-amination of the 4-position of tetrahydrocarbazole derivatives. The reaction can be carried out under stoichiometric as well as catalytic conditions. In the stoichiometric version, the iodine(I) reagent was used to obtain a large series of aminated tetrahydrocarbazoles with different substitutions at the arene core and at the aliphatic ring, all of them isolated in good to excellent yields. When the aliphatic ring was substituted, with this methodology the ratio of *cis*-*trans* diastereoisomers could be controlled by the temperature: low temperature led to the *cis*-compound, however with high temperature, the *trans*-compound was formed preferably. The catalytic version, in which the bromine(I) reagent is formed in situ, allows for the oxidative amination of different tetrahydrocarbazoles with substitution in the aromatic and aliphatic ring. In the case that diastereoisomers can be formed, the reaction is diastereospecific with the *trans*-compound formed exclusively when in *p*-position has a bulky group as phenyl or *tert*-butyl. Finally, it was shown, that the deprotection of the phthalimide can be achieved under mild conditions with a methyl or benzyl protecting group at the nitrogen of the tetrahydrocarbazole.

3.4. EXPERIMENTAL SECTION

3.4.1. General procedure

Synthesis of the iodine(III) reagent 15

A mixture of phenyliodine(III) bis(trifluoroacetate) (4.65 mmol, 1 equiv.) and potassium phthalimide (9.30 mmol 2 equiv.) in 44 mL of acetonitrile was stirred at 40ºC in an oil bath for 12 h. The brown precipitate was collected, washed with cold acetonitrile and dried under vacuum.

Synthesis of the iodine(I) reagent 16

A mixture of iodine(III) reagent (0.066 mmol, 1 equiv.) and tetrabutylammonium iodide (0.066 mmol, 1 equiv.) in 3 mL of acetonitrile was stirred at 47 ºC in an oil bath for 12 h. Then the cold ether was added and the product crystallized when the mixture was cooling at -20 ºC.

Synthesis of the bromide(I) reagent 28

Step 1: **27**

To a solution of dimethyldioctadecylammonium bromide (2.48 mmol, 1.15 equiv.) in 6.5 mL of methanol was added silver oxide (2.16 mmol, 1 equiv.), then the mixture was stirred for 1 h. The mixture was filtered through Celite and phthalimide (2.48 mmol, 1.15 equiv.) was added to the filtrate. Then the solid was dried in vacuo.

Step 2: **28**

Phthalimide salt (0.14 mmol, 1 equiv.) was added to a solution of *N*-bromophthalamide (0.14 mmol, 1 equiv.) in DMF (1.0 mL). The solution was stirred during 30 min at 40 ºC. When the mixture cooled down to room temperature, 8 mL of ether was added and the product was crystallized when the mixture was cooling at -20 ºC. The mixture was filtered and washed with ether to give the white product.

General procedure for the stoichiometric oxidative amination of tetrahydrocarbazole derivatives, 21a-n.

In a schlenk flask was added iodine(I) reagent (0.14 mmol, 1.2 equiv.), and tetrahydrocarbazole derivative (0.12mmol, 1 equiv.) in 1.5 mL of dry DMF and the mixture was stirred overnight at 70 ºC. The crude was diluted with EtOAc, washed with water (2x) followed by 2M NaOH (2x). Then the mixture was concentrated in vacuo and the residue was purified by column chromatography (eluents: n-hexane/EtOAc, 7/3 v/v).

General procedure for the catalytic oxidative amination of tetrahydrocarbazole derivatives, 22a-l.

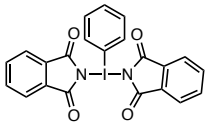
In a schlenk flask was added iodine(III) reagent (0.14 mmol, 1.2 equiv.), DDAB (0.024 mmol, 20%) and tetrahydrocarbazole derivative (0.12 mmol, 1 equiv.) in 1.5 mL of dry CH_3CN and the mixture was stirred overnight at 40 ºC. The crude was diluted with EtOAc, washed with water (2x) followed by 2M NaOH (2x). Then the mixture was concentrated in vacuo and the residue was purified by column chromatography (eluents: n-hexane/EtOAc, 8/2 v/v).

Deprotection of phthalimide 29

A flask was charged with tetrahydrocarbazole derivative (0.150 g) and 2.4 mL of NH_2NH_2. Subsequently, 4 mL of THF and 4 mL of MeOH were added. The mixture was stirred overnight at 25 ºC. The solvents were removed under reduced pressure and the resulting crude product was dissolved in chloroform and filtered in order to remove the by-product. The solvent was evaporated to yield the free amine in quantitative yields.

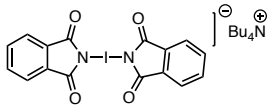
3.4.2. Compound characterization

Diphthalimide(iodobenzene) 15



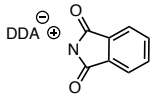
^{1}H NMR (400 MHz, MeOD): δ = 7.60 (m, 2H). 7.80-7.88 (m, 9H), 8.03-8.07 (m, 2H).
^{13}C NMR (125 MHz, MeOD): δ = 121.2, 122.7, 130.6, 130.8, 131.9, 132.9, 133.9, 169.5.
IR (cm^{-1}) = 3190, 1732, 1668, 1272, 1115, 710.
mp: 354 ºC.

tetrabutyl ammonium [bisphthalimideiodine(I)] 16



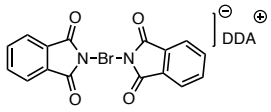
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88-1.03 (m, 12H), 1.32-1.51 (m, 8H), 1.60- 1.77 (m, 8H), 3.30-3.45 (m, 8H), 7.55-7.62 (m, 4H), 7.69-7.75 (m, 4H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 19.8, 24.1, 59.0, 122.6, 133.2, 134.3, 172.2.
IR (cm^{-1}) = 2964, 2872, 1678, 1597, 1112, 708.
mp: 142.6 ºC.

Dimethyldioctadecylammonium phthalimideiodine 27



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.8 Hz, 6H), 1.10-1.15 (m, 60H), 1.59-1.73 (m, 4H), 3.32-3.45 (m, 10H), 7.40-7.46 (m, 2H), 7.54-7.62 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ= 26.2, 29.1, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9, 51.3, 63.8, 120.4, 130.8, 138.7, 186.1.
IR (cm^{-1}) = 3500, 1923, 2846, 1577, 1370.
mp: 58 ºC

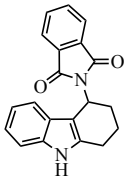
Dimethyldioctadecylammonium [bisphthalimidebromine(I)] 28



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 6.9 Hz, 6H), 1.16-1.40 (m, 60H), 1.68-1.80 (m, 4H), 3.42 (s, 6H), 3.44-3.50 (m, 4H), 7.55-7.64 (m, 4H), 7.68-7.77 (m, 4H).

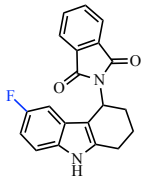
^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 22.8, 26.3, 29.2, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 51.5, 64.4, 121.8, 132.3, 135.3, 175.4.
IR (cm^{-1}) = 2923, 2839, 1668, 1280, 1131, 716.
mp: 95 ºC.

2-(2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21a



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90-2.02 (m, 1H), 2.19-2.35 (m, 2H), 2.38-2.48 (m, 1H), 2.71-2.81 (m, 1H), 2.91-3.02 (m, 1H), 5.78-5.85 (m, 1H), 6.87-6.93 (m, 1H), 7.04-7.10 (m, 2H), 7.26-7.30 (m, 2H), 7.69-7.75 (m, 2H), 7.80-7.85 (m, 2H), 7.94 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1, 22.9, 28.5, 45.2, 107.6, 110.8, 117.4, 119.6, 121.2, 123.2, 126.2, 132.0, 133.8, 135.6, 136.5, 168.3.
IR ν(cm^{-1}): 3347, 1700, 1392, 1110, 716.
mp: 197 ºC.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{20}H_{16}N_2NaO_2$ 339.1104, found; 339.1108.

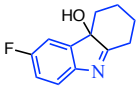
2-(6-fluoro-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21b



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86-2.00 (m, 1H), 2.16-2.31 (m, 2H), 2.36-2.46 (m, 1H), 2.36-2.73 (m, 1H), 2.80-2.91 (m, 1H), 5.67-5.82 (m, 1H), 6.69-6.82 (m, 3H), 7.14 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.71-7.76 (m, 2H), 7.81-7.88 (m, 2H), 8.07 (s, 1H).
^{19}F(H) NRM (376 MHz, $CDCl_3$): δ= -124.7.
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 22.9, 28.5, 45.0, 102.6 (d, *J* = 23.7 Hz), 107.7 (d, *J* = 4.4 Hz), 109.1 (d, *J* = 26.1 Hz), 111.3 (d, *J* = 9.8 Hz), 123.3, 126.4 (d, *J* = 9.9 Hz), 131.9, 132.1, 134.0, 138.5, 157.8 (d, *J* = 234.0 Hz), 168.3.
IR ν(cm^{-1}): 3367, 1702, 1366, 1586, 1107.

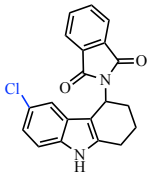
mp: 195 ºC.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{20}H_{15}FN_2NaO_2$ 357.1010, found; 357.1003.

6-fluoro-1,2,3,4-tetrahydro-4aH-carbazol-4a-ol 25b[F]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (td, *J* = 13.8, 4.0 Hz, 1H), 1.26-1.39 (m, 1H), 1.62-1.73 (m, 1H), 1.87-2.06 (m, 1H), 2.07-2.18 (m, 1H), 2.25-2.38 (m, 1H), 2.47-2.63 (m, 2H), 4.72 (s, 1H), 6.94 (td, *J* = 8.8, 2.6 Hz, 1H), 6.98-7.04 (m, 1H), 7.12 (dd, *J* = 7.5, 2.5 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 28.7, 29.2, 29.7, 38.8, 82.1 (d, *J* = 2.1 Hz), 110.2 (d, *J* = 24.7 Hz), 115.7 (d, *J* = 23.7 Hz), 120.9 (d, *J* = 8.7 Hz), 143.5 (d, *J* = 8.1 Hz), 148.8, 61.37 (d, *J* = 245.4 Hz).
^{19}F(H) NRM (376 MHz, $CDCl_3$): δ = -116.7.
HRMS (ESI): Cald. for $[M+H]^+$ $C_{12}H_{13}N_2FNO$ 206.0976, found; 206.0975.
IR ν(cm^{-1}): 3144, 2938, 1468, 1183, 1096, 840.
mp: 80 ºC.

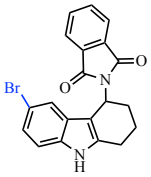
2-(6-chloro-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21c



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.81-2.00 (m, 1H), 2.10-2.46 (m, 3H), 2.59- 2.86 (m, 2H), 5.69-5.81 (m, 1H), 6.95-7.06 (m, 2H), 7.07-7.1 7 (m, 1H), 7.69-7.79 (m, 2H), 7.80-7.88 (m, 2H), 8.15 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 22.8, 28.7, 44.9, 107.1, 111.7, 116.8, 121.4, 123.3, 125.1, 127.2, 131.8, 134.1, 138.3, 168.4.
IR ν(cm^{-1}): 3419, 2957, 1705, 1388, 1307.
mp: 206 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{20}H_{15}ClN_2NaO_2$ 373.0714, found; 373.0711.

2-(6-bromo-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21d



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85-2.00 (m, 1H), 2.13-2.41 (m, 3H), 2.64-2.76 (m, 1H), 2.78-2.90 (m, 1H), 5.69-5.78 (m, 1H), 7.05-7.15 (m, 2H), 7.17-7.22 (m, 1H), 7.71-7.79 (m, 2H), 7.79-7.91 (m, 2H), 8.15 (s, 1H).

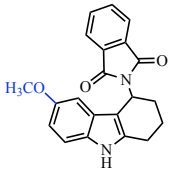
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 22.8, 28.7, 44.8, 107.1, 112.2, 112.8, 119.9, 123.3, 124.0, 127.9, 131.8, 134.0, 134.3, 138.1, 168.4.

IR ν(cm^{-1}): 3410, 2936, 1707, 1388, 1322.

mp: 199 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{20}H_{15}BrN_2NaO_2$ 417.0209, found; 417.0207.

