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Transformations promoted by the hypervalent iodine reagents

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Transformations promoted by the hypervalent iodine reagents

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Revisedby: / Vist i plau

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ABSTRACT

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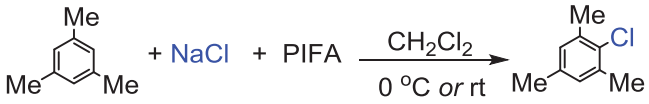
ABBREVIATIONS

ACN:	acetonitrile
AcOEt:	Ethyl acetate
AcOH:	Acetic acid
anh:	anhydrous
aq:	aqueous
atm:	atmosphere
ATR (for IR):	Attenuated Total Reflectance
b.p.:	boiling point
cat:	catalytic
^{13}C-NMR	13Carbon Nuclear Magnetic Resonance
Conc.:	concentrated
Δ:	heating
d (NMR):	doublet
dd (NMR):	doublet of doublets
δ (NMR):	chemical shift
DMF:	*N,N*-dimethylformamide
DMSO:	dimethylsulfoxide
dq (NMR):	doublet of quartets
dt (NMR):	double triplet
DMSO:	dimethylsulfoxide
EtO:	ethoxy
EA:	elemental analysis
equiv:	equivalent
Et_2O:	Diethyl ether
EtOH:	ethanol
Exp:	experiment
ESI:	Electrospray Ionization
GC:	Gas Chromatography
GC-MS:	Gas Chromatography with a Mass Spectrometry detector
^{1}H-NMR:	Proton Nuclear Magnetic Ressonance

h:	hour
J (NMR):	Coupling constant
Lit.:	literature
M:	molar
m (NMR):	multiplet
m	meta
Me:	methyl
MeOH:	methanol
Mes:	Mesityl
min:	minutes
mol%:	Molar percentage
MS:	Mass Spectrometry
MW:	molecular weight
Nap	naphthyl
o:	*ortho*
p-TsOH:	p-toluenesulfonic acid
p:	*para*
Prot:	protective group
p-XRD:	Powder X-Ray Diffraction
q (NMR):	quartet
Rf:	retention factor
r.t.:	room temperature
s (NMR):	singlet
TLC:	Thin Layer Chromatography
m.p.:	melting point
THF:	tetrahydrofuran
TMS:	trimethysilyl
t (NMR):	triplet
v (IR):	frequency

ABSTRACT

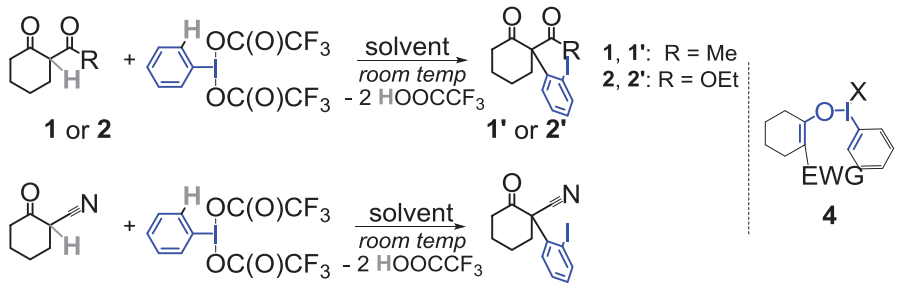
The group's interest in the use of hypervalent iodine reagents for direct arene functionalization has led us to discover that a combination phenyliodine(bis-trifluoroacetate), **PIFA**, with simple alkali metal chlorides can be used to carry out chlorination of aromatic hydrocarbons in really mild conditions. Initially, a model reaction of the mono-chlorination of mesitylene (Scheme 1) was optimized. We then went on to explore the halogenation of other arenes. This work constitutes the first objective of the present doctoral thesis.



optimization parameters:
- sources of Cl^-
- solvent
- reaction time/temperature

Scheme 1 Optimized conditions: > 85% yield in 12 h

More recently, as second main objective of this work, we studied and found that **PIFA** reacts directly with β-diketones, β-ketoesters and 2-oxocyclohexanecarbonitrile to give an α-arylation product, with a unique feature that the newly incorporated arene retains the iodine atoms *ortho* to the new C-C bond (Scheme 2). Given the synthetic potential of this reaction, we focused on improving the yields and the scope of this methodology and on preliminary mechanistic assays. The method is complementary to the metal-catalyzed α-arylation where C-I bond is converted into C-C.



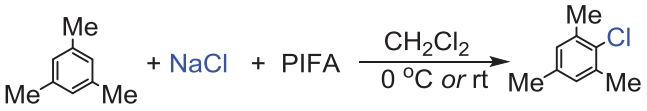
Scheme 2

Our mechanistic hypothesis (unconfirmed) is a [3,3] sigmatropic rearrangement ("iodonium Claisen") of the species **4**(Scheme 2) formed through the condensation of PIFA and **1-3**-enol.

The presence of the *o*-iodine on the aromatic ring of **1'**, **2'** and **3'** allows for easy access to derivatives

RESUM

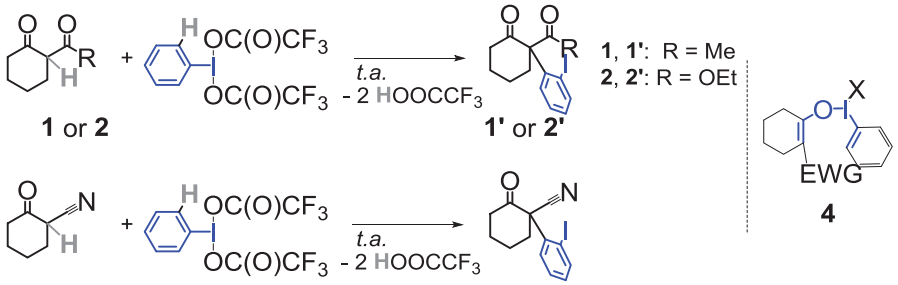
El interès del grup en els reactius de iode hipervalents per la funcionalització directa d'arens ens a portat a descobrir que amb una combinació de [bis(trifluoroacetoxi)iode]benzè, **PIFA,** i clorurs metàl·lics senzills s'obté la cloració de compostos aromàtics en condicions molt suaus. Inicialment s'ha optimitzat com a reacció model la mono-cloració del mesitilè (Esquema 1) i després s'ha estes la metodologia altres arens. Aquest treball constitueix el primer objectiu de la tesis.



paràmetres optimitzats:
- fonts de Cl^-
- dissolvent
- temps de reacció/temperatura

Esquema 1 Condicions Optimitzades: > 85% rdto (12 h.)

Mes recentment i com a segon objectiu de la present tesis doctoral s'ha estudiat i descobert que el reactiu **PIFA** pot reaccionar directament amb β-dicetones, β-cetoesters i amb 2-oxociclohexancarbonitril obtenint-ne el producte de α-arilació. A mes a mes, l'arè incorporat mante l'àtom de iode en *ortho* al nou enllaç C-C (Esquema 2). Donat el potencial d'aquesta reacció en la present tesis doctoral ens hem centrat en optimitzar les condicions de reacció per millorar els rendiments, en estudiar l'abast de la nova metodologia, així com en establir un estudis mecanistics preliminars. La metodologia es complementaria a la α-arilació sota catàlisis metàl·lica on un enllaç C-I es converteix en un enllaç C-C.



Esquema 2

La nostra hipòtesis mecanistica (no confirmada) es basa en una reacció [3,3] sigmatròpica ("*iodonium Claisen*") de les especiestipus **4** (Esquema 2)formades a traves de la condensació del reactiu **PIFA** i el corresponent enol de **1-3**.

La presencia del iode en la posició *ortho* dels compostos aromàtics (**1'-3'**) ha permès la seva derivatització senzilla cap a productes de interès.

1. INTRODUCTION: HYPERVALENT IODINES REAGENTS IN ORGANIC SYNTHESIS

1.1. General consideration.

In the past several years, the organic chemistry of iodine has experienced a rapid development. Among iodine compounds we want to focus on hypervalent iodine reagents, since their special reactivity and properties render them highly attractive in organic synthesis. For the purpose of the present study, this introduction will focus mainly on the formal Iodine(III) species, although reagents containing Iodine(V) will also be mentioned. Throughout this work, the term *hypervalent Iodine* will refer to Iodine(III) species. Among the properties that set such reagents apart, making them of particular interest in synthesis, three (interrelated!) features should be mentioned from the outset:

a) ability to act as a mild oxidant

b) a relatively labile (metal-like) T-shaped coordination environment favorable for the key substrate-iodine interaction

c) the regeneration, in most cases, of the parent iodoarene as a byproduct in the target oxidation process, hence the possibility to regenerate the iodine (III) reagent..

In organic synthesis, a relatively reduced number of hypervalent iodine reagents have been applied in a large variety of selective oxidative transformations, including those involving complex structures. The field has experienced a resurgence in the last two decades due to the discovery of new mode of employing the hypervalent iodine reagents, initially as oxidants (particularly in atoms transfer processes) in metal catalyzed transformations, and more recently as versatile oxidant and group transfer agents (including as an aryl source) in metal-free processes. The field has been the subject of several books and review articles, particularly by Varvoglis as well and Zhdankin and Stang, among others.[1]

1.2. Classification and general structural features of hypervalent iodine(III) reagents

1.2.1. *Classification.*

Certain reactivity patterns of the hypervalent iodine, particularly the substitution lability of the iodine center, are paralleled in metal (transition and main group)

coordination compounds. It is not surprising, therefore, that the term “ligand” has been used to refer to the substituents on the central iodine atom, and that the hypervalent iodine(III) reagents are classified accordingto the ligands present in each case. As discussed below, essentially all of common iodine(III) reagents feature three formally anionic ligands bound to the iodine center to form a T-shaped coordination environment. Although in principle a large number of substitution sets are possible, the organoiodane sub-class is characterized by the presence of at least one organic ligand, most commonly an aryl group. Thus, as described by Zhdankin and Stang,[1c, p] the following classification of the hypervalent iodine(III) reagents have been adopted (Figure 1.1): (difluoroiodo)arenes **A**, (dichloroiodo)arenes **B**, bis(acyloxy)iodo]arenes **C**, iodosylarenes **D** and aryliodine(III) organosulfonates **E**, all belonging to the general structural type $PhIX_2$ (or PhIXY). In some cases, one of the X ligands (typically *O* or *N*) is covalently bound to the arene *ortho* position leading to the five-membered iodine hetercycles, such as the benziodoxoles **F** and benziodazoles **G**.Interestingly, the so-called iodosobenzene, formulated as PhIO, might at first site, appear to be an exception as it is often drawn with an iodine-oxygen double bond: PhI=O, **H**. In reality, however, the solid state structure of this species is believed to be polymeric made up of chains ofthe PhI-O units with the O atom of one unit making a bond to the iodine atom of the next unit. Accordingly, this bright-yellow solid, commonly used as an oxygen-transfer agent, is essentially insoluble in solvents with which it does not react.Compounds bearing two organic ligands are exemplified by the so-called diaryliodonium salts, with the anionic character due to the generally weak interaction between the cationic Ar_2I^+ fragment and the third anionic ligand (type **I**). This labile environment is a particularly important feature of this class of compounds, as it allows for a range of aryl transfer processes to be initiated through the binding of the acceptor substrate to the empty coordination site. Finally, the iodonium ylides **J** and iodonium imides **K** can be considered as the carbon and the nitrogen analogs of the iodosobenzene, and, hence, have been used in the corresponding *atom transfer* reaction.

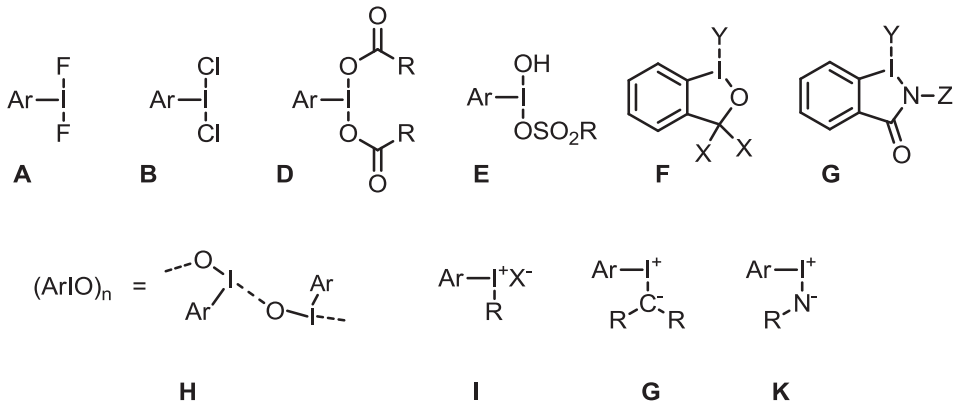


Figure 1.1 Common classes of polyvalent organoiodine(III) compounds.

The main uses of the (difluoroiodo)arenes (**A**) and the (dichloroiodo)arenes (**B**) are in the fluorination and chlorination reactions, respectively. Iodosylarenes (**H**), in addition to their use as an oxygen transferagent, are widely used, alongside the aryliodine(III) carboxylates (**D**) and organosulfonates (**E**),as oxidizing agents, including in the selective oxidative functionalization of organic substrates. Of the latter two families of reagents, some of the important commercially available representatives include:

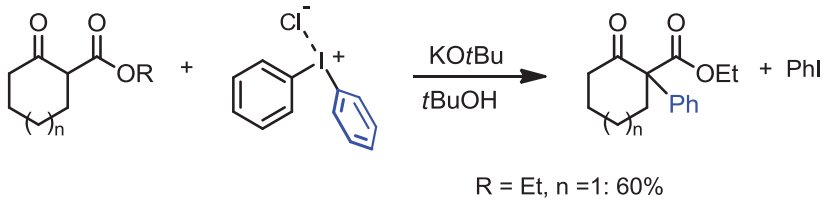
i. (diacetoxyiodo)benzene, $PhI(OAc)_2$, which has several commonly used abbreviations, such as DIB, PID, PIDA (phenyliodine diacetate), IBD, or IBDA(iodosobenzene diacetate)

ii. [bis(trifluoroacetoxy)iodo]benzene, $PhI(OCOCF_3)_2$, abbreviated as BTI or **PIFA**, the latter standing for phenyliodinebis(trifluoroacetate), an abbreviation which will be used throughout this dissertation

iii. the Koser reagent PhI(OH)(OTs), employed both in the general oxidation and in tosyloxylation reactions

The stability of the heterocyclic iodines **F** and **G**(Figure 1.1) is considerably higher than that of their acyclic analogues, which allowed for the isolation of some unstable iodine(III) reagents. The diaryliodonium salts of type **H**, although in general not considered to be strong oxidants, have found a widespread application mainly due to the exceptional leaving group ability of the “I-Ar” fragment, enabling them to productively transfer the second aryl fragment. This mode of arylation is particularly relevant to the present doctoral research and will be discussed in greater detail in Section 1.4.2 and in Chapter 4. For the sake of introduction, however, we’ll mention

that the diaryliodonium salts have been used in the oxidative α-arylation of the carbonyl compounds. The process was discovered in the 1960's by Beringer *at al.* and takes place under strongly basic condition to ensure the formation of the active anionic enolate species. In one of the early example, the diphenyliodonium chloride, $[Ph_2I]Cl$, was used to prepare the 2-phenyl cycloxanone-2-carboxylate in a 60% yield from the corresponding ketoester substrate using potassium *tert*-butoxide as base (Scheme 1.1).[2]



Scheme 1.1. Phenylation of a cyclic ketoester using Ph_2ICl (*Beringer et al.,* 1963).

1.2.2. *The structure.*

A comprehensive description of the structure and bonding in the hypervalent iodine compounds can be found in one of the volumesof the*Topics in Current Chemistry* authored by Ochiai *et al.*[1b] Thus, according to the IUPAC nomenclature, all the iodine(III) structure types illustrated in Figure 1 are classified as λ^3-iodanes. The total electron count on the central iodine atom is 10, of which 4 electrons are found on two lone pairs. The 5 stereoactive groups – 3 ligands and 2 lone pairs, form an overall distorted trigonal bipyramid, with the aryl group and the two lone pairs occupying the three equatorial positions and the remaining two ligands theequatorial positions. Thus, the geometrical disposition of the three ligands corresponds to a T-shaped molecule, in which the equatorial aryl group forms the "stem" and the linear X-I-X' unit the "head" of the T (Figure 1.2). Indeed, in a vast majority of the structurally characterized λ^3-iodanes, the X-I-Ar and the X-I-X' angles are close to 90º and 180º, respectively. The category also includes the diaryliodonium salts, as they also feature the Ar-I-Ar angle close to 90º.

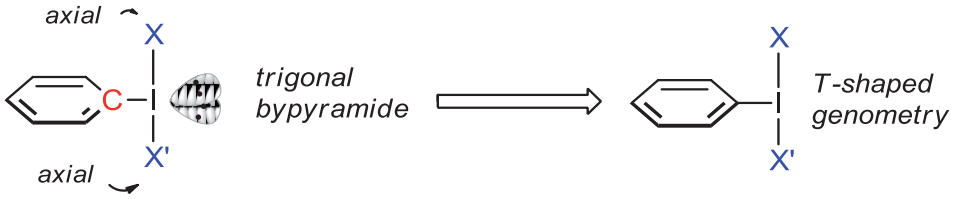


Figure 1.2. T-shaped geometry ubiquitous in λ^3-iodanes

The bonding in the λ^3-iodanes (i.e. RIX_2) is conveniently treated within the so-called hypervalent model, in which the iodine non-hybridized 5p orbital are invoked to construct the linear X-I-X unit. The linear three-center, four-electron (3c-4e) arrangement leads to the polarization, lengthening and weakening of each of the X-I is bonds, when compared to a regular covalent bond, such as the I-Ar_{eq} bond in the same molecule. This "hypervalent" nature of the I-X bond inλ^3-iodanes leads to an increased electrophilicity of the X substituents and has been credited with the unique reactivity of the iodine(III) reagents. The structural studies of the hypervalent iodine compounds have been addressed by a large number of groups,[1c,3,5] most notably in a series of publications from the A. Katritzky laboratory between 1989-1900.[3] A practical and useful nomenclature to describe the hypervalent iodine species was also introduced by Arduengo and Martin in a seminal 1980 publication.[4] The nomenclature, applicable in principle to any bonding pattern, is based on the descriptor N-E-L, where E is the chemical element, the N is the number of valence electrons and the L is the number of ligands bound to the center in question (Figure 1.3).Thus, a radical sulfur species shown in Figure 3 is classified as 9-S-3, while the parent carbene CH_2 is described as a 6-C-2 species (6 valence electrons and 2 hydrogen substituents). For the hypervalent iodine species, the nomenclature readily distinguishes between λ^3-iodanes with the three ligands firmly bound (the 10-I-3 family) and those that have undergone the dissociative loss of one of the X ligands (e.g. as cationic 8-I-2 salt).

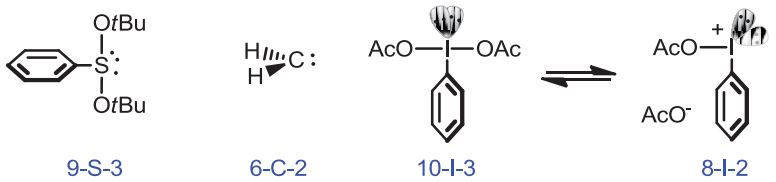


Figure 1.3. The Martin-Arduengo classification of the λ^3-iodanes and other compounds.

Some of the recent research on new structural research motifs in the hypervalent iodine chemistry[5] includes the study of the interaction of crown ethers with iodane,[5a] as well as the incorporation of nitrogen substituent into the hypervalent iodane structure[5b,c] The T-shaped geometry and the unusual electronic properties have also made hypervalent iodine reagents an interesting candidate for building a variety of supramolecular structures.[5d] Intramolecular secondary bonding in 10-I-3 iodaneshave also attracted considerable attention.[5g-l]

The solution structure of the hypervalent iodine compounds has been studied by a variety of techniques.[6] As an interesting example, NMR and LC-MS was used to

assess the subtle differences between the solution structures (in MeOH) of the parent iodosylbenzene, PhIO, and the iodosylarenes substituted in the *para* position.[6a] Based on the LC-MS results, it was established that iodosylbenzene has a polymeric structure, the 4-substituted iodosylarenes appear to dissociate freely and tend to be monomeric in solution. It should be mentioned that for iodosylarenes, the structural studies in solution are often complicated by the reversible solvation (resulting in a new T-shaped species), as occurs in alcohols and with certain acids, and by the non-reversible solvent oxidation, as observed in DMSO (Figure 1.4).

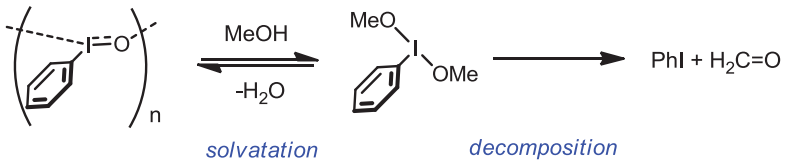


Figure 1.4. Behavior of the iodosylbenzene PhI=O in methanol.

In a separate study, the ^{17}O NMR spectroscopy was used to demonstrate that thesolid state T-shaped structure of the bis(acyloxy)iodoarenes (type **D**, Figure 1.1) is preserved in a chloroform solution.[6b] Not surprisingly, given the weakened (through *trans* effect) I-OAc bond in such species, the carboxylic ligandsshow a dynamic behavior (clearly observable by the ^{17}O NMR) consisting in the position exchange between the anionic iodine-bound and the carbonyl oxygen atoms. The DFT studies revealed that the dynamic process takes place through a [1,3] sigmatropic shift of the iodine atom between the two oxygen atoms of the carboxylic groups (Figure 1.5), with the energy barrier for the process highly dependent on the nature of the substituents.[6b]

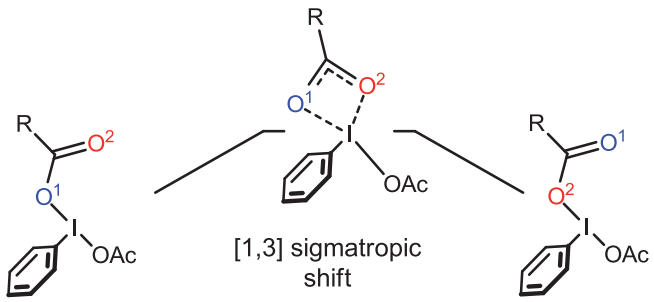


Figure 1.5. Dynamic behavior of the bis(acyloxyiodobenzenes).

A complementary approach to investigate the solution state structure of the λ^3-iodanes are the electrospray ionization mass spectrometry (ESI-MS) and tandem mass spectrometry (ESI-MS/MS).[6c] These techniques were used by Silva and coworkers to assess the solution structure of the phenyliodine diacetate in a variety of solvents,

including acetonitrile, carboxylic acid solvents and methanol. The study revealed that under the electrospray conditions, the major species detected are $[PhI(OAc)_2M]^+$ (M = Na, K), $[PhI]^+$, $[PhIOAc]^+$, $[PhIOH]^+$, $[PhIO_2Ac]^+$, $[PhIO_2H]^+$as well as the dimeric $[Ph_2I_2O_2Ac]^+$.[6c] It should be mentioned, however, that despite the wealth of information obtained in such study, the correlation between the species produced upon ionization and those present in the original solution is not straightforward, given the complexity of the ionization process itself. Computational studies, including those using the DFT methods, have also proved highly valuable to investigate the structure and properties of hypervalent iodine compounds.[7,8]

As mentioned above, the hypervalent nature of the linear X-I-X' unit in the T-shaped λ^3-iodanes leads to the lengthening of the I-X bond with respect to the conventional covalent bond. A statistical analysisof the iodine-oxygen bonds of a wide range of the T-shaped 10-I-3 iodine(III) derivatives using the Cambrige Crystallographic Database and *ab initio* MO calculations was performed to assess the interplay between the two X ligands in the 3-center 4-electron environment. The bond length analysis[7a] and further theoretical investigation clearly showed that, as expected, the *trans* influence in the X-I-X' unit is significant and directly affects the stability of such species.[7b] Thus, two "matching" trans influences are required for an iodane to prove stable, such as in the combination of a large and small *trans* influences found in PhI(OH)OTs, or in two ligands with moderate *trans* effect, as in $PhI(OAc)_2$.

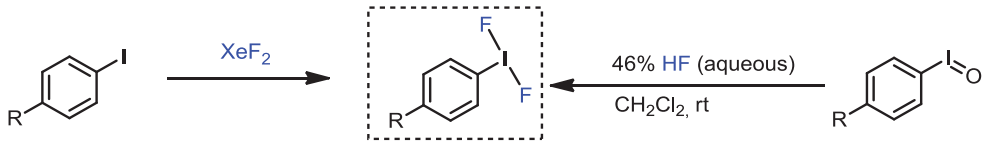
Importantly, theoretical studies have been a key tool in establishing the mechanism of a range of transformations involving the hypervalent iodine reagents.[8] Thus, DFT calculations have been used by Su and Goddard to study the mechanism of alcohol oxidation with 2-iodoxybenzoic acid (IBX).[8a] The study found that the rate-limiting step in the process is not the ligand exchange to bring the alcoxide into the coordination sphere of the iodine, but rather a rearrangement denoted as *hypervalent twist* and defined by the authors as "*a coordinated motion of ligands driven by the necessity of generating a stable, planar form of the byproduct IBA from an <initial> IBX-alcohol intermediate complex*". The study, in addition to explaining the ability of the IBX to oxidize large alcohols faster than small ones, has led the authors to make a prediction that a new sterically hindered (through o*rtho* substitution) IBX analog would accelerate such*hypervalent twist* to the point where the ligand exchange would become rate-limiting.[8a] Very recently, Quideau and coauthors reported DFT calculations of spiroheterocylic iodine(III) intermediates to validate their participation in the $PhI(OAc)_2$-mediated spiroketalization of phenolic alcohols.[8b]

1.3. Preparation of iodine(III) compounds

1.3.1. *(Dihaloiodo)arenes*

As mentioned above, dichloroiodobenzene was the first hypervalent iodine reagents reported. It was described by Wilgerodt in 1886 following an attempted chlorination of iodobenzene with chlorine gas.[10a] Today, more than a century later, the dichloro- and difluoroiodoarenes have become important reagents in organic synthesis, and a great number of studies has been dedicated to their preparation and usage. The most straightforward strategy, perhaps, is that of the formal oxidative addition of a fluorine-containing oxidant to an iodoarene. To this end, in addition to the molecular F_2, a number of such agents has been used, including ClF, CF_3OCl, BrF_5, $C_6F_5BrF_2$, $C_6F_5BrF_4$ as well as thexenon difluoride or the XeF_2/BF_3 combination.[1d] Direct fluorination of iodobenzene and *p*-iodotoluene has also been accomplished (in CH_3CN) using the commercially available Selectfluor as fluorinating reagent.[9a]

The preparation of the (difluoroiodo)arenes through ligand exchange with the pre-formed 10-I-3 iodanes has the advantage of separating the oxidation and the fluorination steps, thus allowing for the use of the non-oxidizing fluorine sources. In fact, one of the oldest procedures involves the replacement of the chloride ligands in (dichloroiodo)arenes with fluoride using a combination of the mercuric oxide and HF_{aq}, with the driving force provided by the conversion of HgO to the $HgCl_2$.[9b] To overcome the drawback of using a large quantity of the mercury salts, amore recent procedure consists in treating iodosylarenes with a concentrated hydrofluoric acid (Scheme 1.2); the product can then be convenient obtained in pure formupon recrystallization.[9c,d]

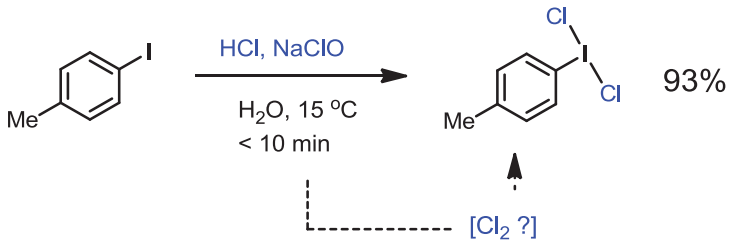


Scheme 1.2. Two approaches to the preparation of the (difluoroiodo)arenes.