2-(6-methoxy-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21e



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83-2.03 (m, 1H), 2.11-2.32 (m, 2H), 2.35-2.50 (m, 1H), 2.60-2.78 (m, 1H), 2.76-2.96 (m, 1H), 3.56 (s, 3H), 5.74-5.81 (m, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.14 (dd, *J* = 8.7, 0.5 Hz, 1H), 7.66-7.74 (m, 2H), 7.79-7.85 (m, 2H), 7.90 (s, 1H).

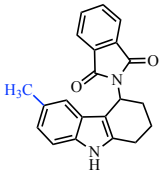
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 23.0, 28.5, 45.3, 55.6, 100.2, 107.3, 110.4, 111.4, 123.2, 126.56, 130.8, 131.9, 133.9, 137.5, 153.9, 168.4.

IR ν(cm^{-1}): 3403, 2926, 1706, 1389, 1111.

mp: 186 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{18}N_2NaO_3$ 369.1210, found; 369.1198.

2-(6-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21f



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-2.00 (m, 1H), 2.17-2.33 (m, 2H), 2.26 (s, 3H), 2.35-2.45 (m, 1H), 2.66-2.77 (m, 1H), 2.85-2.95 (m, 1H), 5.79 (ddt, *J* = 7.5, 5.8, 1.6 Hz, 1H), 6.85-6.91 (m, 2H), 7.16 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.90 (d, *J* = 2.8 Hz, 1H).

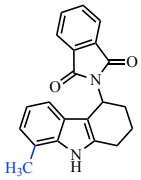
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 22.0, 22.9, 28.8, 45.2, 106.9, 110.4, 117.2, 122.7, 123.2, 126.4, 128.7, 132.0, 133.8, 133.9, 136.8, 168.4.

IR ν(cm^{-1}): 3420, 2936, 2858, 1707, 1390, 1110.

mp: 196 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{18}N_2NaO_2$ 353.1260, found; 353.1251.

2-(8-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21g



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89-2.03 (m, 1H), 2.18-2.35 (m, 2H), 2.36-2.50 (m, 1H), 2.42 (m, 3H), 2.75-2.84 (m, 1H), 2.96-3.06 (m, 1H), 5.75-5.87 (m, 1H), 6.80-6.89 (m, 2H), 6.91-6.96 (m, 1H), 7.69-7.74 (m, 2H), 7.80-7.85 (m, 2H), 7.88 (s, 1H).

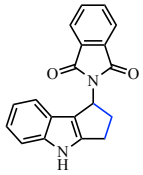
^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.6, 22.2, 23.0, 28.6, 45.3, 108.1, 115.1, 119.8, 119.7, 122.0, 123.2, 125.6, 132.0, 133.8, 135.1, 136.1, 168.4.

IR ν(cm^{-1}): 3409, 2953, 1698, 1329, 716.

mp: 146 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{18}N_2NaO_2$ 353.1260, found; 353.1254.

2-(1,2,3,4-tetrahydrocyclopenta[b]indol-1-yl)isoindoline-1,3-dione 21h



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.78-2.96 (m, 3H), 3.01-3.16 (m, 1H), 3.42-3.54 (m, 1H), 5.93-6.00 (m, 1H), 6.97-7.06 (m, 1H), 7.06-7.13 (m, 1H), 7.23-7.33 (m, 2H), 7.33-7.40 (m, 1H), 7.64-7.71 (m, 2H), 7.75-7.85 (m, 2H), 8.13 (s, 1H).

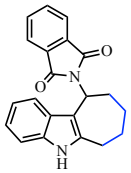
^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 34.6, 49.1, 111.6, 117.1, 118.2, 119.9, 123.0, 123.2, 132.2, 133.8, 141.2, 146.8, 168.3.

IR ν(cm^{-1}): 3411, 2919, 2850, 1699, 1393, 1314.

mp: 150 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{19}H_{14}N_2NaO_2$ 325.0947, found; 325.0943.

2-(5,6,7,8,9,10-hexahydrocyclohepta[b]indol-10-yl)isoindoline-1,3-dione 21i



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76-1.86 (m, 2H), 2.05-2.19 (m, 3H), 2.46-2.56 (m, 1H), 2.85 (dt, *J* = 15.6, 4.0 Hz, 1H), 3.64 (ddd, *J* = 16.3, 12.4, 4.8 Hz, 1H), 5.95-6.02 (m, 1H), 6.98-7.04 (m, 1H), 7.05-7.11 (m, 1H), 7.25-7.28 (m, 1H), 7.41-7.36 (m, 1H), 7.67 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.88 (d, *J* = 4.6 Hz, 1H).

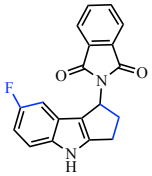
^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 26.6, 27.6, 32.5, 47.0, 108.1, 110.4, 117.4, 119.6, 121.1, 123.0, 128.7, 132.1, 133.7, 134.4, 139.8, 168.5.

IR ν(cm^{-1}): 3383, 2921, 1697, 1350, 1323.

mp: 130 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{23}H_{19}N_3NaO_2$ 392.1369, found; 392.1377.

2-(7-fluoro-1,2,3,4-tetrahydrocyclopenta[b]indol-1-yl)isoindoline-1,3-dione 21j



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.76-2.95 (m, 2H), 3.01-3.13 (m, 1H), 3.40-3.51 (m, 1H), 5.91 (dt, *J* = 9.0, 2.0 Hz, 1H), 6.81 (td, *J* = 9.1, 2.6 Hz, 1H), 6.98 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.17 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.67-7.74 (m, 2H), 7.78-7.84 (m, 2H), 8.14 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 34.6, 48.9, 103.5 (d, *J* = 23.9 Hz), 109.0 (d, *J* = 26.1 Hz), 112.0 (d, *J* = 9.8 Hz), 117.2 (d, *J* = 4.3 Hz), 123.1, 123.5 (d, *J* = 10.3 Hz), 132.1, 133.9, 137.6, 148.6, 157.9 (d, *J* = 234.7 Hz), 168.3.

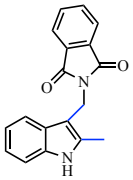
^{19}F(H) NRM (376 MHz, $CDCl_3$): δ = -124.2.

IR ν(cm^{-1}): 3400, 2937, 1694, 1429, 1108.

mp: 183 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{19}H_{13}FN_2NaO_2$ 343.0853, found; 343.0851.

2-((2-methyl-1H-indol-3-yl)methyl)isoindoline-1,3-dione 21k



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 3H), 4.99 (s, 2H), 7.10 – 7.15 (m, 2H), 7.25-7.28 (m, 1H), 7.65-7.71 (m, 2H), 7.79-7.84 (m, 2H), 7.86-7.92 (m, 2H).

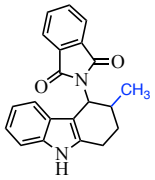
^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.9, 32.1, 107.2, 110.0, 119.0, 119.9, 121.4, 123.1, 127.9, 132.3, 133.7, 134.8, 135.0, 168.4.

IR ν(cm^{-1}): 3411, 2921, 1699, 1393, 710.

mp: 100 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{18}H_{14}N_2NaO_2$ 313.0947, found; 313.0963.

2-(3-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21m



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.0 Hz, $3H_{min}$), 1.14 (d, *J* = 6.7 Hz, $3H_{maj}$), 1.67-1.89 (m, $1H_{maj}$-$1H_{min}$), 2.08 – 2.15 (m, $1H_{maj}$-$1H_{min}$), 2.33 – 2.46 (m, $1H_{maj}$-$1H_{min}$), 2.59-2.67 (m, $1H_{maj}$-$1H_{min}$), 2.88-2.71 (m, $2H_{maj}$-$2H_{min}$) 5.38 (d, *J* = 9.4 Hz, $1H_{maj}$), 5.78 (d, *J* = 4.4 Hz, $1H_{min}$), 6.92 – 6.85 (m, $1H_{maj}$), 7.03 – 6.96 (m, $1H_{min}$), 7.12 – 7.04 (m, $2H_{maj}$-$2H_{min}$), 7.28 – 7.20 (m, $1H_{maj}$-$1H_{min}$), 7.69 – 7.63 (m, $2H_{min}$), 7.77 – 7.70 (m, $2H_{maj}$), 7.90 – 7.83 (m, $2H_{maj}$), 7.96 (d, J = 7.3 Hz, $2H_{min}$) , 8.23 (s, $1H_{maj}$), 8.28 (s, $1H_{min}$).

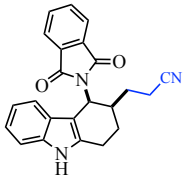
^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 18.7, 22.9, 27.9, 31.3, 33.3, 33.9, 47.4, 52.7, 60.4, 106.8, 108.0, 110.8, 110.8, 117.2, 119.5, 119.6, 121.0, 121.2, 122.9, 123.3, 123.6, 126.0, 126.4, 131.8, 132.7, 133.9, 134.3, 135.9, 136.0, 136.3, 137.5, 167.9, 168.5.

IR ν(cm^{-1}): 3379, 2928, 1690, 1351, 1113, 717.

mp: 98 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{18}N_2NaO_2$ 353.1260, found; 353.1270.

3-(4-(1,3-dioxoisoindolin-2-yl)-2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanenitrile 21n (*cis*)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.82 (m, 2H), 1.94-2.07 (m, 1H), 2.27-2.32 (m, 1H), 2.41-2.62 (m, 2H), 2.67-2.77 (m, 1H), 2.81-2.89 (m, 1H), 3.01-3.13 (m, 1H), 5.65-5.69 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.04-7.10 (m, 1H), 7.29-7.32 (m, 1H), 7.69-7.78 (m, 2H), 7.80-7.88 (m, 2H), 7.94 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.3, 22.7, 25.4, 28.1, 38.4, 45.7, 106.1, 110.8, 117.09, 119.6, 119.8, 121.48, 123.3 (d, *J* = 45.7

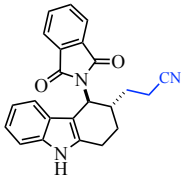
Hz), 126.1, 131.5 (d, *J* = 89.4 Hz), 134.2 (d, *J* = 35.2 Hz), 135.9, 137.3, 169.1 (d, *J* = 164.5 Hz).

IR ν(cm^{-1}): 3421, 2850, 1703, 1318, 1103.

mp: 140 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{23}H_{19}N_3NaO_2$ 392.1369, found; 392.1370.

3-(4-(1,3-dioxoisoindolin-2-yl)-2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanenitrile 21n (*trans*)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67-1.78 (m, 1H), 1.84-1.94 (m, 1H), 1.93-2.03 (m, 1H), 2.34-2.57 (m, 2H), 2.57-2.66 (m, 1H), 2.87-2.99 (m, 1H), 3.04-3.12 (m, 1H), 5.48-5.51 (m, 1H), 6.92-7.02 (m, 1H), 7.06-7.12 (m, 1H), 7.17-7.21 (m, 1H), 7.29-7.32 (m, 2H), 7.58-7.80 (m, 2H), 7.94 (s, 1H).

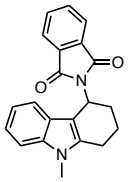
^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.9, 22.4, 27.6, 28.5, 37.7, 49.9, 107.1, 111.0, 117.1, 119.5, 119.8, 121.4, 123.5, 125.9, 131.6, 134.2, 136.0, 136.0, 168.4.

IR ν(cm^{-1}): 3242, 2926, 1607, 1449, 1296, 740.

mp: 156 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{23}H_{19}N_3NaO_2$ 392.1369, found; 392.1374.

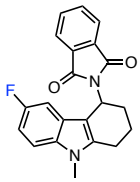
2-(9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22a



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91-2.05 (m, 1H), 2.16-2.27 (m, 1H), 2.31-2.51 (m, 2H), 2.73-2.53 (m, 1H), 2.90-3.06 (m, 1H), 3.68 (s, 3H), 5.79-5.87 (m, 1H), 6.84-6.95 (m, 1H), 7.06-7.20 (m, 2H), 7.22-7.30 (m, 1H), 7.67-7.75 (m, 2H), 7.77-7.87 (m, 2H).

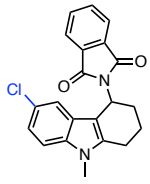
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 22.0, 28.4, 29.2, 45.4, 106.7, 108.9, 117.3, 119.2, 120.7, 123.2, 125.7, 132.0, 133.8, 136.9, 138.0, 168.4.
IR ν(cm^{-1}): 2938, 1703, 1386, 1347, 1110, 712.
mp: 190 ºC.
HRMS (ESI): Cald. for $[M+H]^+$ $C_{21}H_{19}N_2O_2$ 331.1441, found; 331.1442.

2-(6-fluoro-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22b



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91-2.04 (m, 1H), 2.14-2.25 (m, 1H), 2.27-2.47 (m, 2H), 2.73-2.83 (m, 1H), 2.87-3.01 (m, 1H), 3.67 (s, 3H), 5.72-5.83 (m, 1H), 6.73 (dd, *J* = 9.6, 2.5 Hz, H), 6.83 (td, *J* = 9.1, 2.5 Hz, 1H), 7.16 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.69-7.77 (m, 2H), 7.78-7.91 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 21.9, 28.4, 29.5, 45.2, 102.5 (d, *J* = 23.7 Hz), 106.7 (d, *J* = 4.6 Hz), 108.7, 109.4 (d, *J* = 10.0 Hz), 123.3, 125.7 (d, *J* = 9.9 Hz), 131.9, 133.5, 134.0, 139.7, 157.7 (d, *J* = 233.8 Hz), 168.3.
^{19}F(H) NRM (376 MHz, $CDCl_3$): δ = -125.1.
IR ν(cm^{-1}): 2920, 1708, 1465, 1353, 1028.
mp: 153 ºC.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{17}FN_2NaO_2$ 371.1166, found; 371.1166.

2-(6-chloro-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22c



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-2.07 (m, 1H), 2.12-2.25 (m, 1H), 2.26-2.46 (m, 3H), 2.68 -2.84 (m, 1H), 2.84-3.06 (m, 1H), 3.66 (s, 4H), 5.68-5.80 (m, 1H),

7.00-7.08 (m, 3H), 7.10-7.19 (m, 1H), 7.69-7.77 (m, 3H), 7.79-7.88 (m, 3H).

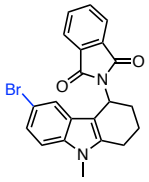
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 21.8, 28.6, 29.4, 29.7, 44.96, 106.4, 109.9, 116.8, 120.9, 123.3, 124.9, 126.6, 131.9, 134.0, 135.3, 139.6, 168.3.

IR ν(cm^{-1}): 2924, 1702, 1388, 1330, 1111, 714.

mp: 187 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{17}ClN_2NaO_2$ 387.0871, found; 387.0861.

2-(6-bromo-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22d



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04-1.91 (m, 1H), 2.24-2.12 (m, 1H), 2.43-2.26 (m, 2H), 2.84-2.72 (m, 1H), 3.00-2.89 (m, 1H), 3.66 (s, 3H), 5.80-5.72 (m, 1H), 7.14-7.09 (m, 1H), 7.22-7.15 (m, 2H), 7.77-7.69 (m, 2H), 7.88-7.79 (m, 2H).

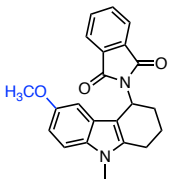
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 21.8, 28.6, 29.4, 29.7, 44.9, 106.3, 110.3, 112.6, 119.9, 123.3, 123.5, 127.3, 131.9, 134.0, 135.6, 139.5, 168.4.

IR ν(cm^{-1}): 2918, 1702, 1331, 1045, 715.

mp: 165 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{21}H_{17}BrN_2NaO_2$ 341.0366, found; 341.0365.

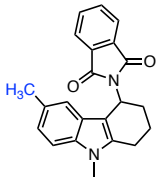
2-(6-methoxy-9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22e



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90-2.02 (m, 1H), 2.28-2.49 (m, 2H), 2.73-2.82 (m, 1H), 2.88-2.99 (m, 1H), 3.56 (s, 3H), 3.65 (s, 3H), 5.77-5.83 (m, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.4 Hz, 1H),

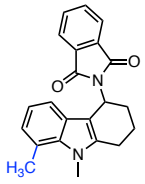
7.09-7.19 (m, 1H), 7.68-7.74 (m, 2H), 7.78-7.85 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ =
IR ν(cm^{-1}): 2910, 1707, 1463, 1350, 732.
mp: 156 ºC.

2-(6,9-dimethyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22f



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85-2.02 (m, 1H), 2.11-2.24 (m, 1H), 2.24 (s, 3H), 2.27-2.43 (m, 2H), 2.75 (dt, *J*=16.9, 5.0 Hz, 1H), 2.85-2.99 (m, 1H), 5.74-5.83 (m, 1H), 6.81-6.87 (m, 1H), 6.90 (dd, *J*=8.3, 1.6 Hz, 1H), 7.12 (d, *J*=8.3 Hz, 1H), 7.64-7.74 (m, 2H), 7.76-7.87 (m, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 22.3, 22.4, 29.2, 45.9, 106.50, 109.1, 117.7, 122.8, 123.7, 126.5, 128.9, 132.6, 134.3, 135.9, 138.7, 169.0.
IR ν(cm^{-1}): 2929,1702, 1388, 1111, 716.
mp: 185 ºC.
HRMS (ESI): Cald. for $[M+Na]^+$ $C_{22}H_{20}N_2NaO_2$ 367.1417, found; 367.1423.

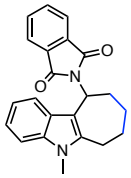
2-(8,9-dimethyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22g



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87-2.01 (m, 1H), 2.12-2.23 (m, 1H), 2.27-2.43 (m, 2H), 2.70-2.79 (m, 4H), 2.84-2.96 (m, 1H), 3.93 (s, 3H), 5.74-5.82 (m, 1H), 6.71-6.79 (m, 2H), 6.89-6.93 (m, 1H), 7.64-7.72 (m, 2H), 7.75-7.83 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 22.5, 22.6, 29.2, 32.9, 45.8, 107.3, 115.9, 119.9, 121.4, 123.7, 124.5, 127.2, 132.6, 134.3, 136.4, 139.0, 168.9.
IR ν(cm^{-1}): 2950, 1707, 1387, 1113, 750.
mp: 179 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{22}H_{20}N_2NaO_2$ 367.1417, found; 367.1428.

2-(5-methyl-5,6,7,8,9,10-hexahydrocyclohepta[b]indol-10-yl)isoindoline-1,3-dione 22i



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65-1.76 (m, 1H), 1.77-1.87 (m, 1H), 1.97-2.08 (m, 1H), 2.08-2.20 (m, 2H), 2.49-2.61 (m, 1H), 3.13-3.23 (m, 1H), 3.32-3.43 (m, 1H), 3.58 (s, 3H), 5.77-5.83 (m, 1H), 7.08-7.18 (m, 1H), 7.19-7.30 (m, 2H), 7.62-7.68 (m, 1H), 7.71-7.77 (m, 2H), 7.81-7.90 (m, 2H).

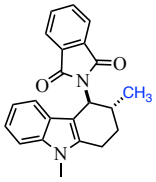
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 23.0, 26.6, 29.7, 29.8, 48.0, 108.8, 116.5, 118.7, 118.7, 121.8, 123.3, 127.3, 130.8, 131.9, 134.1, 136.8, 167.7.

IR ν(cm^{-1}): 2924, 1703, 1319, 717.

mp: 126 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{22}H_{21}N_2O_2$ 368.1598, found; 368.1525.

2-((3R,4S)-3-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22j (*trans*)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.7 Hz, 3H), 1.78-1.86 (m, 1H), 2.20-2.26 (m, 1H), 2.72-2.80 (m, 1H), 2.81-2.87 (m, 1H), 2.95-3.04 (m, 1H), 3.67 (s, 3H), 5.42 (d, *J* = 9.4 Hz, 1H), 6.87-6.91 (m, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 7.09-7.13 (m, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.70-7.76 (m, 2H), 7.82-7.89 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7, 21.7, 29.3, 31.3, 33.1, 52.9, 107.1, 109.0, 117.2, 119.2, 120.6, 123.3, 125.5, 131.7, 133.9, 137.2, 137.7, 168.5.

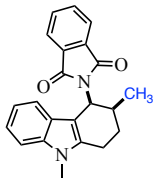
IR ν(cm^{-1}): 2925, 1699, 1315, 1109, 748.

mp: 215ºC.

HRMS (ESI): Cald. for $[M+H]^+$ $C_{22}H_{21}N_2O_2$ 345.1598, found;

345.1599.

2-((3S,4S)-3-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22j (*cis*)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, J = 6.3 Hz, 3H), 1.92-1.98 (m, 1H), 2.36-2.45 (m, 2H), 2.75-2.85 (m, 1H), 3.05-3.13 (m, 1H), 3.70 (s, 3H), 5.78-5.84 (m, 1H), 6.92-7.01 (m, 1H), 7.09-7.15 (m, 1H), 7.21-7.28 (m, 2H), 7.59-7.68 (m, 2H), 7.69-7.76 (m, 1H), 7.95 (d, J = 7.4 Hz, 1H).

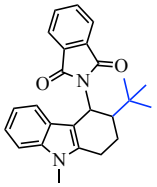
^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 21.9, 27.9, 29.2, 33.8, 47.5, 105.9, 108.9, 117.2, 119.2, 120.7, 122.9, 123.3, 126.0, 131.5, 132.16, 133.7, 133.9, 137.2, 138.9, 168.7, 169.7.

IR ν(cm^{-1}): 2925, 1699, 1314, 748.

mp: 204 ºC.

HRMS (ESI): Cald. for $[M+H]^+$ $C_{22}H_{21}N_2O_2$ 345.1598, found; 345.1599.

2-(3-(tert-butyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22k



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 1.69-1.79 (m, 1H), 2.35-2.44 (m, 1H), 2.59-2.69 (m, 1H), 2.79-2.89 (m, 1H), 2.98-3.10 (m, 1H), 3.67 (s, 3H), 5.82 (d, *J* = 7.6 Hz, 1H), 6.89-6.99 (m, 1H), 7.04-7.12 (m, 1H), 7.19-7.29 (m, 2H), 7.62-7.71 (m, 2H), 7.73-7.84 (m, 2H).

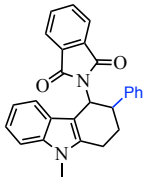
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 26.0, 28.1, 29.2, 33.6, 46.4, 46.6, 107.7, 108.7, 117.7, 119.3, 120.5, 123.1, 125.7, 132.0, 133.7, 137.2, 140.2, 168.6.

IR ν(cm^{-1}): 2923, 1704, 1395, 1108, 717.

mp: 240 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{23}H_{28}N_2NaO_2$ 387.2043, found; 387.2056.

2-(3-phenyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 22l



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28-2.42 (m, 2H), 2.90-3.00 (m, 1H), 3.10-3.20 (m, 1H), 3.71 (s, 3H), 3.94-4.05 (m, 1H), 5.95 (d, J = 10.2 Hz, 1H), 6.82-6.89 (m, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.09-7.14 (m, 1H), 7.18-7.25 (m, 1H), 7.25-7.36 (m, 5H), 7.64-7.69 (m, 2H), 7.74 (dd, J = 5.4, 3.1 Hz, 2H).

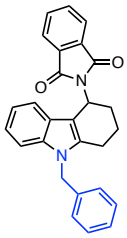
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 29.4, 31.1, 44.3, 52.1, 107.6, 109.0, 117.4, 119.3, 120.7, 123.2, 125.4, 126.9, 127.6, 128.6, 131.6, 133.8, 137.2, 137.3, 142.6, 168.1.

IR ν(cm^{-1}): 2914, 2832, 1470, 1376, 732.

mp: 159 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{27}H_{22}N_2NaO_2$ 429.1573, found; 429.1563.

2-(9-benzyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 23



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91-2.04 (m, 1H), 2.17-2.36 (m, 2H), 2.38-2.50 (m, 1H), 2.72 (dt, J = 17.1, 5.4 Hz, 1H), 2.84-2.96 (m, 1H), 5.34 (d, J = 2.5 Hz, 2H), 5.90 (ddt, J = 7.6, 5.8, 1.6 Hz, 1H), 6.89-6.96 (m, 1H), 7.01-7.09 (m, 3H), 7.14-7.18 (m, 1H), 7.20-7.26 (m, 2H), 7.30-7.36 (m, 2H), 7.67-7.77 (m, 2H), 7.81-7.90 (m, 2H).

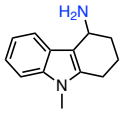
^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 21.9, 28.5, 45.3, 46.4, 107.3, 109.5, 117.5, 119.5, 121.0, 123.2, 126.0, 126.01, 127.3, 128.8, 132.0, 133.8, 136.7, 137.8, 138.1, 168.3.

IR (cm^{-1}) = 2934, 1689, 1467, 1350, 1109, 718.

mp: 145 ºC.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{27}H_{22}N_2NaO_2$ 429.1573, found; 429.1580.