Given the facility with which the (difluoroiodo)arenes are hydrolyzed in air, these reagents are often generated in solution immediately prior to their use. An efficient method to generate such solutions was recently reported by DiMagno, whereby the $PhIF_2$ is generates quantitatively via ligand exchange of $PhI(OAc)_2$ with TBAF in acetonitrile.[9c]

Interestingly, for the preparation of (dichloroiodo)arenes the reaction between of an iodoarene with Cl_2, first described by Willgerodt in the 19th century, continues to be the method of choice for the large-scale applications, where the inconvenience of working with chlorine gas is compensated by the low cost of the process.[10] Thus, $PhICl_2$ has been prepared on a multi-kilogram scale by the reaction of iodobenzene with chlorine at low temperature in a CH_2Cl_2 solution.[10c] Other reagents prepared by this method include thecorresponding hypervalent dichloride derivatives of the 4,4'-bis-iodo-biphenyl and the 3-iodobenzoic acid, wwith the latter serving as a recyclable (through acid-base extractions) iodoarene platform.[10d]

On the other hand, for small laboratory scale synthesis, where convenience often outweighs cost, the chlorination of iodoarenes can be effected using non-gaseous chlorination agents. Thus, the reaction can be performed using a combination of an aqueous chloride solution (including HCl)with an oxidant, including potassium permanganate, the perchlorate, periodate and perborates, as well as various forms of hydrogen peroxide.[11a] In all cases, the reaction may proceed either via the initial oxidation of the iodoarene, followed by the ligand exchange of the intermediate λ^3-iodate with the Cl^-, or, more likely, via the reaction of the *in situ* generated chlorine molecule with the iodoarene. A "textbook" example of the latter mode is exemplified by the recently reported generation of $PhICl_2$ using a combination of HCl with sodium hypochlorite (NaClO, i.e. bleach). Indeed, the comproportionation of the Cl^-/ClO^- to Cl_2 is rapid, and allows for the efficient chlorination processes, as observed in this case with iodoarenes (Scheme 1.3).[11b]

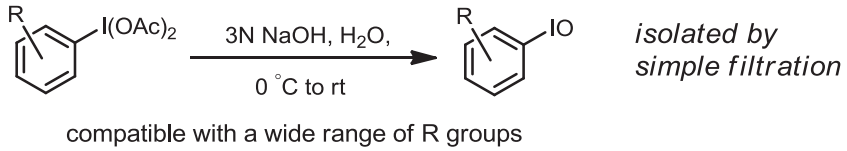


Scheme 1.3. Chlorination of iodoarenes using non-gaseous Cl_2 equivalents.

As was the case for the difluorides, the benchlife of the isolated (dichloroiodo)arenes is generally rather short, even at low temperatures. In solution, these reagent decompose within days or even hours, usually to the parent iodoarene and chlorine gas.

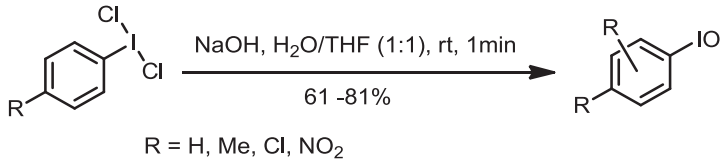
1.3.2. *Iodosylarenes and [bis(acyloxy)iodo]arenes*

The term iodosylbenzene referes to a compound formulated as PhIO and often depicted with a iodine-oxygen double bond. The compound gained prominence in the late 1990's an oxygen transfer agent, particularly in metal-catalyzed epoxidation reactions, including in biomimetic applications,[12] producing the relatively innocent iodobenzene as the sole byproduct. As a practical matter, the completion in such reactions is often signaled by the disappearance of the bright yellow solid. Iodosylbenzene is usually prepared by the treatment of the $PhI(OAc)_2$ with an aqueous basic solution.[13a] The alkaline treatment of a variety of (diacetoxyiodo)arenes has also been used to prepar a range substituted iodosylbenzenes (Scheme 1.4).[6a,13] As an example, the method has been applied to the preparation of 4-methoxyiodosylbenzene,[6a] and iodosylarenes bearing tert-butylsulfonyl[13a] or diphenylphosphoryl[13b] groups in the ortho-position.



Scheme 1.4. Hydrolysis of (bisacyliodo)arenes to iodosylarenes.

A closely related procedure involves the alkaline hydrolysis of (dichloroiodo)arenes (Scheme 1.5).[13d] In addition to its improved atom-economy, the method offers a potential cost advantage in large scale application, given that the $ArICl_2$are accessible directly from a iodoarenes and molecular chlorine.[13e]



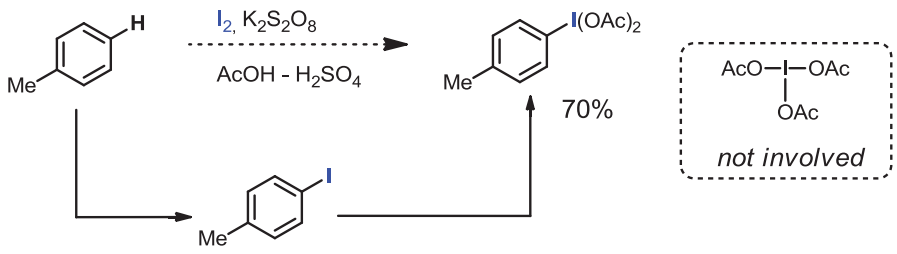
Scheme 1.5. Iodosylarene from bis(dichloroiodo)arenes.

[Bis(acyloxy)iodo]arenes are perhaps the most commonly used family of the hypervalent 10-I-3 iodine reagents. Their relatively large shelf life and a versatile reactivity have made them a staple in organic synthesis.As discussed in section 1.2.2 the reasonable stability of the dicarboxylates is due, in part, to the matchingly moderate *trans* influences of the two carboxylates ligands in the linear AcO-I-OAc moiety. As with the dihalides, the strategies for the preparation of [bis(acyloxy)iodo]arenes are based either on the oxidation of iodoarenes in the presence of the corresponding carboxylic

acid, or, alternatively, on the ligand exchange reaction of the readily available (diacetoxyiodo)benzene(PIDA) (or another λ^3-iodane) with the desired carboxylic acid.

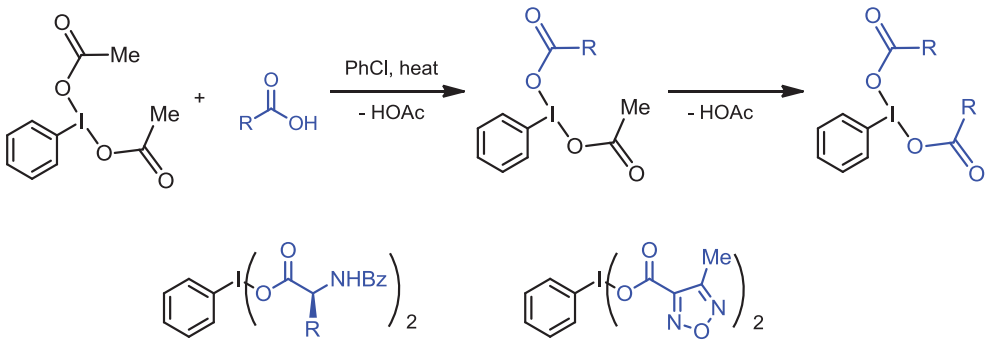
Perhaps, the most straightforward synthesis of the iodobenzene(dicarboxylates) is that of the oxidation of iodobenzene by the corresponding acid peroxide. Thus, $PhI(OAc)_2$, **PIDA**, is synthesized through a reaction of iodobenzene with the readily available peracetic acid using acetic acid as solvent. The method is quite general, and has been applied to a wide range of iodoarenes. Thus, the versatility of the approach can be seen in the synthesis of a polymer-supoported PIDA analog through the oxidation the iodostyrene-based polymer with CH_3CO_3H (peroxyacetic acid).[1g, 14b, 14c] Ionic PIDA derivatives are also readily accessible through the peracid treatment of the imidazolium-bound iodoarenes.[14d,e] Through the use of the peroxytrifluoroacetic acid, the protocol can easily be adapted to the synthesis of the more reactive trifluoroacetate derivatives of the type $ArI(O_2CCF_3)_2$,[14f,g] although this method has been largely replaced by the more recent mild oxidation approaches (see below).

Rather than using a percarboxylic acid, the oxidative dicarboxylation of iodoarenes can be accomplished by a combination of the acetic (or trifluoroacetic) acid with an appropriate oxidant, such as periodates,[15a,b] m-chloroperoxybenzoic acid,[15c,d] potassium peroxodisulfate (Oxone®),[15e] or hydrogen peroxide.[15d,g,h] On a laboratory scale, this is most often accomplished using perborates in an acetic acid medium at a mildly elevetated temperature,[15d,g,h] with the efficiency somewhat improved by adding CF_3SO_2OH.[15i] In 2006, the Kitamura group showed that a number of $ArI(OAc)_2$ derivatives could be prepared directly from the arene (ArH) using a combination of molecular iodine, $K_2S_2O_8$ (or Oxone) and acetic acid (Scheme1.6).[15j] The method, while attractive due to the step-economy, has the obvious limitation of being governed by the inherent chemoselectivity of the electrophilic aromatic iodination with I_2 (the intermediacy of the iodane $I(OAc)_3$ was discarded by the authors).



Scheme 1.6. Direct conversion of an arene into a [bis(acyloxy)iodo]arene.

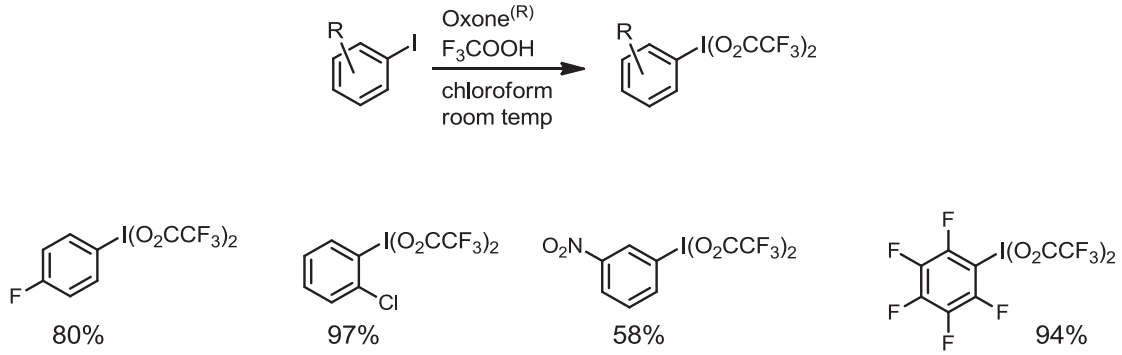
Once prepared, PIDA itself can be used as precursor to other [bis(acyloxy)iodo]arenes thanks to the facile ligand exchange between dicarboxylate derivatives. As a practical matter, the method is most often applied to the high molecular weight carboxylic acid, since the reaction can then be driven through the distillative removal of the acetic acid byproduct using a high boiling solvent (toluene, chlorobenzene etc.) (Scheme 1.7).[16] This procedure, in particular, was recently used for the preparation of the protected amino acid derivatives[16a] as well as cinnamate derivatives.[16c]



examples of bis(acyloxy)iodobenzenes obtained through ligand exchange

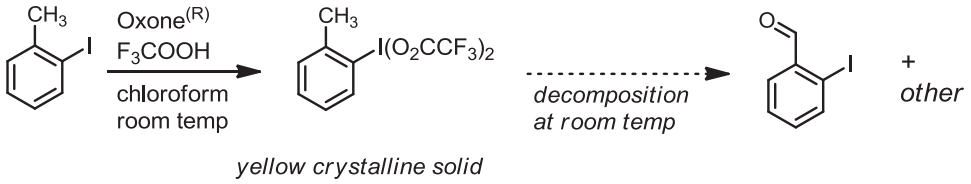
Scheme 1.7. [Bis(acyloxy)iodo]arenes

A highly favorable equilibrium can be achieved between PIDA and a strong (relative to acetic acid) carboxylic acid. Using this procedure, the bis(trifluoroacetate) derivative is easily obtained bymixingPIDAwith trifluoroacetic acid and reducing the reaction volume to drive off the acetic acid.[16e] Nevertheless, in our hands the method of choice for the preparation of the phenyliodine bis(trifluoroacetate), **PIFA**, is the procedure reported in 2010 by Zhdankin and coworkers, that consists in treating iodobenzene with Oxone (i.e. potassium peroxysulfate) in a mixture of trifluoroacetic acid and $CHCl_3$ at room temperature. Using this method, PIFA can be obtained in a >90% yield upon single recrystallization.[16f] Importantly, the approach is equally effective for a wide range of iodoarenes (Scheme 1.8), with a range of new PIFA derivatives prepared using this method during this work (see Chapter 4).