9-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-amine 29b



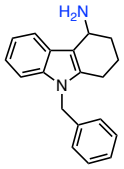
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75-1.83 (m, 1H), 1.90-1.97 (m, 1H), 2.00-2.17 (m, 2H), 2.32-2.58 (m, 2H), 2.63-2.70 (m, 1H), 2.77 (dt, *J* = 16.4, 5.4 Hz, 1H), 3.63 (s, 3H), 4.37 (t, *J* = 4.9 Hz, 1H), 7.11-7.16 (m, 1H), 7.20-7.24 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 22.1, 29.0, 33.7, 44.4, 108.8, 113.3, 118.3, 119.1, 120.8, 126.3, 136.4, 134.0.

IR (cm^{-1}) = 3036, 2839, 1457, 1457, 1307, 1243, 728.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{19}H_{20}N_2Na$ 299.1519, found; 299.1519.

9-benzyl-2,3,4,9-tetrahydro-1H-carbazol-4-amine 29c



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79-1.91 (m, 2H), 1.97-2.13 (m, 2H), 2.52-2.62 (m, 1H), 2.64-2.75 (m, 1H), 2.90 (s, 2H), 4.42 (t, J = 4.5 Hz, 1H), 5.21-5.30 (m, 2H), 7.00-7.06 (m, 2H), 7.09-7.11 (m, 2H), 7.20-7.32 (m, 4H), 7.70-7.76 (m, 1H).

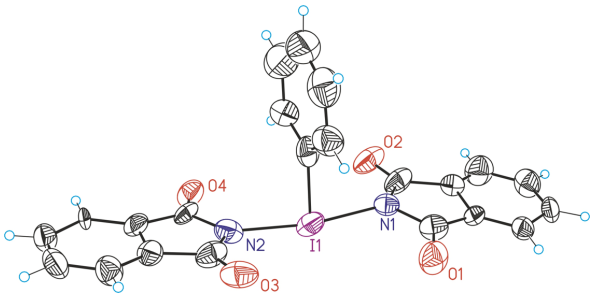
^{13}C NMR (125 MHz, $CDCl_3$): δ =137.8, 136.8, 136.5, 128.8, 127.3, 126.5, 126.2, 121.1,
119.4, 118.4, 113.2, 109.3, 46.3, 44.4, 33.1, 22.1, 19.1.

HRMS (ESI): Cald. for $[M+Na]^+$ $C_{13}H_{16}N_2Na$ 223.1206, found; 223.1203.

IR (cm^{-1}) = 3053, 2927, 2846, 1460, 1450, 1347, 738,

3.4.3. X-Ray analytical data

Bisphthalimide(iodobenzene) 15

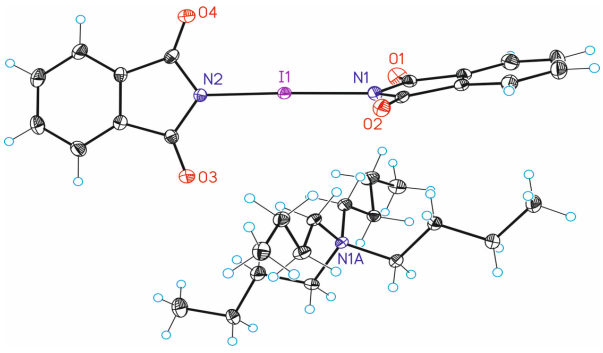


Crystal data and structure refinement for **15**

Empirical formula	C22 H13 I N2 O4	
Formula weight	496.24	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.226(4)≈	α= 90∞.
	b = 7.651(3)≈	β = 100.90(4)∞.
	c = 21.207(10)≈	γ = 90∞.
Volume	1947.9(14) $\approx^3$	
Z	4	
Density (calculated)	1.692 Mg/m^3	
Absorption coefficient	1.676 mm^{-1}	
F(000)	976	
Crystal size	0.02 x 0.02 x 0.01 mm^3	
Theta range for data collection	1.956 to 23.223∞.	

Index ranges	-13<=h<=13,-8<=k<=8,-22<=l<=22
Reflections collected	3804
Independent reflections	3804[R(int) = ?]
Completeness to theta =23.223∞	98.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.951 and 0.732
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3804/ 168/ 263
Goodness-of-fit on F^2	0.802
Final R indices [I>2sigma(I)]	R1 = 0.0654, wR2 = 0.1349
R indices (all data)	R1 = 0.1871, wR2 = 0.1794
Largest diff. peak and hole	0.745 and -0.776 e.≈$^{-3}$

tetrabutyl ammonium [diphthalimideiodine(I)] 16

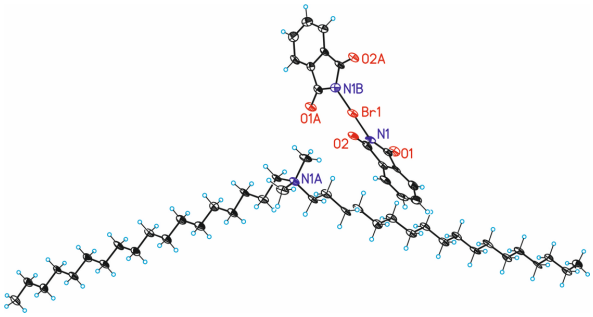


Crystal data and structure refinement for **16**

Empirical formula	C32 H44 I N3 O4	
Formula weight	661.60	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 47.535(2)≈	α= 90∞.
	b = 8.3624(4)≈	β = 91.1684(17)∞.
	c = 15.8508(9)≈	γ = 90∞.
Volume	6299.4(6) ≈^{3}	
Z	8	
Density (calculated)	1.395 Mg/m^3	
Absorption coefficient	1.056 mm^{-1}	
F(000)	2736	
Crystal size	0.30 x 0.15 x 0.04 mm^3	
Theta range for data collection	0.857 to 32.403∞.	
Index ranges	-70<=h<=52,-12<=k<=9,-23<=l<=23	
Reflections collected	34277	
Independent reflections	10275[R(int) = 0.0442]	
Completeness to theta =32.403∞	90.9%	
Absorption correction	Empirical	
Max. and min. transmission	0.959 and 0.816	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	10275/ 0/ 365
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0336, wR2 = 0.0620
R indices (all data)	R1 = 0.0532, wR2 = 0.0682
Largest diff. peak and hole	1.168 and -0.691 e.$\approx^{-3}$

Dimethyldioctadecylammonium [diphthalimideiodine(I)] 28



Crystal data and structure refinement for **28**

Empirical formula	C54 H88 Br N3 O4
Formula weight	923.18
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	a = 11.8696(11)Å, α= 90°
	b = 9.4925(8)Å, β =91.496(9)°
	c = 46.207(5)Å, γ= 90°
Volume	5204.4(8) $Å^3$
Z	4
Density (calculated)	1.178 Mg/m^3
Absorption coefficient	0.835 mm^{-1}
F(000)	2000
Crystal size	0.05 x 0.02 x 0.01 mm^3
Theta range for data collection	1.763 to 28.216°.
Index ranges	-15<=h<=15,-8<=k<=12,-58<=l<=60
Reflections collected	12299
Independent reflections	12299[R(int) = ?]
Completeness to theta =28.216°	82.9%
Absorption correction	Multi-scan
Max. and min. transmission	0.992 and 0.763
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12299/ 0/ 285
Goodness-of-fit on F^2	1.057
Final R indices [I>2sigma(I)]	R1 = 0.1194, wR2 = 0.3217
R indices (all data)	R1 = 0.1666, wR2 = 0.3510

Largest diff. peak and hole	3.429 and -1.821 e.Å^{-3}

2-(2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21a

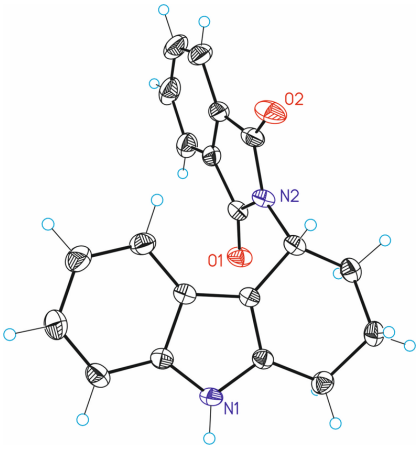


Table 1. Crystal data and structure refinement for **21a**

Empirical formula	C20 H16 N2 O2
Formula weight	316.35
Temperature	100(2) K
Wavelength	0.71073 ≈
Crystal system	Tetragonal
Space group	P4(2)/n
Unit cell dimensión	a = 17.8385(6)≈ α= 90∞.
	b = 17.8385(6)≈β = 90∞.
	c = 9.9114(4)≈γ = 90∞.
Volume	3153.9(2) ≈^{3}
Z	8
Density (calculated)	1.332 Mg/m^3

Absorption coefficient	0.087 mm^{-1}
F(000)	1328
Crystal size	0.15 x 0.10 x 0.10
mm^3	
Theta range for data collection	2.283 to 30.506∞.
Index ranges	-25<=h<=14,-13<=k<=25,-8<=l<=14
Reflections collected	18735
Independent reflection	4809[R(int) = 0.0422]
Completeness to theta =30.506∞	99.9%
Absorption correction	Empirical
Max. and min. transmission	0.991 and 0.915
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4809/ 0/ 217
Goodness-of-fit on F^2	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0493, wR2 = 0.1126
R indices (all data)	R1 = 0.0847, wR2 = 0.1296
Largest diff. peak and hole	0.378 and -0.216 e.≈$^{-3}$

6-fluoro-1,2,3,4-tetrahydro-4aH-carbazol-4a-ol 25b

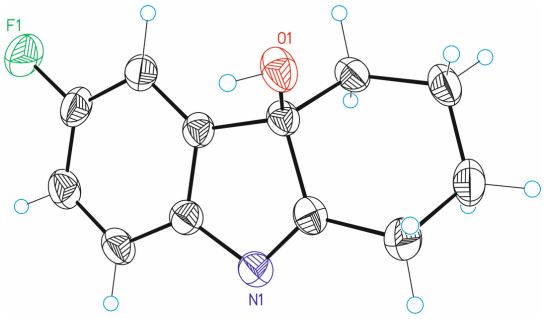


Table 1. Crystal data and structure refinement for **25b**

Empirical formula	C12 H12 F N O
Formula weight	205.23
Temperature	100(2) K
Wavelength	0.71073 ≈
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 9.591(2)≈α= 90∞.
	b = 9.0611(18)≈ β = 100.937(7)∞.
	c = 12.174(3)≈ γ = 90∞.
Volume	1038.8(4) ≈^{3}
Z	4
Density (calculated)	1.312 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	432
Crystal size	0.15 x 0.15 x 0.05
mm^3	
Theta range for data collection	2.163 to 26.612∞.
Index ranges	-11<=h<=10,-11<=k<=10,-14<=l<=15
Reflections collected	6296
Independent reflections	2123[R(int) = 0.0544]
Completeness to theta =26.612∞	97.5%
Absorption correction	Empirical
Max. and min. transmission	0.995 and 0.649
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2123/ 0/ 137
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2

= 0.1203	
R indices (all data)	R1 = 0.0866, wR2 = 0.1378
Largest diff. peak and hole	0.212 and -0.209 e.≈$^{-3}$

22-(3-methyl-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 21m

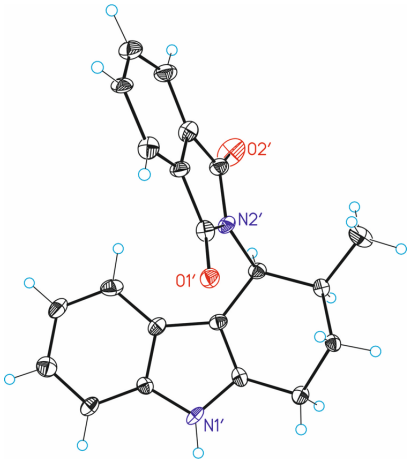


Table 1. Crystal data and structure refinement for **21m**

Empirical formula	C21 H18 N2 O2
Formula weight	330.37
Temperature	100(2) K
Wavelength	0.71073 ≈
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 11.7592(4)≈ α= 90∞.
	b = 9.6394(3)≈ β = 93.250(3)∞.

	c = 14.8441(4)≈ γ = 90∞.
Volume	1679.90(8) ≈^{3}
Z	4
Density (calculated)	1.306 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	696
Crystal size	0.20 x 0.15 x 0.05 mm^3
Theta range for data collection	2.521 to 37.378∞.
Index ranges	-14<=h<=19,-16<=k<=15,-24<=l<=24
Reflections collected	20275
Independent reflections	8093[R(int) = 0.0331]
Completeness to theta =37.378∞	92.2%
Absorption correction	Empirical
Max. and min. transmission	0.995 and 0.765
Refinement method.	Full-matrix least-squares on F^2
Data / restraints / parameters	8093/ 1216/ 454
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1285
R indices (all data)	R1 = 0.0660, wR2 = 0.1366
Largest diff. peak and hole	0.555 and -0.262 e.≈$^{-3}$

CHAPTER IV: APPLICATION OF IODINE(I) REAGENT OR BROMINE CATALYSIS TO THE TOTAL SYNTHESIS OF (±)- ASPIDOPERMIDINE

4.1. INTRODUCTION: ASPIDOPERMA ALKALOIDS

The aspidosperma alkaloids are a family of more than 250 compounds, which share a pentacyclic skeleton and an indoline core.[91] Those alkaloids can be found in the plant *Aspidosperma* genus (Apocynaceae). They have interesting biological activities and pharmacological properties, such as analgesic, antimalarial, anti-inflammatory and psychotropic to anticancer effects. Therefore, they have been widely employed throughout history in traditional medicine.[92] In general, the aspidorperma alkaloids family contains polycyclic frameworks with multiple stereogenic centers and some of them are shown in the Figure 9.