Scheme 1.8. Syntheis of bis(trifluoroacetoxy)iodoarenes according to Zhdankin and co-workers

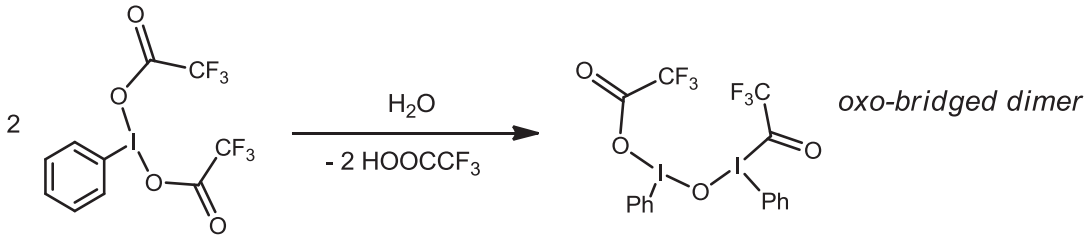
Many of the [bis(acyloxy)iodo]arenes are colorless or yellow stable microcrystalline solids, which can be easily recrystallized and stored for extended periods of time. However, the stability of the bis(acyloxy)iodoarenes derived from electron-rich iodoarene can be significantly reduced, particularly in the bis(trifluoroacetate) derivatives. As an example, the bis(acetate) λ^3-iodoane derived from 3-iodothiophene can be prepared, although will decompose within days at room temperature; in contrast, the bis(trifluoroacetate) analog has never been, likely due to its instability. The stability of a bis(acyloxy)iodoarene is also affected by the presence of a methyl group *ortho* to the iodine. Thus, the crystalline [2-bis(trifluoroacetoxy)iodo]toluene prepared during this doctoral project was only stable for a few days at room temperature, and decomposed within a week from a yellow crystalline solid to a pungent red oil, identified as a mixture of *ortho*-carboxyiodobenzene (Scheme 1.9). This is not entirely surprising, given that in this molecule the relatively reactive benzylic $CH_3$is brought within close proximity of the strongly oxidizing Iodine(III) center.



Scheme 1.9. Formation and decomposition of a PIFA derivative with an *ortho* Me group.

The bis(acyloxy)iodobenzene are also fairly stable when dissolved in dry solvents, but get hydrolyzed instantly in the presence of even traces of water. In fact, the NMR spectra of the bis(trifluoroacetoxy)iodobenzene and its derivatives usually contain a second set of resonances corresponding to the dimeric oxo-bridged species (Scheme 1.10). In cases where a “pure” spectrum is sought, theresonance spectrum may be

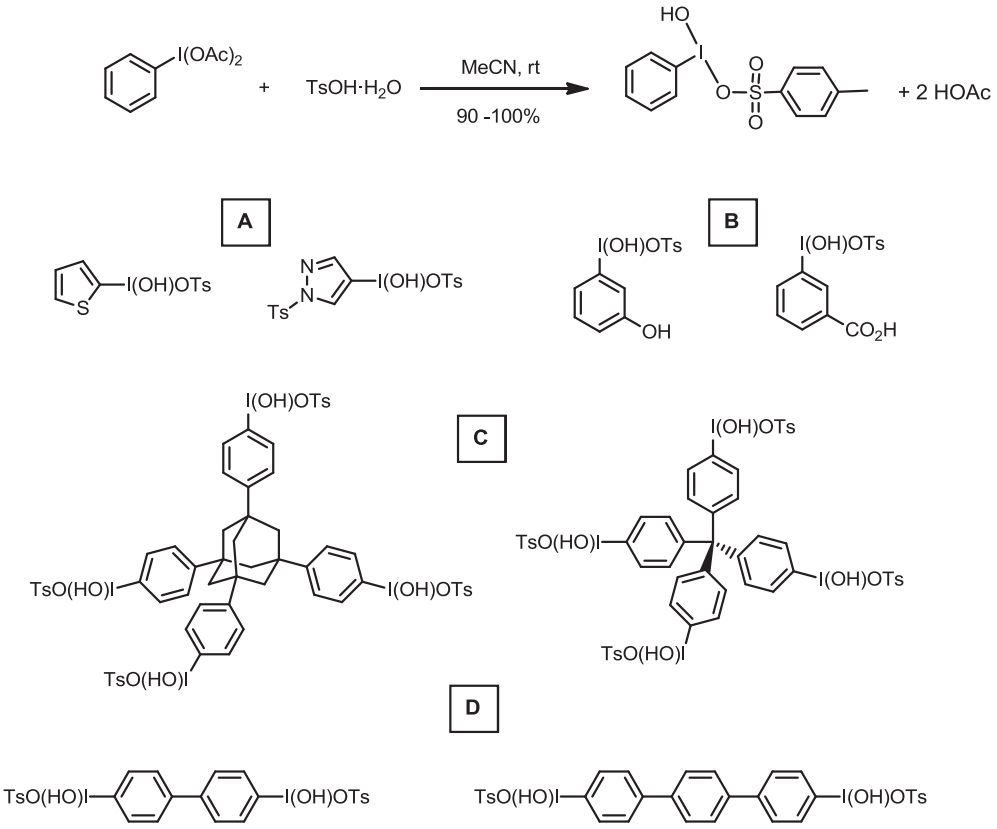
recorded in the presence of an added trifluoroacetic acid or trifluoroacetic acid anhydride,[16f] both of which suppress the hydrolysis process.



Scheme 1.10. Hydrolysis of the bis(acyloxy)iodoarenes

1.3.3. *Aryliodine(III) organosulfonates*

As discussed above, the λ^3-iodane bearing the matching (strong/weak trans effect) OH/OTf combination are relatively stable and have found a widespread use in organic synthesis, both as simple oxidants and as sulfoxide transfer agents. Most famously, the Koser's reagents, PhI(OH)(OTs) can be prepared through a ligand exchange reaction of between PIDA and *p*-toluenesulfonic acid monohydrate in acetonitrile (Scheme 1.11).[15d,17a-f] The method can be adapted as a general approach to the hydroxyl-tosylate derivatives, and indeed a number of these have been synthesized in recent years, including the heteroaromatic derivatives (**A**)[17c] and those bearing potentially "delicate" substituents on the aromatic ring (**B**).[17b,c] The method has also been applied to prepare branched or multi-iodane reagents (**C**).[17e,f] Rather than parting from a preformed PIDA-type λ^3-iodane, the hypervalent Koser-type hydoxy-sulfonates can be formed directly through the oxidation of an iodoarene by the *meta*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of the corresponding sulfonic acid.[17d]The method was recently applied to the synthesis of new biphenyl- and terphenyl-based hypervalent iodine reagents (**D**).[15d]



Scheme 1.11. Preparation of aryliodine(III) organosulfonates

A highly practical method for the preparation of hydroxy(organosulfonyloxy) iodo]arenes has been described under solvent-free conditions, whereby the ligand exchange takes place simply by grinding of $ArI(OAc)_2$ with the appropriate sulfonic acid, followed by the removal of the acetic acid byproduct with a diethyl ether wash.[17g] This approach was applied to the synthesis the Koser's reagents as well as several other derivatives in high yields.

It should be noted that the development of new efficient methods for the synthesis of hydroxy(organosulfonyloxy)iodo]arenes has been driven, in part, by their unique ability to transfer a tosyloxygroup to a suitable acceptor. A well-studied example is the oxidative introduction of an OTs group to the α position of a carbonyl compound. Given that the reaction leads to the reduction of the λ^3-iodane employed to the parent iodoarene, a polymer-bound iodane was developed by Togo and coworkers for use a a recyclable reagent. This poly(iodostyrene) is oxidized to a poly-$ArI(OAc)_2$ under standard condition, and then converted to the polymer-supported [hydroxy(toxyloxy)iodo]benzene by treatment with *p*-toluenesulfonic acid monohydrate in chloroform at room temperature.[17h]Although beyond the scope of this introduction, the regeneration of the parent iodoarene has also allowed for the development of

methods catalytic in the organoiodine, whereby a hypervalent tosyloxy iodane is generated in situ from an iodoarene and a terminal oxidant. The method was pioneered by Ochiai, Togo and others.[17i, j] While all of the examples reported thus far involve aromatic iodoarenes, a recent doctoral work by W. Guo at the UAB showed that catalytic amounts of iodoalkanes can aslo act as efficient precatalysts, in this case via the oxidative breakdown of the organoiodine to the inorganic hypoiodite.[17k]

Closely related to the hydroxy(sulfoxy) family of the λ-3 iodanes is Zefirov's phenyliodine(III) trifluoromethanesulfonate formulated as $(PhIO)_2 \cdot Tf_2O$. Structurally, the reagent can be considered a product of the dehydrative condensation of two PhI(OH)OTf molecules to give rise to the *μ*-oxo-bridged [PhI(OTf)]O species isolated as a yellow microcrystalline solid that can be handled for brief periods in air and stored for longer periods under inert atmosphere. The compound is prepared by the treatment of PIDA with the corresponding sulfonic acid,[18a] or by the addition of the triflic anhydride to iodosylbenzene.[18b] The latter protocol can be conveniently used to generate the Zefirov reagent in situ immediately prior to its use.[18c] It should be noted that the same condensation phenomenon leading to the formation of the oxobridged species will lead, upon prolonged storage of the reagent, to the formation of the oxo-bridged oligomeric structures.[18d]

1.4. Diaryliodonium salts: an emerging family of aryl transfer reagents.

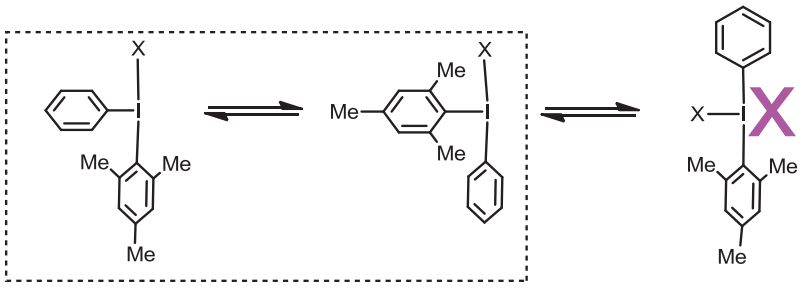
In 2009 a review by Merritt and Olofsson covering the chemistry of the diaryliodonium salts appeared in the Angewandte Chemie.[19] Fittingly, the title of the article,*Diaryliodonium Salts: A Journey from Obscurity to Fame,* reflected the growing importance of this class of compounds in organic synthesis, mainly as aryl transfer agents.

1.4.1. *History, structure and preparation.*

In modern literature, both the IUPAC-compliant term "diaryl-λ^3-iodanes", and the older term diaryliodonium are used or this compound class. A molecule with two phenyl groups bound to a formal iodine(III) center was first obtained by Meyer and Hartmann in the 19th century through a reaction between iodosobenzene (PhIO) and iodoxybenzene ($PhIO_2$) in the presence of silver (I) oxide.[20] Despite the denomination as "salts", a number of the diaryl-λ^3-iodanes are formally neutral T-shaped 3-coordinate molecules in the solid state, with the heroatomic anion occupying the third coordination site. Nevertheless, the solution state structure of these reagents is a still a matter of

discussion, with the anion dissociation likely for the less coordinating anions in a polar medium.

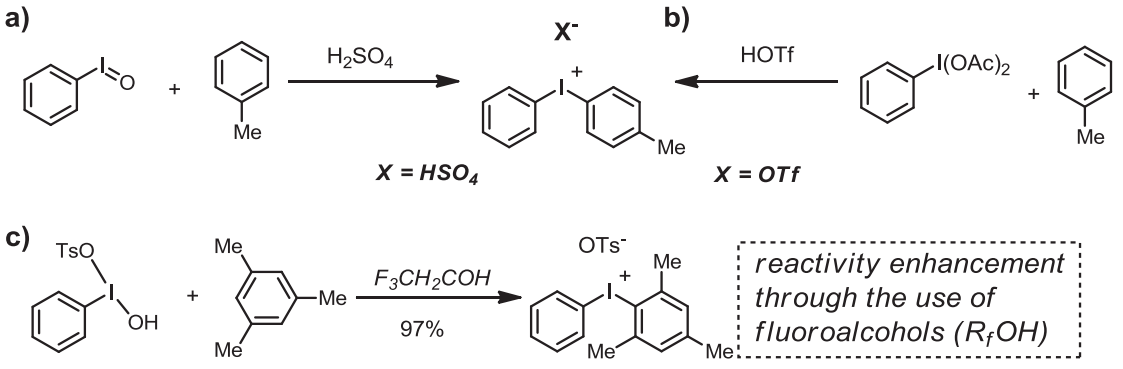
The diaryl-λ^3-iodanes can be symmetric, that is bearing two identical aryl groups, or asymmetric with two different aryl groups. In the latter case, equilibriumis expected between the two T-shaped conformations, with the prevalence of one or another conformer depending on the steric and electronic properties of the two organic groups (Scheme 1.12). The third possible structure, with the heteroatomic X ligand occupying an equatorial position is not expected to have a significant contribution, since it would force the two strongly trans-influencing aryl ligands to compete for the same iodine *p* orbinal.[7b] The importance of this equilibrium lies in its influence on the selectivity and efficiency of the aryl transfer reactions employing the diaryliodonium reagents (see section 1.4.2), and has been discussed in great detail by Grushin and coworkers.[21] Incidentally, the unfavorable *trans* placement of organic C-ligands is also one of the reasons for the extreme instability of the λ^3-iodane bearing all three aryl ligands.



Scheme 1.12. Two T-shaped molecular structures in equilibrium.