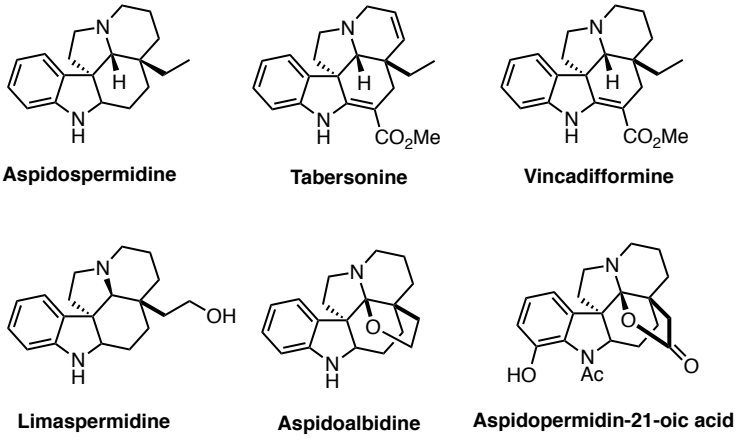
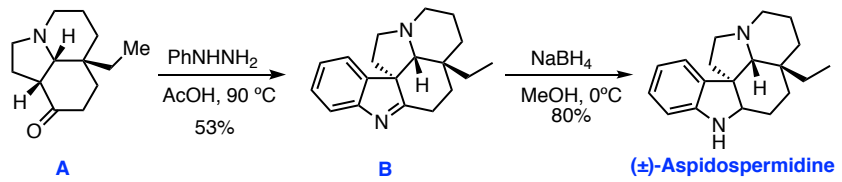


Figure 9: Representative structures of aspidosperma alkaloids.

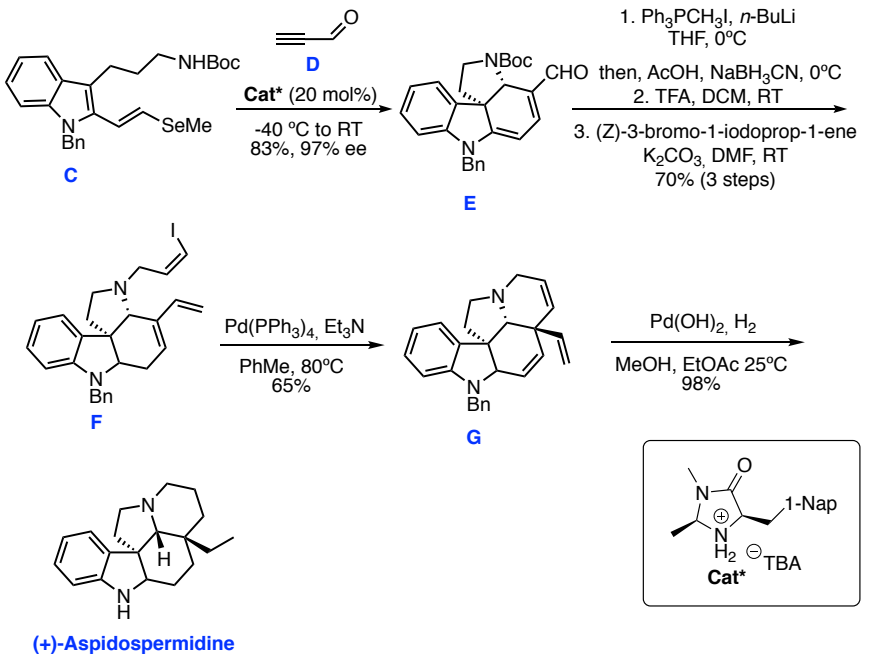
Aspidospermidine was first isolated by Biemann *et al*. in 1961[93] from the bark of *Aspidosperma Quebracho-blanco.* Since then, many researchers have developed elegant synthetic methods and strategies for the preparation of aspidospermidine over the past few decades.[94]

The most common pathway to synthesize aspidospermidine is through the transformation of tricycle **A** and was first described by Stork *et al*. in 1963.[95] Since then, many authors have used this intermediate **A** to access natural compounds that belong to the aspidosperma alkaloid family.[96] Tricycle **A**, was used in a Fischer indolization to obtain **B**, followed by a sodium borohydride reduction to afford (±)-aspidospermidine (Scheme 59).[97]



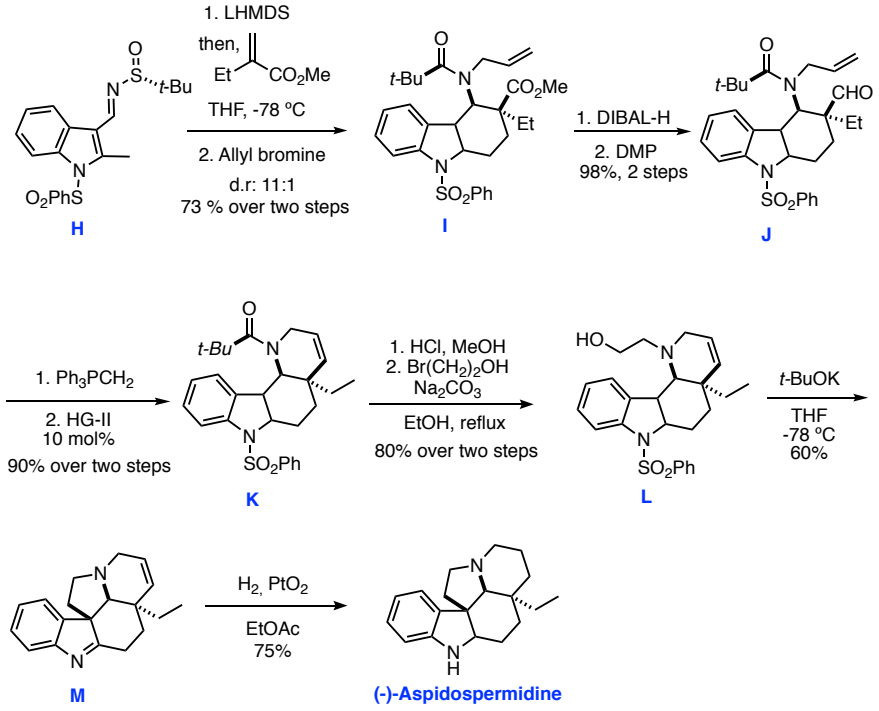
Scheme 59: Synthesis of (±)-aspidospermidine from compound **A**.

MacMillan *et al.* developed a new cascade reaction between a 2-vinyl indole **C** derivative and propynal **D** using an imidazolidinone catalyst. This reaction proceeds through an organocatalytic Diels-Alder reaction with subsequent *β*-elimination of methyl selenide, followed by a 5-*exo-trig* cyclization with the internal secondary amine to give intermediate **E**. A Wittig reaction was then followed by the conversion of the *N*-Boc group into the *N*-allyl derivative **F**. A Heck cyclization closed the last remaining ring to give intermediate **G**. Finally, perhydrogenation with Pearlman´s catalyst $Pd(OH)_2$ afforded (+)-aspidospermidine (Scheme 60). [98]



Scheme 60: MacMillan´s synthesis of (+)-aspidospermidine

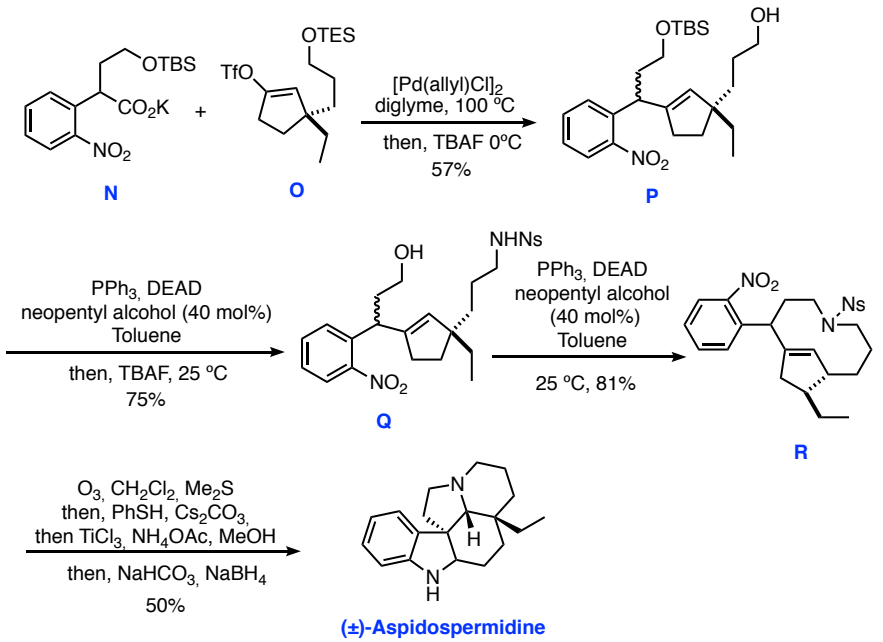
Andrade *et al*. published in 2013 an alternative synthesis of (+)-aspidospermidine.[99] Starting from chiral *N*-sulfinyl indole **H**, a domino Michael/Mannich/*N*-alkylation reaction sequence afforded *N*-sulfinyl derivative **I** with excellent diastereoselectivity and in good yield. The following sequence includes a reduction and oxidation step to form the aldehyde **J**, Wittig methylenation and ring-closing metathesis (using the Hoveyda-Grubbs II catalyst) to give **K**. Then, deprotection and *N*-alkylation with 2-bromoethanol led to **L**. Finally, a Bosch-Rubiralta cyclization closed the last ring (intermediate **M**) and double bond hydrogenation in the presence of PtO_2 provided the natural product (-)-aspidospermidine (Scheme 61).



Scheme 61: Andrade´s synthesis of (-)-aspidospermidine

Another noteworthy total synthesis of (±)-aspidospermidine was presented by Zhu *et al.* in 2014.[100] The synthesis started with Pd(0)-catalyzed decarboxylative coupling between the two fragments **N** and **O**, followed by the addition of TBAF providing compound **P**. Mitsunobu reaction of **P** with nosylamine under Walker´s conditions[101] followed by the addition of TBAF afforded nosylamine derivative **Q**, which was subsequently converted to macrocycle **R** by a second Mitsunobu reaction. Then, an ozonolysis step cleaved the double bond, the *N*-nosyl group was removed under Fukuyama´s conditions,[102] the nitro group was reduced with $TiCl_3$ in an ammonium acetate buffer, and finally the addition of aqueous $NaHCO_3$ solution followed by $NaBH_4$ directly provided the target

compound (±)-aspidospermidine as a single diastereoisomer (Scheme 62).



Scheme 62: Zhu´s synthesis of (±)-aspidospermidine

4.2. General objectives

Despite the large number of reported synthetic approaches to synthesize aspidospermidine that have been carried out within a remarkable number of different strategies, we wanted to demonstrate the versatility and performance of the discussed halogen reagents as a tool towards the realization of a novel synthetic approach within an unprecedented C-H amination. Such an access should significantly streamline the synthesis of aminated complex natural products.

4.2. RESULTS AND DISCUSSION

We started this project synthesizing a model compound, which is shown in Figure 10. Our first strategy was to employ the newly developed iodine(I) reagent **16** to provide the oxidative amination in the 4-position of the tetrahydrocabazole derivative.

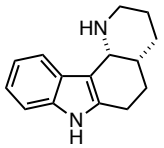
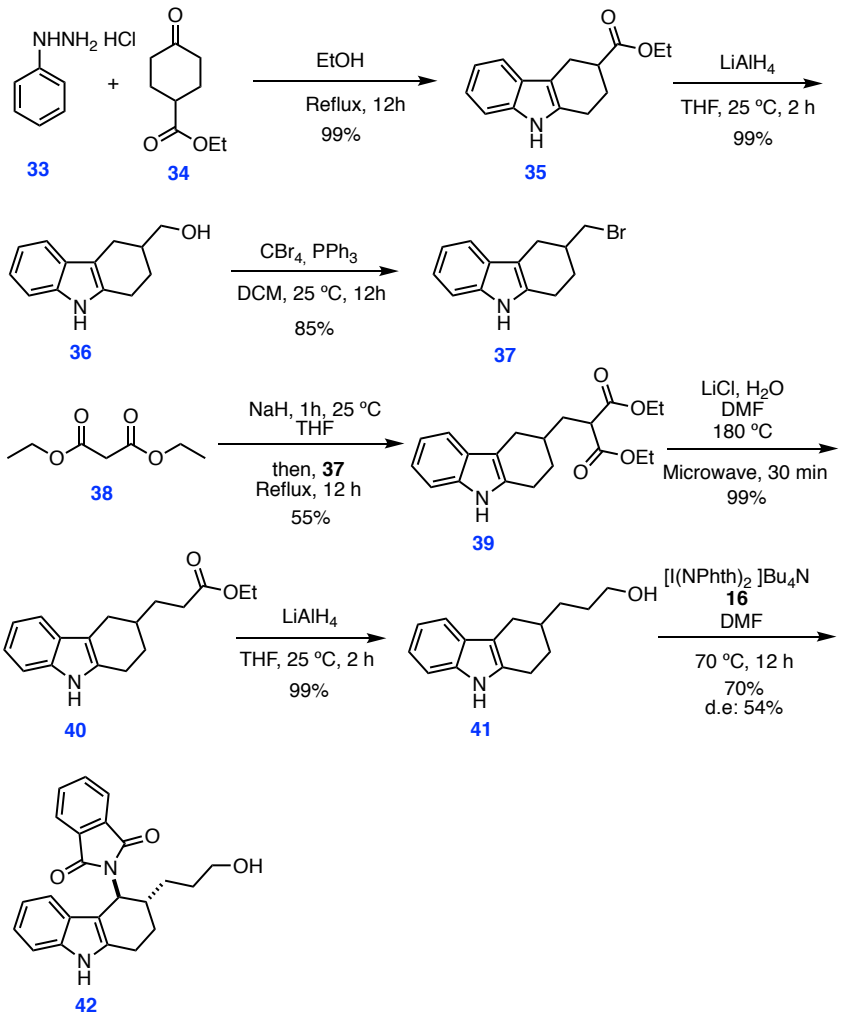


Figure 10: Model compound

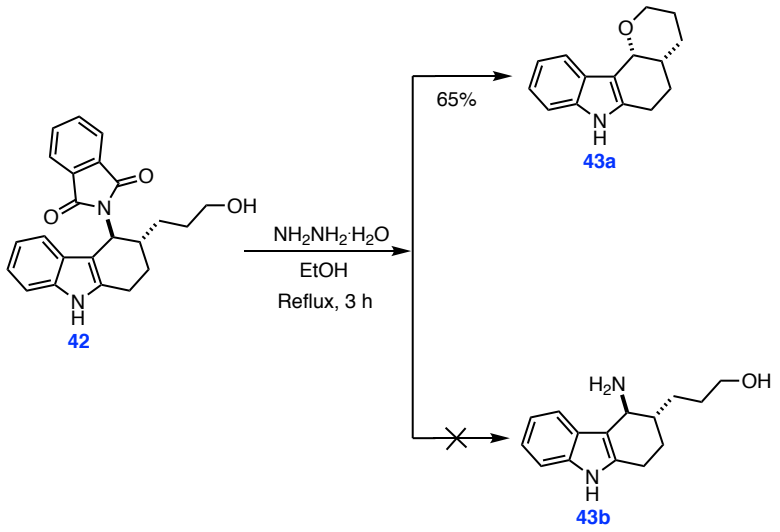
The synthesis started with the preparation of the tetrahydrocarbazole **35** through a Fischer indole reaction with phenylhydrazine hydrochloride **33** and ethyl 4-oxocyclohexanecarboxylate **34** (99%). Compound **35** was reduced to the alcohol **36** (99%) with $LiAlH_4$. Appel reaction provided bromide **37** (85%). Alkylation of **37** with diethyl malonate yielded diester **39** (55%). Upon heating in the microwave at 180 ºC, during 30 min, the di-ester underwent thermal decarboxylation to form **40** (99%), followed by $LiAlH_4$ reduction to provide alcohol **41**. The next step was the oxidative amination at the 4-position of the tetrahydrocarbazole to afford **42** (70%, d. e.: 54%). Our methodology was effective in this step and the *trans*-diastereomer was separated by column chromatography (Scheme 63).



Scheme 63: Initial steps in the synthesis of the model compound.

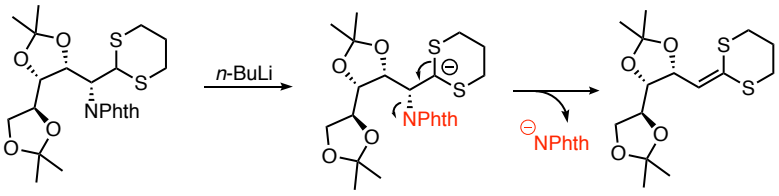
However, when preparing for the next step, which is shown in Scheme 64, the phthalimide deprotection had not yet been accomplished (Chapter 3, section 3.2.3.). As a result, the classical conditions of deprotection using hydrazine were tested and the cyclic

ether **43a** was obtained in 65% instead of the expected amino alcohol **43b**.



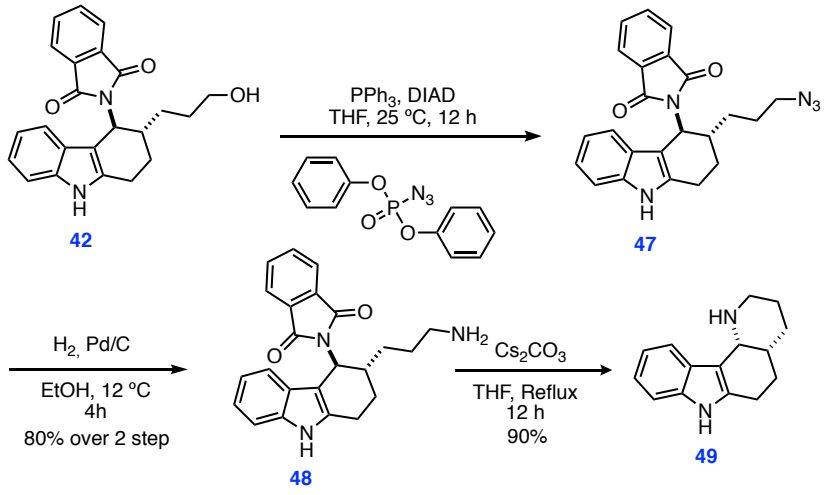
Scheme 63: Formation of the cyclic ether **43a**.

This unexpected result demonstrated that phthalimide can apparently act as a good leaving group. This unexpected result is widely unknown in phthalimide chemistry. As to a noteworthy exception, Fröhlich *et al*. studied the synthesis of carbohydrate derivatives in 2008.[103] They discovered that **44** in the presence of butyllithium at –78 °C forms the 1,2-elimination product **46**. They assumed that the anion **45** was generated and it immediately eliminated the adjacent amide, which formed a well-stabilized amide anion as a very good leaving group, to give the unsaturated product **46** (Scheme 64).



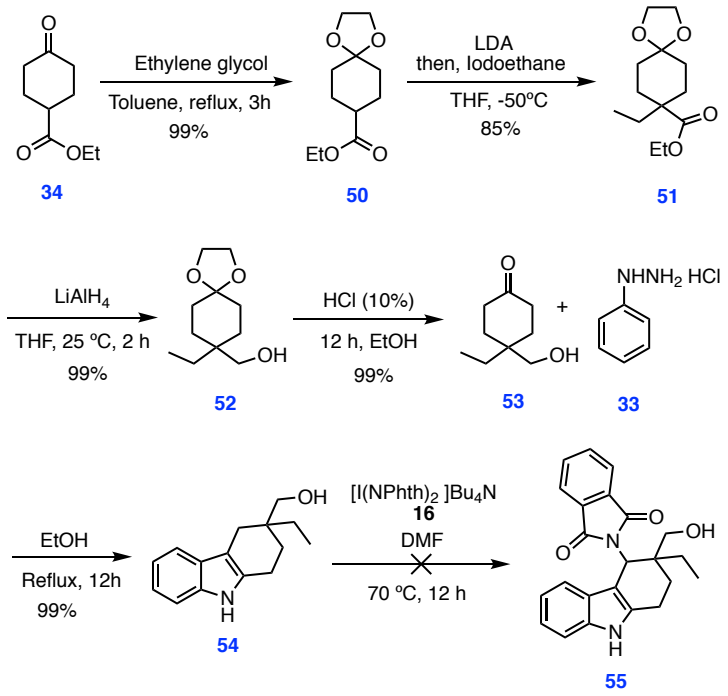
Scheme 64: Fröhlich´s discovery of the ability of phthalimide to act as a good leaving group.

When the property of phthalimide as good leaving group was discovered, we thought to use this observation and implement an intramolecular amination step into our synthesis of aspidospermidine. Mitsunobu reaction of **42** with diphenyl phosphoryl azide using DIAD and triphenylphosphine provided the azide **47**, which was reduced to the corresponding amine **48** (80%, over two steps) with H_2 and Pd/C. Finally, when **48** was treated with Cs_2CO_3 the cyclized compound **49** was formed in 90% (Scheme 65).



Scheme 65: Synthesis towards the model compound **49**.

Once we had the certainty that with our methodology the piperidine core of **49** could be formed, this pathway was intended to be used towards the synthesis of the natural product (±)-aspidospermidine. This work was carried out by Dr. Julien Bergès. The approach started with the protection of **34** with ethylene glycol to form **50** with 99% of yield. When LDA was added, the enolate was formed, which gave rise to an S_N2 reaction with iodoethane to afford **51** (85%). $LiAlH_4$ reduced **51** to **52** (99%) and then, the deprotection of ethylene glycol to form **53** (99%). A Fischer indole reaction was carried out to give the target tetrahydrocarbazole compound **54** with 99 % of yield. At this point, we decided to try if the oxidative amination with the iodine(I) reagent **16** could provide the aminated product **55**. Unexpectedly, it was not formed, and this outcome is believed to arise from the steric hindrance at the neopentylic 4-position (Scheme 66).

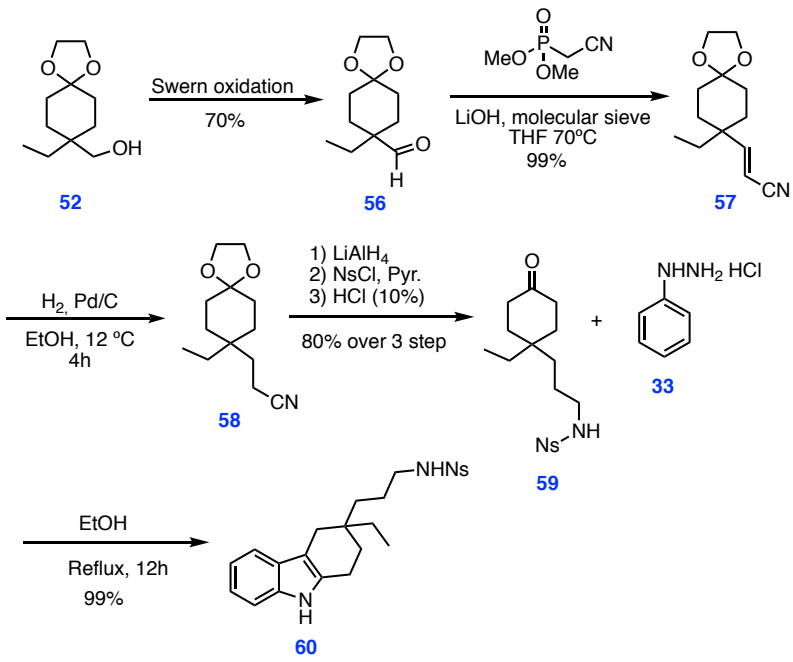


34 50 51 52 53 33 54 55

Scheme 66: Amination with iodine(I) reagent did not form the product **55**.