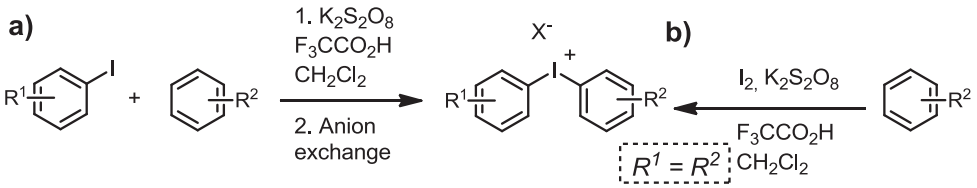
The diaryl-λ^3-iodanes can be generated through an electrophilic aromatic substitution involving an activated aryl λ^3-iodane at an appropriate arene substrate. The activation is almost always achieved through the use of acid medium, a phenomenon attributed to the generation of a more electrophilic partially (or fully) cationic species of the type ArI(X)$^+$. An early example of this protocol is the synthesis, in the 1950's, of the diaryliodonium salts in the Beringer laboratories by using iodosylbenzene PhIO in the presence of various acids, including H_2SO_4 (Scheme 1.13a).[22] In this approach, the final diaryliodonium species includes the counterion of the acid used as activator, and a ligand exchange reaction is then used to produce the salt with the desired anion. In this context, the use of the triflic acid (trifluoromethane sulfonic acid, TfOH) in combination with a second solvent was found to be both efficient in activating the hypervalent iodine precursor, and convenient, given that the diaryl product thus obtained already incorporates the triflate counterion commonly found in the diaryl λ^3-iodanes (Scheme

13b).[23] In 2007, an interesting modification of the method was reported by Kita and coworkers, who found that a fluoroalcohol medium is highly efficient in enhancing the electrophilicity of the organoiodine(III) reagents. As an example, a reaction between PhI(OH)OTs and 1,3,5-trimerthylbenzene in trifluoroethanol afforded a 97% yield of the desired PhI(Mes)OTs in just 2 hours at room temperatures (Scheme 1.13c).[24]



Scheme 1.13. Synthesis of the diaryl λ^3-iodane through an electrophilic activation of arenes.

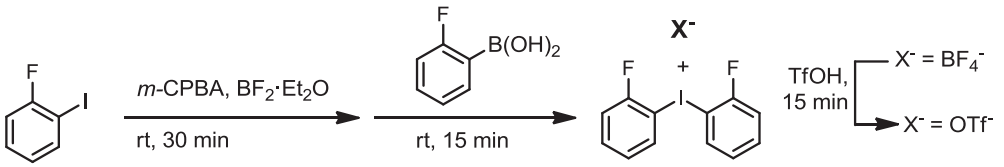
It should also be mentioned that that variants of the protocol have been developed and popularized in recent years whereby the iodine(III) reagent, used as the electrophilic component, is generated in situ from an iodoarene in the presence of a terminal oxidant,[25] such as the peroxysulfate, as demonstrated by the work from the Kitamura laboratory (Scheme 1.14a).[25a] For certain symmetric diaryl λ^3-iodanes, this *one pot* approach, in fact, can be taken a step further to combine the arene iodination, organoiodine oxidation and, finally, an electrophilic activation of the second arene molecule. From the procedural point of view, the latter approach is highly convenient, and involves mixing the arene, molecular iodine and the oxidant in the presence of the desired acid (Scheme 1.14b).[25b,c]



Scheme 1.14. The *one pot* approach to the synthesis the diaryl λ^3-iodanes.

Despite the convenience of the synthesis of the diaryliodonium species via the electrophilic activation of arenes, the scope of the target salts is limited by the inherent regiochemical preference of the EAS reactions. Thus, the use of toluene as substrate will favor the formation of the *p*-tolyl derivative, and is thus unsuitable if a *meta* or an

ortho derivative is needed.One of the early examples of the regiospecific synthesis of the diaryl λ^3-iodanes came from the laboratory of G. Koser in 1980. The synthesis was based on "tagging" the target site on the arene ring through the prior introduction of a trimethylsilyl group. With the tag in place, the reaction of Koser's PhI(OH)Ots with this arylsilane in the absence of acid took place exclusively through the iodine-silyl transmetallation process, thus overriding the inherent preference of an EAS reaction.[26] This approach has since been extended to the use of a wide range of organosilanes, organostannanes and organoboronates, and has made virtually any diaryliodonium salt available from the corresponding monoaryl hypervalent iodine reagent and the Ar-M substrates.[27] Particularly important in this field is the work from the group of Olofsson, which, among other contributions, reported in 2008 an efficientone-pot approach to the regioselective synthesis of the diaryliodanes from an aryliodide and boronic acids.[28] Using this method, for example, the bis (*2*-fluorophenyl)iodonium triflate (unobtainable using the "electrophilic" route) was prepared in less than 1 h in an overall 75% yield from 2-fluoroiodobenzene and the 2-fluorobenzene boronic acid (Scheme 1.15)

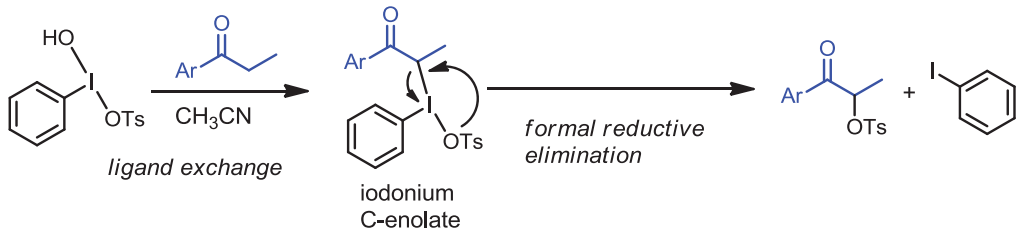


Scheme 1.15. The *one pot* oxidation-transmetallation sequence used to prepare diaryl λ^3-iodane unobtainable through the electrophilic substitution of arenes.

1.4.2. *Diaryliodonium salts as aryl transfer reagents.*

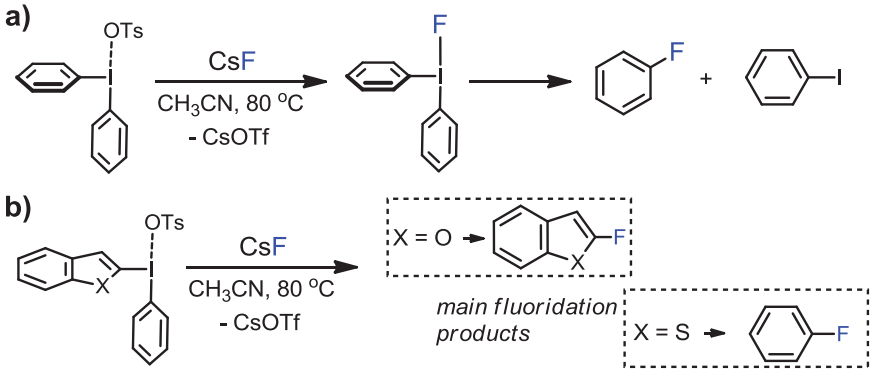
The popularity of the λ^3-iodanes in organic synthesis is due both to their use as "pure" oxidants, and as group transfer agents in oxidative functionalization processes. A series of examples of the former family of reactions, developed in our group and elsewhere via the use of PIFA as a mild oxidant in direct arene-arene coupling will be discussed in the next section (1.5). However, perhaps the most promising direction in terms of versatility and potential for the discovery of new reactions is the use of the hypervalent iodine reagentsin transferring one of the three ligands to a suitable substrate. Incidentally, the substrate itself can be conveniently activated through binding to the iodine(III) center, thus becoming one of the three ligands in the iodine(III) coordination sphere. This metal-like reactivity pattern of the trivalent iodine is best illustrated by a simple method for the oxidative transfer of a tosyl group from Koser's PhI(OH)OTs to the α position of an aliphatic ketone (Scheme 1.16). The reaction is believed to proceed through the formation of an iodonium enolate species (C-enolate

or O-enolate). Following with the analogy between the reactivity of an iodine(III) center and that of a transition metal, the formation of the C-O bond has been described as a "reductive elimination" process, indeed affording iodobenzene as the reduced iodine species. This iodobenzene molecule can be re-oxidized *in situ* to PhI(OH)OTs in the presence, for example, of an *m*-CPBA andTsOH, making the process catalytic.[17i,j]It should be noted that the mechanism depicted below has been greatly simplified for the sake of illustration, ignoring, for example, the fact that product formation through reductive elimination likely requires a cis-placement of the coupling partner in the T-shaped iodonium intermediate (currently depicted in trans-arrangement.



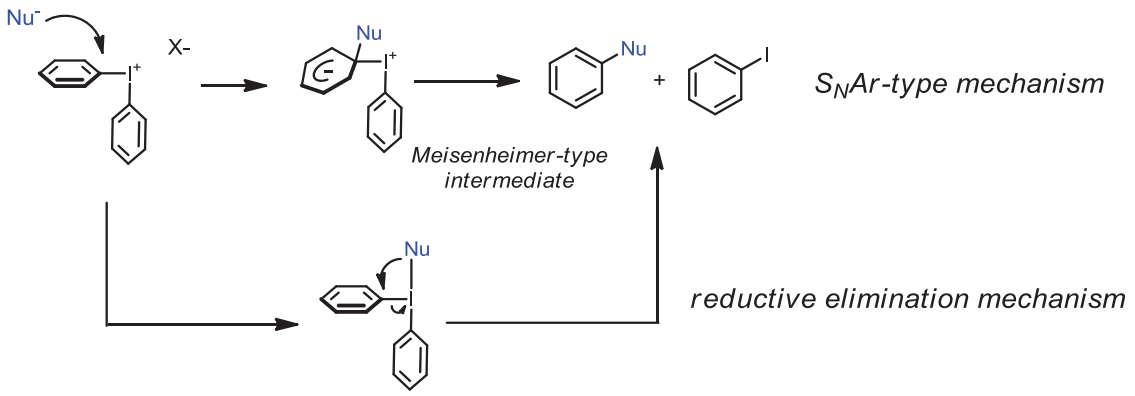
Scheme 1.16. An exemple of an oxidative group transfer from an iodine(III) reagent: α-tosyloxylation of ketones.

In the case of the diaryliodonium salts, an aryl transfer process can take place, opening the door to a wide range of oxidative arylation processes. Thus, a reaction with a potential nucleophile can lead to a Nu-Ar product in a formal nucleophilic aromatic substitution process. For example, the use of a fluoride ion affords a fluoroarene and a molecule of an aryliodide side product, that is, fluorobenzene and iodobenzene in the case of the diphenyliodonium salts (Scheme 1.17a). The use of unsymmetrical diaryl-λ^3-iodane, however, implies the possibility of two different fluoroarene products, with the chemoselectivity governed by a complex set of steric and electronic parameters affecting both the ground and the transition state energies. For the case at hand, the chemoselectivity was studied in 2000 by Rzepa, Widdowson and coworkers both experimentally and through theoretical predictions.[29] An illustrative example from that work is the fluoridation of the (phenyl)(heteroaryl)iodonium triflate salts. Thus, while the fluoridation of the benzofuran-based salt afforded 2-fluorobenzofuran as the main product, the closely related benzothiophene derivative afforded fluorobenzene as the main fluoridation product (Scheme 1.17b). These examples demonstrate that even subtle changes in substrate structure can lead, through small energetic changes, to a reversal in the chemoselectivity of the process.



Scheme 1.17. Fluoridation of symmetric and unsymmetric diaryliodonium tosylates.

Incidentally, two distinct mechanisms could account for this and related aromatic substitutions involving diaryliodonium species. Thus, the reaction could take place through a path closely resembling the Nucleophilc Aromatic Substitution (S_NAr) reaction. Here, the nucleophile would attack the *ipso* carbon atoms of one of the two aryl groups to form a Meisenheimer-type intermediate, which would then eliminate iodoarene to give the Nu-Ar product. Indeed, the leaving group ability of the [PhI] in S_N2 reactions involving hypervalent iodoarenes was found to be orders of magnitude higher than that of the conventional leaving groups (Hal^-, triflates or sulfonates), both due to enthalpic and entropic reasons. This phenomenon led to a denominationof the hypervalent iodine substituent as “hyperleaving group”.[30] However, in the case of aromatic substitutions, a growing body of experimental and theoretical evidence points to a second mechanism, already shown in Scheme 16, whereby the product is formed through reductive elimination from a three-coordinate T-shaped intermediate (Scheme 1.18).[31]



Scheme 1.18. The feasible mechanisms for nucleophile addition to diaryl λ^3-iodanes.