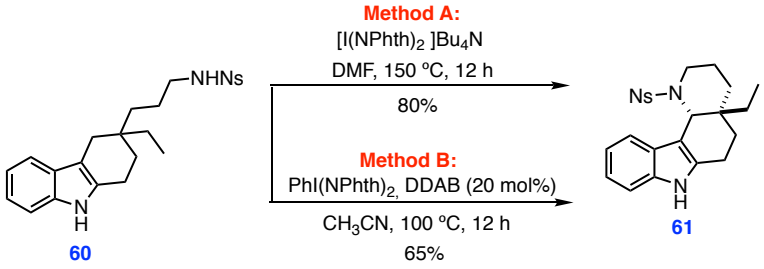
In view of the previous results, we changed the synthetic route to the compound **60** bearing the required nitrogen within a sulfonamide moiety, to see if the halogen(I) reagent could activate the benzylic position to make use of an intramolecular reaction and provide the desired cyclization at the neopentylic position.

To arrive at the target compound, the alcohol **52** was oxidized under Swern conditions to give the aldehyde **56** in 70%. Wittig reaction led to homologated nitrile **57** (99%) and then, the hydrogenation of the double bond was carried out with H_2 and Pd/C to furnish **58** (99%). After that, the reduction of the nitrile, protection of the free amine with nosyl and deprotection of the ketone afforded the cyclohexanone **59** with 80% of yield over 3 steps. The final Fischer indole synthesis gave rise to the formation of the tetrahydrocarbazole core **60** (99%, Scheme 67).



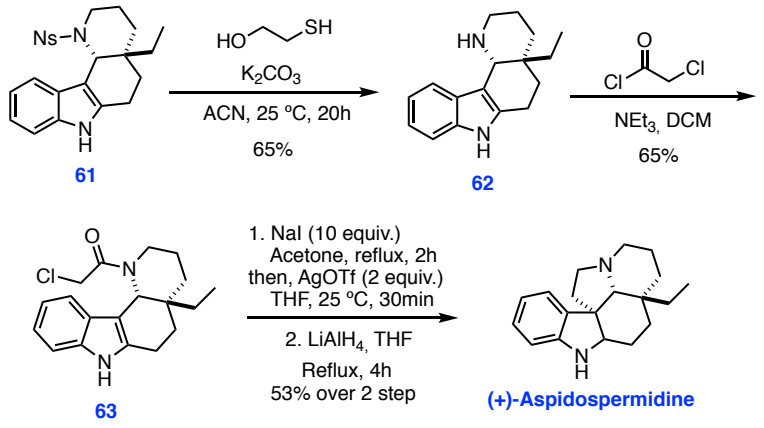
Scheme 67: New strategies towards (±)-aspidospermidine.

At this point, the stochiometric reaction with iodine(I) reagent **16** was carried out and the compound **61** was formed with 80% of yield (Method A, Scheme 68). Once we had realized that the reagent **16** could successfully activate the benzylic position, we decided to check if the product could be formed exploiting the corresponding bromine catalysis as well. Indeed, **61** was isolated with 65% (Method B, Scheme 68).



Scheme 68: Stoichiometric and catalytic version using halogen reagent.

When we observed that halogen reagents allowed the formation of tetracyclic compound **61**, the next goal was to synthesize the last cycle. In order to do that, the nosyl group was removed using thioethylene glycol and K_2CO_3 to give **62** (65%). The next step was carried out following the protocol developed by Cho.[92] The resulting amine product reacted with chloroacetyl chloride to afford **63** in 65% yield. Subsequent application of the protocol developed previously by Heathcock[104] completed the asymmetric total synthesis of (±)-aspidospermidine with 53% of yield over two steps (Scheme 69).



Scheme 69: Last steps toward the synthesis of (±)-aspidospermidine.

This successful approach to aspidospermidine demonstrates that halide-based oxidation methodology can provide innovative solutions to the selective C-H amination of elaborated hydrocarbon frameworks. It demonstrates that metal-free oxidation catalysis is now becoming a more and more useful tool in organic synthesis.

4.3. CONCLUSION

In this section we have demonstrated the ability of phthalimide as a good leaving group in the benzylic position of the tetrahydrocarbazole derivative and we have developed a concise total synthesis of (±)-aspidospermidine that relies on an intramolecular C-H amination as the key step. This reaction can be carried out using an iodine(I) reagent as stochiometric oxidant or within the novel bromine(-I/I) catalytic mainfold.

4.4. EPERIMENTAL SECTION

4.4.1. General procedure

Ethyl 2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate 35
Phenylhydrazine hydrochloride (0,85 g, 5.8 mmol, 1.0 equiv.) and cyclohexanone derivative (1g, 5.8 mmol,1 equiv.) were dissolved in EtOH (10 mL) and the mixture was stirred under refluxed overnight. After solvent removal in vacuo, the pure compound **35** was used without further purification for the next step.

(2,3,4,9-tetrahydro-1H-carbazol-3-yl)methanol 36
$LiAlH_4$ (0.214 g, 6.13 mmol, 2.0 equiv) was added slowly to a solution of the ester (1 g, 3.6 mmol, 1 equiv.) in THF (25 mL) at 0 ºC and then the solution was stirred for two hours at room temperature. After that, a solution of NaOH (2M) was added carefully until a white solid precipitated. After filtration over $MgSO_4$ and evaporation of the solvent, the crude alcohol **36** was obtained in quantitative yield.

3-(bromomethyl)-2,3,4,9-tetrahydro-1H-carbazole 37
A solution of the alcohol derivative **36** (1g, 4.9 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 ºC was treated with CBr_4 (2.14 g, 6.5 mmol, 1.3 equiv) followed by the portionwise addition of triphenylphosphine (1.7 g, 6.5 mmol, 1.3 equiv). The reaction was allowed to warm to 25ºC and the mixture was stirred overnight. After that, the solvent was evaporated under reduced pressure. The crude product was purified by chromatography (eluent: *n*-hexane/EtOAc, 95/5 v/v) to give the pure bromide product **37**.

Diethyl l2-((2,3,4,9-tetrahydro-1H-carbazol-3-yl)methyl)malonate 39
Diethyl malonate (2.1 mL, 13.1 equiv, 2. equiv) was added drop-wise to a suspension of NaH (55%, 0.330 g, 13.75 mmol, 1.1 equiv) in

THF (20 mL) at 0 ºC and was stirred for 60 min. The bromide compound was added in one portion and the resulting milky mixture was stirred at reflux for 12 h. The reaction was then cooled and quenched by the addition of H_2O. THF was removed under reduced pressure and the resulting crude was dissolved in Et_2O and washed with water. The aqueous layer was extracted with Et_2O (4x), and the combined organics layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by chromatography (eluent: *n*-hexane/EtOAc, 90/10 v/v) to give the pure product **39**.

Ethyl 3-(2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanoate 40
The diethyl malonate derivative **39** (0.4 g, 1.16 mmol, 1 equiv.) was dissolved in DMF (19 mL) in a microwave vial (20 mL). LiCl (0.149 g, 3.5 mmol, 3 equiv.) and water (20 drops) were added and the sealed vial was irradiated in a microwave oven at 180 °C for 30 minutes. The cooled mixture was diluted with diethyl ether, washed with water, and dried (MgSO4). The solvent was removed under vacuum to give the pure compound **40**.

3-(2,3,4,9-tetrahydro-1H-carbazol-3-yl)propan-1-ol 41
$LiAlH_4$ (0.172 g, 5.0 mmol, 2.0 equiv) was added slowly to a solution of the ester **40** (0.67 g, 2.5 mmol, 1.0 equiv) in THF (20 mL) at 0 ºC and then the solution was stirred for two hours at room temperature. After that, a solution of NaOH (2M) was added carefully until a white solid precipitated. After filtration over $MgSO_4$ and evaporation of the solvent the crude alcohol **41** was obtained in quantitative yield.

2-((3S,4S)-3-(3-hydroxypropyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 42
In a schlenk flask was added iodine(I) reagent (1.44 g, 2.2 mmol, 1.0 equiv.), and tetrahydrocarbazole derivative **41** (0.5 g, 2.2 mmol, 1.0

equiv.) in 40 mL of dry DMF and the mixture was stirred overnight at 70 ºC. The crude was diluted with EtOAc, washed with water (4x). Then the mixture was concentrated in vacuo and the residue was purified by column chromatography (eluent: *n*-hexane/EtOAc, 4/6 v/v).

(4aS,11cR)-2,3,4,4a,5,6,7,11c-octahydropyrano[3,2-c]carbazole 43

The tetrahydrocarbazole derivative **42** (0.06 g, 0.16 mmol, 1 equiv.) was treated with hydrazine hydrate (0.150mL, 1.92 mmol, 12 equiv.) in the presence of 6 mL of EtOH and 1 mL of H_2O at reflux during 3 h. The solvent was removed by reduced pressure, and the residue was extracted with EtOAc (×2). The combined organic layers were washed with H_2O, dried, filtered, and then concentrated to a residue that was purified by column chromatography (eluent: *n*-hexane/EtOAc, 8/2, v/v).

2-((3R,4S)-3-(3-azidopropyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 47

Indole derivative (0.15 g, 0,4 mmol, 1 equiv.) was dissolved in 3 mL of THF. Then, triphenylphosphine (0.21 g, 0.8mmol, 2 equiv.), DIAD (0.16 g, 0.8 mmol, 2 equiv.) and diphenyl phosphoryl azide (0.22 g, 0.8 mmol, 2 equiv.) were added at 0 ºC. The reaction mixture was stirred 12 h at 25 ºC. The cooled mixture was diluted with ethyl acetate, washed with water, brine and dried with Na_2SO4. The solvent was removed under reduced pressure. The crude mixture was filtered through a short pad of silica. The solvent was removed under reduced pressure and product was subjected to the next reaction without further purification.

2-((3R,4S)-3-(3-aminopropyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 48

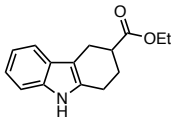
Indole derivative **47** (0.2 g, 0,5 mmol, 1 equiv.) was dissolved in 3 mL of THF then, Pd/C (60 mg, 30%) was added and the mixture was stirred during 4 hours under a hydrogen balloon. After filtration over celite and concentration in vacuo, the crude was dissolved in DCM and a yellow solid precipitated when hexane was added. The product was filtered to give the pure compound **48**.

(4aR,11cR)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole 49

Indole derivative **48** (0.2 g, 0,53 mmol, 1 equiv.) was dissolved in 30 mL of THF. Then, Cs_2CO_3 (60 mg, 30%) was added and the mixture was stirred during 12 hours at 75 ºC. After filtration over celite, the liquid was concentrated under vacuo to give the pure compound **49**.

4.4.2. Compound characterizations

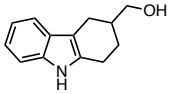
Ethyl 2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate 35



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.2 Hz, 3H), 2.13-2.02 (m, 1H), 2.41-2.31 (m, 1H), 2.90-2.80 (m, 3H), 3.00-2.91(m, 1H), 3.18-3.08 (m, 1H), 4.27 (qd, *J* = 7.1, 1.4 Hz, 2H), 7.21-7.12 (m, 2H), 7.31-7.29 (m, 1H), 7.52 (d, *J* = 7.4, 1.6, 0.8 Hz, 1H), 7.84 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 22.4, 24.0, 25.8, 40.4, 60.9, 108.5, 110.5, 117.8, 119.3, 121.3, 127.5, 133.1, 136.0.

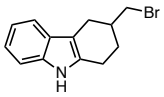
(2,3,4,9-tetrahydro-1H-carbazol-3-yl)methanol 36



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94-1.86 (m, 1H), 2.22-2.02 (m, 2H), 2.47-2.38 (m, 1H), 2.84-2.75 (m, 2H), 2.98-2.90 (m, 1H), 3.84-3.68 (m, 2H), 7.20-7.06 (m, 2H), 7.33-7.28 (m, 1H), 7.49 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.78 (s, 1H),

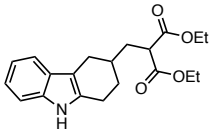
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.43 23.9, 26.0, 37.5, 67.6, 109.1, 110.4, 117.7, 119.2, 121.1, 127.7, 133.9, 140.0.
IR ν(cm^{-1}): 3399, 2916, 1466, 1237, 1040, 738.
HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{13}H_{16}NO$ 202.1226, found; 202.1225.

3-(bromomethyl)-2,3,4,9-tetrahydro-1H-carbazole 37



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-1.64 (m, 1H), 2.34-2.16 (m, 2H), 2.59-2.45 (m, 1H), 2.88-2.67 (m, 2H), 3.12-2.97 (m, 1H), 3.67-3.50 (m, 2H), 7.20-7.08 (m, 2H), 7.35-7.22 (m, 1H), 7.54-7.45 (m, 1H), 7.72 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 26.3, 28.1, 37.2, 39.2, 108.8, 110.5, 117.7, 119.3, 121.3, 127.5, 133.3, 136.0.
IR ν(cm^{-1}): 3379, 2916, 2837, 1452, 1325, 743.
mp: 100 ºC.
HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{13}H_{15}BrN$ 264.0382, found; 264.0371.

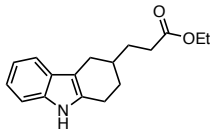
Diethyl l2-((2,3,4,9-tetrahydro-1H-carbazol-3-yl)methyl)malonate 39



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (td, *J* = 7.1, 4.3 Hz, 7H), 1.70-1.58 (m, 2H), 3.62 (dd, *J* = 8.3, 7.2 Hz, 1H), 1.93-1.77 (m, 1H), 2.18-2.00 (m, 2H), 2.40-2.27 (m, 1H), 2.82- 2.72 (m, 1H), 2.97- 2.87 (m, 1H), 4.30- 4.15 (m, 4H), 7.17- 7.01 (m, 2H), 7.33- 7.23 (m, 1H), 7.52- 7.41 (m, 1H), 7.76 (s, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 27.0, 29.3, 32.6, 35.0, 50.0, 61.5, 109.2, 110.4, 117.7, 119.2, 121.2, 127.6, 133.7, 136.0, 169.7, 169.7.
IR ν(cm^{-1}): 3379, 2936, 1727, 1148, 752.
mp: 93 ºC.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{23}H_{23}N_2NaO$ 366.1703, found; 366.1690.

Ethyl 3-(2,3,4,9-tetrahydro-1H-carbazol-3-yl)propanoate 40



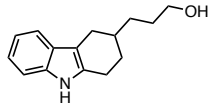
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, 3H), 1.69-1.58 (m, 2H), 1.93-1.79 (m, 2H), 2.10-2.01 (m, 1H), 2.38-2.28 (m, 1H), 2.55-2.43 (m, 2H), 2.82-2.77 (m, 2H), 2.95-2.87 (m, 1H), 4.18 (qd, *J* = 7.2, 0.9 Hz, 2H), 7.19-7.09 (m, 2H), 7.31-7.29 (m, 1H), 7.50-7.45 (m, 1H), 7.72 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 22.8, 27.1, 29.3, 31.2, 32.3, 34.3, 60.3, 109.6, 110.4, 117.7, 119.2, 121.1, 127.7, 133.9, 140.0, 173.9.

IR ν(cm^{-1}): 3401, 2920, 1701, 1455, 1141, 748.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{17}H_{21}NNaO_2$ 294.1464, found; 294.1465.

3-(2,3,4,9-tetrahydro-1H-carbazol-3-yl)propan-1-ol 41



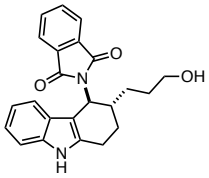
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.50 (m, 2H), 1.68-1.60 (m, 1H), 1.81-1.72 (m, 2H), 1.91-1.84 (m, 1H), 2.10-2.03 (m, 1H), 2.38-2.29 (m, 1H), 2.82-2.75 (m, 2H), 2.96-2.90 (m, 1H), 3.73 (t, *J* = 6.6 Hz, 2H), 7.18-7.06 (m, 2H), 7.32-7.30 (m, 1H), 7.51-7.45 (m, 1H), 7.73 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.9, 27.4, 29.6, 30.5, 32.2, 34.5, 63.3, 109.8, 110.4, 117.7, 119.1, 121.0, 127.7, 133.9, 136.0.

IR ν(cm^{-1}): 3319, 2921, 1454, 1051, 736.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{15}H_{19}NNaO$ 2521359, found; 252.1358.

2-((3S,4S)-3-(3-hydroxypropyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 42



d.e: 54%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86-1.54 (m, 5H), 2.35-2.14 (m, 1H), 2.71-2.59 (m, 1H), 2.85-2.76 (m, 1H), 3.06-2.97 (m, 1H), 3.70-3.58 (m, 2H), 5.49 (d, *J* = 9.1 Hz, 1H), 6.90-6.84 (m, 1H), 7.10-6.99 (m, 2H), 7.28-7.26 (m, 1H), 7.76-7.71 (m, 2H), 7.86-7.80 (m, 2H), 7.98-7.90 (m, 1H).

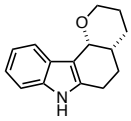
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8, 28.0, 28.6, 29.8, 37.9, 50.6, 63.0, 107.9, 110.8, 117.2, 119.7, 121.2, 123.3, 126.1, 131.8, 134.0, 136.0, 136.4, 168.5.

IR ν(cm^{-1}): 3382, 2927, 1697, 1321, 717.

mp: 103 ºC.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{23}H_{22}N_2NaO_3$ 397.1523, found; 397.1543.

(4aS,11cR)-2,3,4,4a,5,6,7,11c-octahydropyrano[3,2-c]carbazole 43



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43-1.52 (m, 1H), 1.59-1.71 (m, 2H), 1.76-1.90 (m, 2H), 1.94-2.01 (m, 2H), 2.30-2.44 (m, 1H), 2.65-2.84 (m, 2H), 3.72 (td, *J* = 11.0, 2.5 Hz, 1H), 3.93-4.01 (m, 1H), 4.80 (d, *J* = 2.7 Hz, 1H), 7.09-7.16 (m, 2H), 7.23-7.28 (m, 1H), 7.62-7.67 (m, 1H), 7.86 (s, 1H).

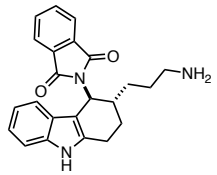
^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 23.0, 23.7, 28.7, 34.2, 67.4, 70.6, 110.4, 111.3, 118.2, 119.7, 121.3, 127.1, 136.1, 136.5.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{15}H_{28}NNaO_3$ 250.1210, found; 250.1208.

IR ν(cm^{-1}): 2925, 1720, 1350, 1300, 1160.

mp: 97 ºC.

2-((3R,4S)-3-(3-aminopropyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)isoindoline-1,3-dione 48



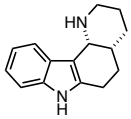
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40-1.53 (m, 1H), 1.60-1.98 (m, 4H), 2.29-2.37 (m, 1H), 2.61-2.70 (m, 1H), 2.82-3.08 (m, 4H), 5.44 (d, *J* = 9.5 Hz, 1H), 6.73 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.78-6.83 (m, 1H), 6.93-6.99 (m, 1H), 7.24-7.29 (m, 1H), 7.82-7.90 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.3, 24.5, 27.8, 28.9, 37.9, 39.7, 50.8, 106.3, 110.7, 116.1, 118.6, 120.3, 122.9, 125.9, 131.6, 134.3, 136.5, 136.6, 168.2.

IR ν(cm^{-1}): 2919, 2850, 1707, 1462, 1380, 800.

HRMS (ESI): Calcd. for $[M+Na]^+$ $C_{23}H_{23}N_3NaO_2$ 396.1682, found; 396.1689.

(4aR,11cR)-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole 49



^{1}H NMR (400 MHz, $CDCl_3$): δ =1.47-1.53 (m, 1H), 1.61-1.71 (m, 2H), 1.80-1.98 (m, 3H), 2.11 (s, 1H), 2.30-2.38 (m, 2H), 2.73-2.78 (m, 1H), 2.88 (td, *J* = 11.8, 2.9 Hz, 1H), 3.03-3.10 (m, 1H), 4.14 (d, *J* = 3.5 Hz, 1H), 7.07-7.14 (m, 2H), 7.23-7.27 (m, 1H), 7.59-7.64 (m, 1H), 7.97 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 23.2, 23.5, 30.1, 34.4, 46.4, 51.3, 110.5, 113.2, 117.8, 119.4, 121.1, 127.0, 135.3, 136.1.

IR ν(cm^{-1}): 3200, 2923, 1118, 1459, 1259, 1014.

mp: 170 ºC.

HRMS (ESI): Calcd. for $[M+H]^+$ $C_{15}H_{19}N_2$ 227.1543, found; 227.1543.

OVERALL CONCLUSIONS

Iodine reagents have been recognized as powerful tools for the oxidative transformation of hydrocarbon molecules. The benefits of this modern functionalization by employing iodine are that they allow avoiding the use of transition metals. We have presented the general syntheses, isolations and characterizations of several important iodine(I) reagents, which contain two carboxylic acid derivatives as ligands and follow the general formula $R_4N[I(O_2CAr)_2]$. These compounds are air- and moisture-stable in the solid state and upon exposure in solution. They represent conceptually new iodine(I) compounds with anions as stabilizers. The stereoselective difunctionalization of alkenes is a highly important transformation to access bioactive molecules and natural products in organic chemistry, which provides the selective and easy addition of two new chemical entities in a single step. Regarding the more concrete case of the halofunctionalization, vicinal halogen atoms with their ease for subsequent transformation may enable an even greater diversification. The previded iodine(I) compounds could indeed be used as powerful reagents for the vicinal iodooxygenation of alkenes within a total of 47 different examples accomplished with good yields. In this versatile application, the reaction mechanism was studied in detail. Furthermore, the initial rates of the individual reactions and the chemo- and regioselectivity of the transformation were investigated. Finally, we discovered the importance of acetamide as a general additive, which once added, activates the intermediate $I\text{-}O_2CAr$ to promote the reaction.

As the indole core is a common structural motif in natural products, and in bioactive and pharmaceutical compounds, considerable efforts have been carried out towards the development of efficient methods for its functionalization and diversificative syntheses. Despite significant progresses in the synthesis of tetrahydrocar-bazoles,

strategies involving the direct α-functionalization of the aliphatic side chain of 2,3-disubstituted indoles are quite limited. Due to this fact, we have presented syntheses, isolations and characterizations including X-ray analyses of stable complex iodine(I) derivatives $R_4N[I(NPhth)_2]$ and bromine(I) derivative $DDA[Br(NPhth)_2]$, using Varvoglis' reagent $PhI(NPhth)_2$, which was also characterized by X-ray analysis for the first time. These reagents were used towards the development of an unprecedented oxidative amination of the 4-position of tetrahydrocarbazole derivatives. The reaction can be carried out under stoichiometric as well as catalytic conditions. In the stoichiometric version, the iodine(I) reagent was used to obtain a large number of aminated tetrahydrocarbazoles with different substitutions at the arene core and at the aliphatic ring, all of which were isolated in good to excellent yields. When the aliphatic ring contained presubstitution, with this methodology, the ratio of *cis*-*trans* diastereoisomers could be controlled by the temperature: low temperature led to the *cis*-compound, however with high temperature, the *trans*-compound was formed preferably. The catalytic version, in which the bromine(I) reagent is formed in situ, allows for the oxidative amination of several tetrahydrocarbazoles with different substitu-tions in the aromatic and aliphatic rings. The reaction is diastereose-lective in favor of the *trans*-product when a bulky group such as phenyl or *tert*-butyl are present at the neighboring carbon. Finally, it was demonstrated that the deprotection of the phthalimide can be achieved under mild conditions with a methyl or benzyl protecting group at the nitrogen of the tetrahydrocarbazole.

Once the anticipated methodology had been fully developed and the new iodine(I) and bromine(I) reagents were tested as useful tools in organic chemistry, we conceived a concise total synthesis of (±)-aspidospermidine that relies on an unprecedented intramolecular C-H amination as the key step. This reaction can be carried out using an iodine(I) reagent as stochiometric oxidant or within the bromine(-I/I)

catalytic mainfold. In this section, we also discovered the ability of phthalimide to act as a competent general leaving group in the benzylic position of the tetrahydrocarbazole derivatives.

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