In a number of cases, the process for the formation of the Ar-Nu product is complimentary to the metal-catalyzed coupling between an ArX (X = Hal or equivalent)

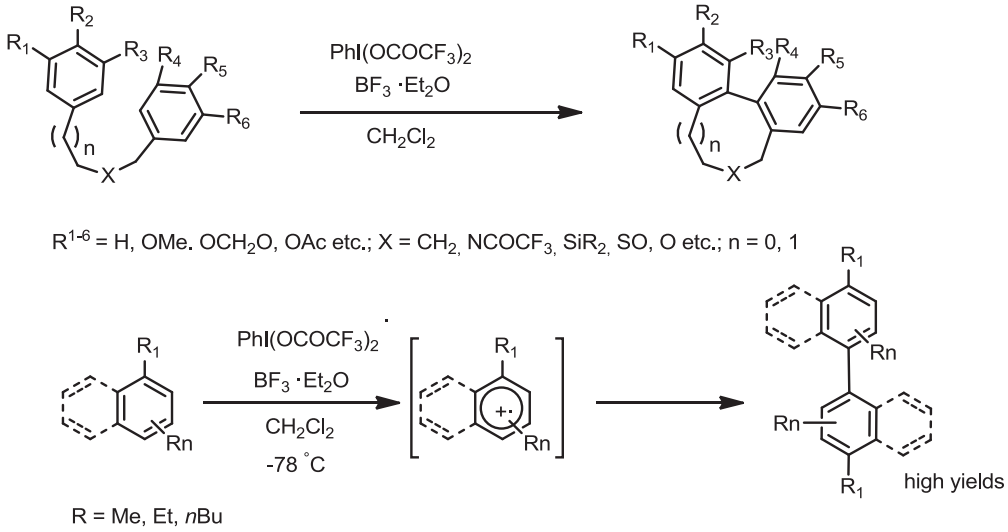
and NuH, and thus particularly attractive in cases where traces of metal are to be avoided. One of the most interesting applications of this reaction manifold is the aryl transfer to carbon nucleophiles, as in metal-free the α-arylation of enolates. First described by Beringer in the 1960's, the method (discussed in detail in the introductory section of Chapter 4) has since been perfected by several groups, and always takes place under basic conditions required to generate the active enolate intermediate that acts as the nucleophilic component (Scheme 1.19).[2,32] Incidentally, these α-arylation processes are directly relevant to the research presented in Chapter 4, where they will be compared to a conceptually different arylation manifold discovered during the course fo this doctoral investigation.

As a final note, it should be mentioned that the aryl transfer from the hypervalent iodine reagents under metal-catalyzed conditions have also shown a great potential in new classes of transformations. Significant progress has also been achieved in the arylation of the *N*- and *O*-nucleophiles, such as anilines, phenols and even carboxylic acids.[33]

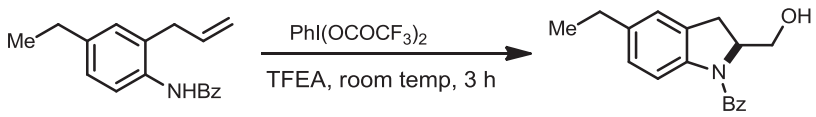
1.5. Previous results on the use of hypervalent iodine(III) compounds in our research group

In addition to their use in oxidative group transfer reactions, several emerging processes utilize λ^3-iodanes derivatives in the oxidative formation of carbon-carbon and heteroatom-heteroatom bonds. In 1912, the first direct oxidative coupling of arenes was reported by Scholl and Seer, who reported the formation of biaryls directly from arenes in the presence of stoichiometric $FeCl_3$.[34] Although several promising metal-catalyzed direct arene-arene (Ar-Ar) coupling reactions have been reported in recent years,[35] variants of the classical Scholl coupling continue enjoying widespread use, especially in intramolecular processes.[36] Despite the prevalent use of metal halides in such processes, a highly promising metal-free protocol has been developedin the last two decades, most notably by Kita and coworkers, which utilizes a combination of $BF_3{\cdot}Et_2O$ with phenyliodine bis(trifluoroacetate) (PIFA) asanexceptionally effective promotorof direct C-C coupling between two aromatic substrates.[37,38] The method was initially used in intramolecular coupling reactions[37a] and later applied to direct intermolecular cross-coupling (Scheme 1.19).[37b] Thus, Ar-Ar coupling between naphthalenes and polyalkylbenzenes was found to take place at the 1 position of the naphthalene.[37c] The process was later used by the Kita group for the arylation of thiophenes and pyrroles[37d] and by others in the construction of C-C[38a,b] and C-N bonds.[38d] A common denominator in all these examples, in addition to the use of a hypervalent iodine reagent, is the

presence of a Lewis or Brönstedt acid, most often $BF_3{\cdot}Et_2O$, found to be crucial in the activation of hypervalent iodine reagent. An interesting recent example from Tse and co-workers[38b] involves an analogous activation of $PhI(OAc)_2$ (PIDA) with a catalytic amount of $HAuCl_4$ to promote arene-arene coupling. The group of E. Domínguez has also found that PIFA can be used for the preparation of heterocycles through oxidative intramolecular hydroxyamidation of olefins (Scheme 1.20).[38e] This last example nicely illustrates two trends that characterize the modern chemistry of the hypervalent iodine reagent. In the first place, the outstanding ability of the high-energy λ^3-iodane molecules to cleanly generate the highly reactive intermediates, a nitrenium cation in this particular case. Secondly, the frequent use of fluorinated alcohols (trifluoroethanol, TFEA, in this case), which are believed to activate the hypervalent iodine reagent in a manner similar to other acidic additives.[24]



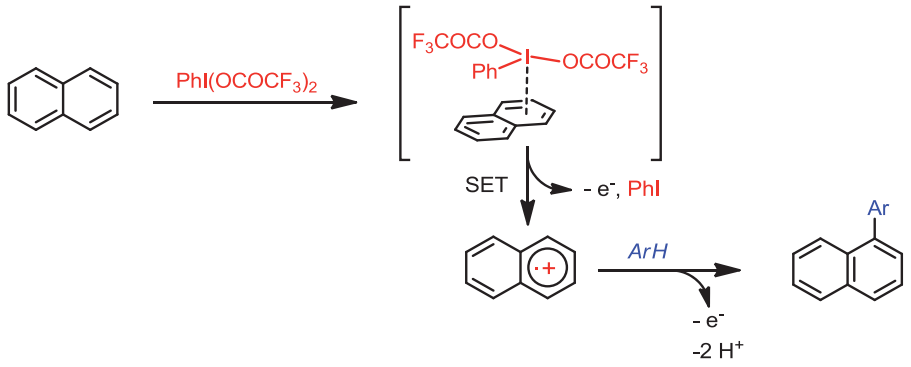
Scheme 1.19. Intra- and inter-molecular Kita's C-C coupling.



Scheme 1.20. Oxidative hydroxiamidation reactions using $PhI(OCOCF_3)_2$.

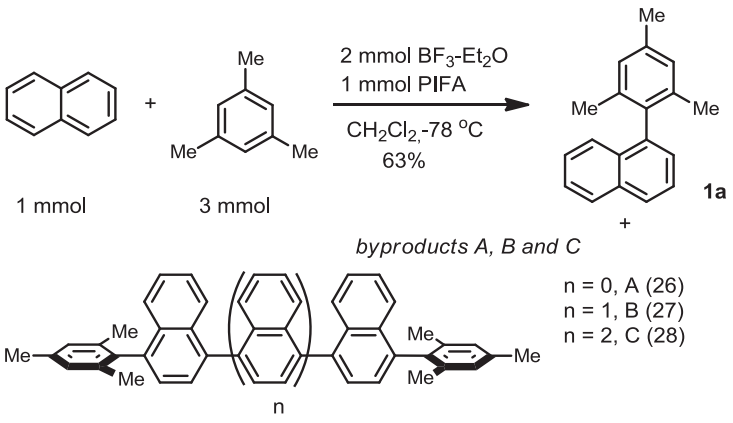
Recently in our research group, we have also begun investigating the use of the hypervalent iodine reagents in the direct C-C coupling reactions. Thus, as part of our group's work on hypervalent iodine reagents, Dr. Enrico Faggi reexamined the Kita protocol for the direct synthesis of 1-mesitylnaphthalene.[37c] As shown in Scheme 1.21, the reaction between naphthalene and mesitylene in the presence of PIFA/ $BF_3{\cdot}Et_2O$ followed the Kita coupling and afforded a 63% yield of 1-mesitylnaphthalene **1a** after 3

h at -78 °C. In the original article, the authors propose a coupling mechanism based on the formation of a transient PIFA-naphthalene complex, and a subsequent Single Electron Transfer from to PIFA affording a naphthalene radical cation which would then coupling with the second arene partner (Scheme 1.21). Although useful as a working hypothesis, several reaction aspects remain unclear, including the role played by the BF_3 additive.



Scheme 1.21. A mechanistic proposal for the Ar-Ar coupling based on a SET mechanism..

Upon further examining the reaction mixture, it was found that, in addition to the main biaryl product, a series of higher molecular weight side products were also produced, as evidenced by a series of new spots on the TLC trace of the reaction mixture. The principal component **A**was identified as 4,4'-dimesityl-1,1'-binaphthyl, **2a**, an assignment confirmed by the X-Ray diffraction analysis (Figure 1.6), and by the compound's independent synthesis *via*the Suzuki coupling between the corresponding 1,1'-dibromobinaphthalene and the mesityl zinc reagent. The minor components were then identified as the higher homologues of **2a**, **3a** and **4a**, respectively (Scheme 1.22).[39]



Scheme 1.22. Coupling between naphthalene and mesitylene

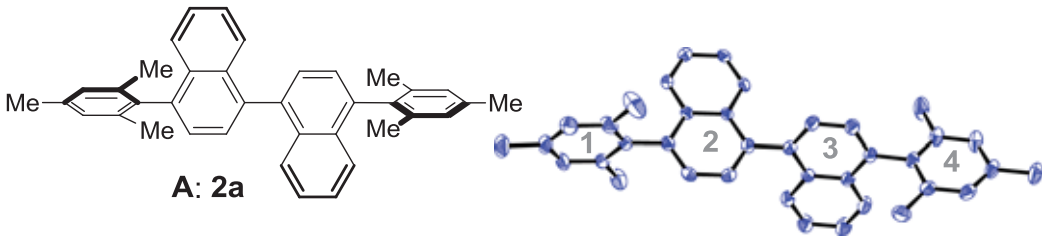


Figure 1.6. Connectivity and molecular structure of **2a** showing one of the two independent molecules.

After some optimization, the method was applied to the synthesis of several 1,1'-diarylated binaphthalenes, always with yields not exceeding the 30-40% yield (Figure 1.7).

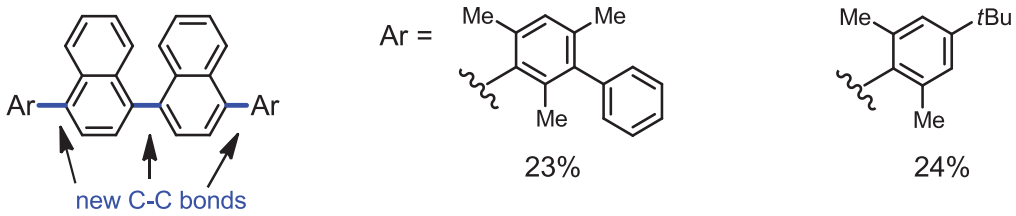
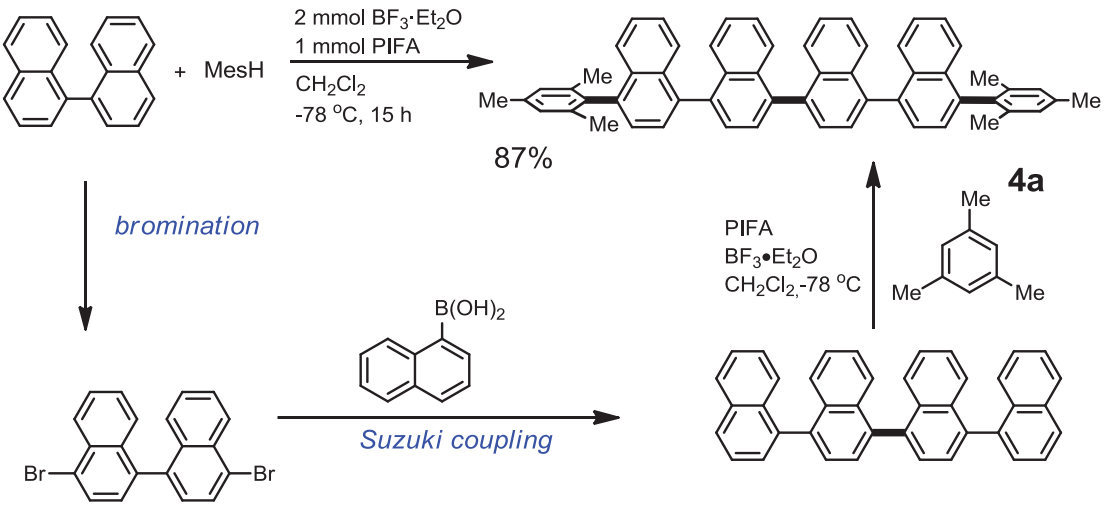


Figure 1.7. Hexaarenes obtained through direct arene-arene coupling

Despite these modest yields, the results were encouraging, as the method allowed for the formation of three new C-C bonds directly from unfunctionalized arenes. Furthermore, the methodology was extendable to the coupling of unfunctionalized 1,1'-binaphthalene with mesitylene to give a linear hexaarene**4** (*i.e.* diarylated quaternaphthalene) product in a remarkable chemoselective manner in 87% yield (Scheme 1.23). The connectivity of this compound was confirmed by its independent synthesis via a bromination/Suzuki coupling sequence (Scheme 1.23, bottom) followed by a Kita arylation step.



Scheme 1.23. Coupling of unfunctionalized 1,1'-binaphthalene with mesitylene

The formation of **4a** could be explained either by the initial mesytylene-binaphthalene coupling followed by dimerization of the product, or through the double arylation of the initially formed linear tetranaphthalene. In fact, further studies showed that the outcome of the process was highly dependent on the structure of the arene coupling partner, and that either the hexaarene **4** or a simple diarylated binaphthalene **2** was obtained depending on the arene structure. For example, the **4**/**2** ratio was found to vary from 17.4 for 1,3,5-trimethylbenzene (*i.e.* hexaarene **4** as main product) to just under 0.04 for pentamethylbenzene (almost exclusive formation of **2**) (Figure 1.8).

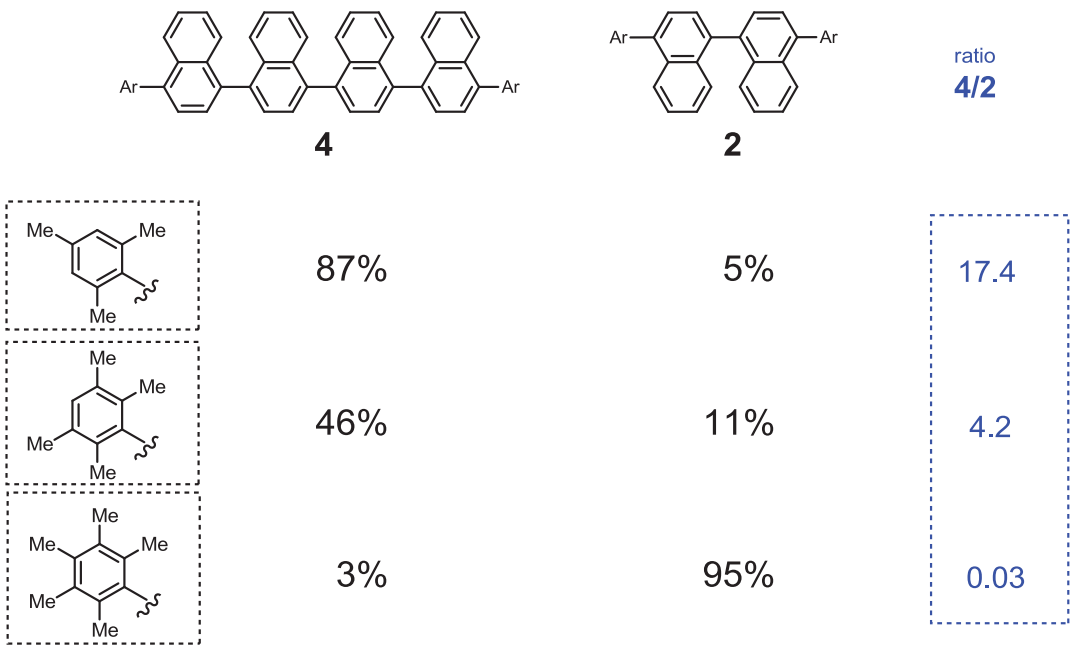
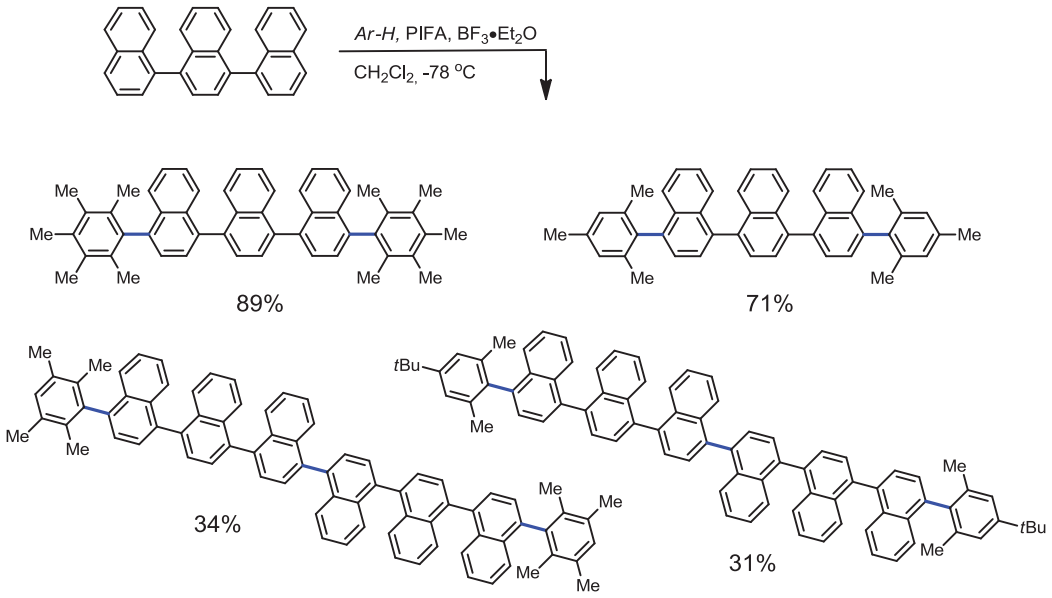


Figure 1.8. Relationship between ArH structure and the outcome of the Kita coupling (% yields) using1,1'-binaphthalene.

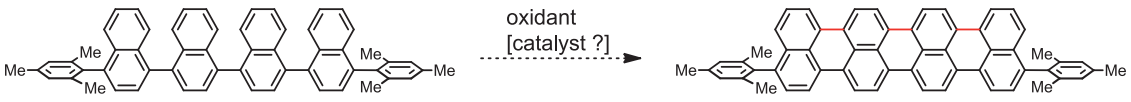
In a separate publication, Dr. Faggi and Wusheng Guo in our laboratories examined the reactivity of Nap_3 with mesitylene under the conditions similar to those used for the binaphthalene.[40] It was found that, unlike for Nap_2, the simple double arylation is somewhat preferred for Nap_3. The reactivity difference between Nap_2 and Nap_3 in the Kita-type arylation is noteworthy. Assuming the monoarylation as the first step, the preference for arylative dimerization in Nap_2 and for selective diarylation in Nap_3 indicates a significantly more favored second arylation in the latter. For example, good yield of the double arylation product in the coupling of **Nap_3** was obtained with pentamethylbenzene (89%), and triethylbenzene (71%) (Scheme 1.24). In contrast, the use of bulkier arenes drastically lowered the efficiency of the double arylation, accompanied by the appearance of the linear hexanapthalenesin yields, however, not exceeding the 30-35% (Scheme 1.24). Despite this modest efficiency, the procedure represents an assembly of a linear octiarene (counting the capping arenes using simple aromatic building blocks.



Scheme 1.24. Kita-type arylation of the parent ternapthalene **Nap$_3$.**

Finally, the oxidative arylation of the next higher homologue Nap$_4$ was found to undergo almost exclusive double arylation, giving the corresponding hexaarenes in good to excellent yields. Nevertheless, small amounts of the dimerizative coupling products were isolated in some cases (Figure 1.8), with efforts to optimize the yields of these oligonaphthalenes currentlyunderway in our laboratories.

Work is currently underway by other members of the group to further improve the oligonaphthalenes synthesis using hypervalent iodine compounds, for example to obtain a higher yield of the octinaphthalenes. The group is also working on converting the oligonaphthalenes thus obtained into short graphene segments through the ring-closing C-C coupling reaction (Scheme 1.25). Such molecules, termed “rylenes” by analogy with pe*rylene*, have been intensely studied in the last decade as promising components in organic electronic materials.[41]



Scheme 1.25. Towards assembly of rylene aromatics.

In addition, the group is studying the role played by Lewis acids, particularly $BF_3{\cdot}Et_2O$, in activating the hypervalent iodine compounds. The importance of this study goes beyond the Kita coupling, since the presence of an acidic additive is a constant leitmotif within the iodine(III)-based synthetic methods. So far, spectroscopic and DFT evidence have been obtained in the group showing an acid-based equilibrium

established in solutions containing bis(acyloxy)iodobeznene and BF3·Et_2O (Scheme 25). Importantly, the Gibbs Free energy (ΔG) in this process was found to range from a -7 kcal (favours the PIFA·BF_3 complex) for bis-acetate derivative (PIDA) to >+3 for the bis-trifluoroacetate analog (PIFA).

Based on this last results and all the introduction we thought to start the present doctoral thesis with a first objective based on an exploratory study of the possible use of PIFA, as an oxidative agent to activate C-H bonds, in the presence of a source of X^- (X = halogen) for the direct logenation of aromatic and/or β-dicarbonilyc compounds.

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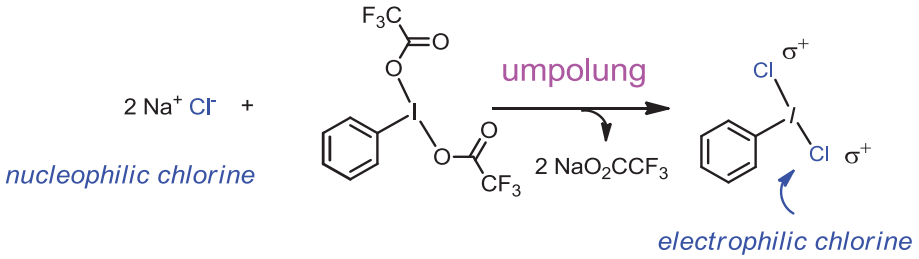
2、OBJECTIVES

Given the unique structural features and the interesting reactivity associated with the hypervalent iodine reagents,[1] and based on the group's precedents in the field[2], the aim of this doctoral work was to explore the use of **phenyliodine bis(trifluoroacetate)**, PIFA, along with the related compounds, in the oxidative functionalization of C-H bonds. During the elaboration of this project, new reactivity patterns were discovered, and their study has been incorporporated as part of this work.

Objective 1. Oxidative umpolung halogenation of arenes and ketones using formal halide (X^-)sources.

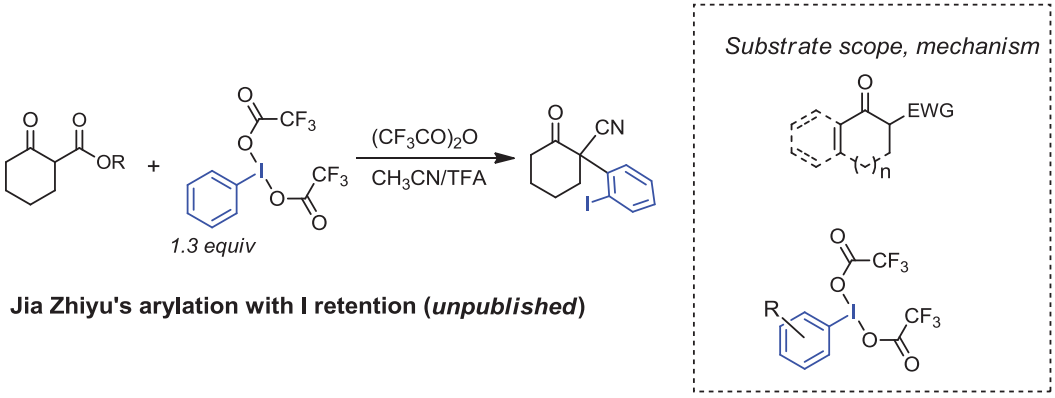
This research project stems from the observation that a charge reversal (*umpolung*) can be achieved for certain anions upon binding to a three-coordinate iodine center. Thus, a chloride anion, upon bonding to iodine(III) would acquire an electrophilic character, leading to the reactivity akin that of a formal Cl^+. The method might thus allow for the use of the readily accessible nucleophilic anions as electrophiles simply by adding a hypervalent iodine reagent.



We will test this phenomenon in two model systems: i) halogenation of arenes, and ii) α-halogenation of ketoesters. This work is the basis for the Chapter 3 of this dissertation.

Objective 2. The α-arylation process using aryliodine bis(trifluoroacetate): The scope and mechanism.

As part of our work on *the umpolung* α-halogenation of ketoesters, a side-product was identified whose structure was rationalized by the arylative transfer of an iodophenyl fragment to the α position of the ketone, with the formation of a new C-C bond. Here, we will aim to maximize the yield of this product and to dvelop the method into a new and versatile metal-free α-arylation process. Incidentally, essentially all of the α-aryl derivatives obtained during this work have been prepared for the first time.

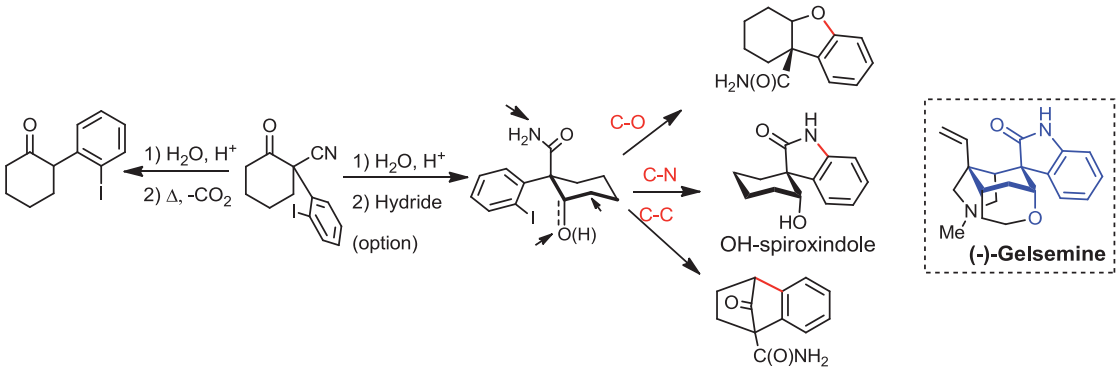


Jia Zhiyu's arylation with I retention (*unpublished*)

Within this line, a preliminary mechanism assessment will be carried out. The results obtained in this work are the basis for the first part of Chapter 4 of this dissertation.

Objective 3. Derivatization and further elaboration of the α-(2-iodoaryl)ketones.

The new iodine-containing α-arylketone offer an ample opportunity for further structure diversification. Thus, the presence of the iodine atom *ortho* to the new C-C bond allows for metal-catalyzed cross-coupling. In addition, further manipulation can be achieved through chemical manipulation of both the ketone group and the electron-withdrawing groups present. These reactivities patterns can be combined to offer an access to valuable matallacycles, such as the spiroxindole fragment present in natural products.



The results obtained in this work are the basis for the second part of Chapter 4 of this dissertation.

3. HALOGENATION USING HYPERVALENT IODINE(III) REAGENTS

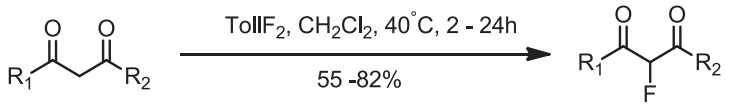
3.1. Overview of halogenation reactions involvng hypervalent iodine(III) reagents

Substitution of hydrogen by a halogen in aromatic compounds is a synthetically important electrophilic aromatic substitution reaction. The reactivity of the halogens in electrophilic aromatic substitution increases in the order $I_2 < Br_2 < Cl_2$. The molecular halogens are only reactive enough to halogenate quite reactive aromatics. Many reactions are run in the presence of Lewis acids, in which case a complex of the halogen with the Lewis acid is probably the active electrophile.

Direct conversion of aromatic and carbonyl compounds into haloaromatic and α-halocarbonyl compounds have been received considerable attention. As an example direct chlorination can be accomplished by using chlorination agents such as copper(II) chloride,[1] sulfuryl chloride,[2] *p*-toluenesulfonyl chloride,[3] N-chlorosuccinimide,[4] and tetraethylammonium trichloride.[5] However, most of these methods generally employed strongly acidic or basic conditions. Recently a lot of effort has been made to the development of new efficient reaction conditions on the halogenations of aromatic and carbonyl.

As we have said, hypervalent iodine(III) compounds have received continuous attention in organic synthesis and among others, have been used with success in fluorinations, chlorination, bromination and iodinations of some organic compounds. Next, we are going to explain the more important results obtained until this moment.

Fluorination. (Difluoroiodo)arenes are powerful fluorinating reagents towards organic substrates. Various β-dicarbonyl compounds can be selectively fluorinated at the α-position by 4-(difluoroiodo)toluene. For example, the monofluorinated products 1 can be prepared from β-ketoesters, β-ketoamides and β-diketones in good yields under mild conditions (Scheme 3.1).[6] Ketones cannot be directly fluorinated by (difluoroiodo)arenes; however, α-fluoroketones can be prepared by the reaction of silyl enol ethers with 4-(difluoroiodo)toluene in the presence of $BF_3{\cdot}OEt_2$ and the Et_3N-HF complex.[7]

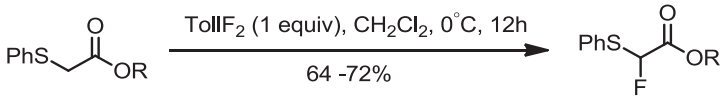


1

R^1 = Me, Pr, Ph, etc.
R^2 = OC_5H_{11}, Ph, Et, Bu^t, NMe_2, NPr^i_2, etc

Scheme 3.1. Fluorination of 1,3-dicarbonyl compounds

Treatment of α-phenylthio esters 2 with one equivalent of 4-(difluoroiodo)toluene affords the α-fluoro sulfides 3 in good overall yield (Scheme 3.2).[8] The α-monofluorination of sulfanyl amides can be achieved by treatment of α-phenylsulfanylacetamides with one equivalent of 4-(difluoroiodo)toluene under similar conditions.[9]

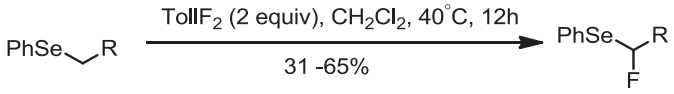


2 3

R = Ph, $CH_2CH{=}CHPh$, $CH_2CH{=}CMe$, etc.

Scheme 3.2. Fluorination of α-phenylthio esters

Arrica and Wirth have reported the monofluorination of a series of α-acceptor-substituted selenides 4 using (difluoroiodo)toluene (Scheme 3.3).[10] Although the yields are only moderate, the reactions are usually very clean and, under the reaction conditions used, no further oxidized products are observed.

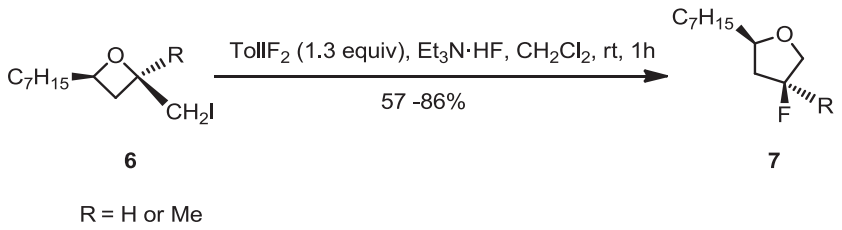


4 5

R = CO_2Et, CO_2Ph, $CO_2CH_2CH{=}CH_2$, CONHMe, CONMe, CN, etc.

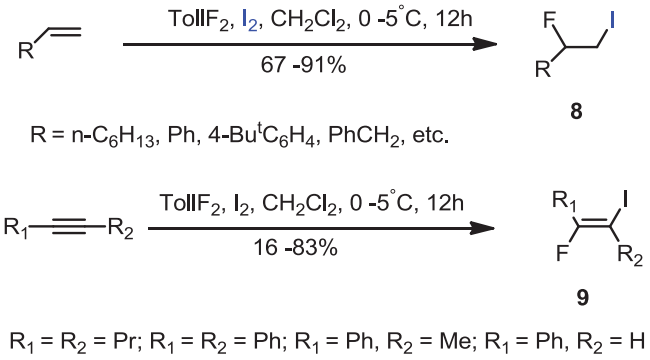
Scheme 3.3. Fluorination of α-acceptor-substituted selenides.

Fluorinated five- to seven-membered cyclic ethers were stereoselectively synthesized from iodoalky substituted four- to six-membered cyclic ethers by fluorinative ring-expansion reaction using (difluoroiodo)toluene.[11] A specific example of a fluorinative ring-expansion reaction leading to five-membered cyclic ethers 7 is shown in Scheme 3.4.[11]



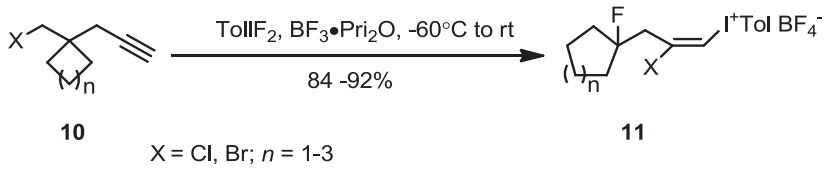
Scheme 3.4. Fluorinative ring-expansion.

The fluorination of alkenes and alkynes with 4-(difluoroiodo)toluene in the presence of iodine affords vic-fluoroiodoalkanes **8** and fluoroiodoalkenes **9** in moderate to excellent yields (Scheme 3.5).[12] This reaction proceeds in a Markovnikov fashion via the initial addition of the electrophilic iodine species followed by nucleophilic attack of fluorine anion. The analogous reaction of alkenes and alkynes with 4-(difluoroiodo)toluene in the presence of diphenyl diselenides affords the respective products of phenylselenofluorination in good yields.[13]



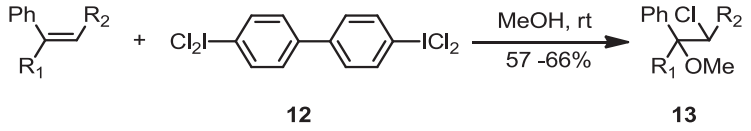
Scheme 3.5. Fluorination of alkenes and alkynes.

The reaction of 4-(difluoroiodo)toluene with a four-, five-, or six-membered carbocycle **10** afforded the ring-expanded (*E*)-δ-fluoro-β-halovinyl iodonium tetrafluoroborates **11** stereoselectively in high yields (Scheme 3.6).[14] This reaction proceeds via a sequence of λ^3-iodanation-1,4-halogen shift-ring enlargement-fluorination steps.



Scheme 3.6. Ring expanded reaction.

Chlorination. (Dichloroiodo)arenes have found practical application as reagents for chlorination of various organic sbustrates. Chlorinations of alkanes with (dichloroiodo)arenes proceed via a radical mechanism and generally require photochemical conditions or the presence of radical initiators in solvents of low polarity, such as chloroform or carbon tetrachloride.[15] The chlorination of alkenes usually has an ionic mechanism.[16] For example, reactions of (dichloroiodo)benzene with various monoterpenes in methanol proceed via the ionic mechanism and afford the respective products of chloromethoxylation of the double bond with high region- and stereoselectivity.[16] Likewise, the reaction of the recyclable chlorinating reagent, 4,4'-bis(dichloroiodo)biphenyl **12** with styrene derivatives in methanol affords exclusively the products of electrophilic chloromethoxylation **13** (Scheme 3.7).[17]

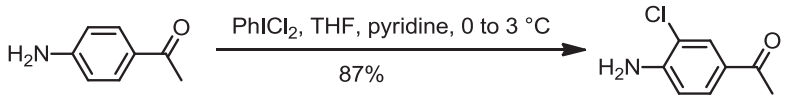


12 **13**

R_1 = H, R_2 = H; R_1 = Ph, R_2 = H; R_1 = H, R_2 = Ph

Scheme 3.7. Electrophilic chloromethoxylation

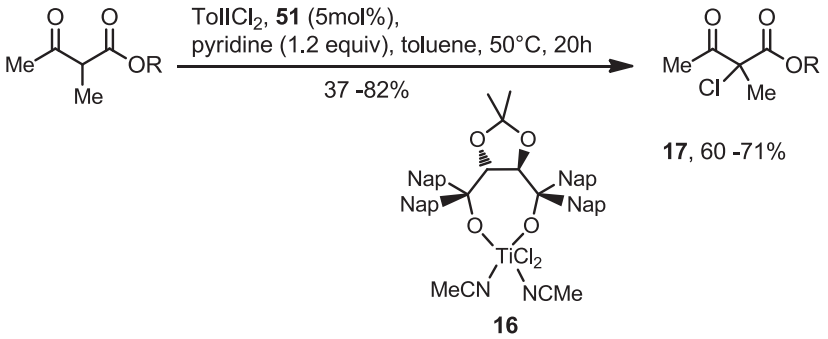
(Dichloroiodo)arenes can also be used for the chlorination of electron-rich aromatic compounds. Aminoacetophenone **14** is selectively chlorinated with (dichloroiodo)benzene to give product **15** in good yield (Scheme 3.8). This process can be scaled up to afford 24.8 kg of product **15** with 94% purity.[18]



14 **15**

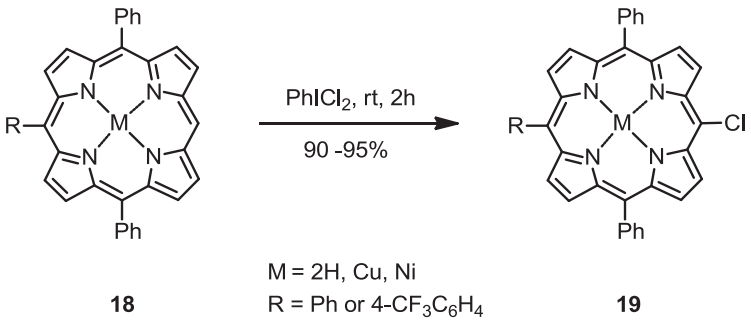
Scheme 3.8. Chlorination of 49

(Dichloroiodo)toluene was found to be an efficient chlorinating reagent in the catalytic asymmetric chlorination of β-keto esters, catalyzed by the titanium complex **16**, leading to the respective α-chlorinated products **17** in generally good yields and enantioselectivities (Scheme 3.9). The enantioselectivity of this reaction showed a remarkable temperature dependence, and the maximum selectivity was obtained at 50 °C.[19]



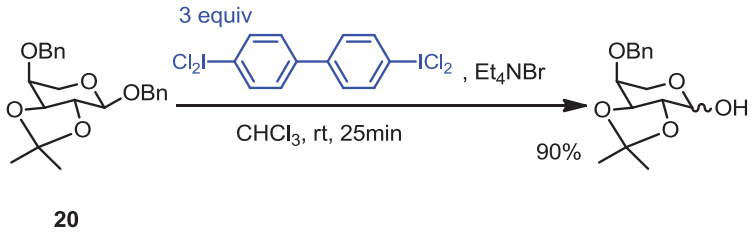
Scheme 3.9. Chlorination of β-ketoesters.

Treatment of 5,10,15-trisubstituted porphyrins **18** with (dichloroiodo)benzene affords the corresponding meso-chlorinated porphyrins **19** (Scheme 3.10).[20] The chlorination of 5,10,15,20-tetraarylporphyrins, in which all meso-positions are substituted, under similar conditions affords β-monochlorinated products in high yields.[20a]



Scheme 3.10. Preparation of meso-chlorinated porphyrins

A simple and mild system using bis(dichloroiodo)biphenyl in combination with tetraethylammonium bromide at room temperature has been developed for selective debenzylation of sugars. Acetates, benzoate, and sensitive glycosidic linkages are unaffected under the reaction conditions. A specific example of the debenzylation of benzyl 4-O-benzoyl 2,3-O-isopropylidene-α-L-arabinopyranoside **20** is shown in Scheme 3.11.[20b]

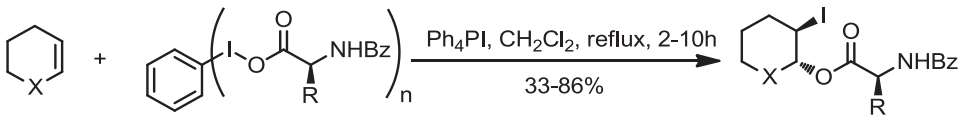


20

Scheme 3.11. Example of debenzylation of sugars.

(Dichloroiodo)benzene is commonly used as a reagent for the oxidation or chlorination of various transition metal complexes. Recent example include the oxidation of d8…d10 heterobimetallic Pt(II)-Au(I) complex to give the d7-d9 Pt(III)-Au(II) complex containing a Pt(III)-Au(II) bond,[21] and oxidations or chlorinations of palladium,[22] cobalt,[23]vanadium,[24] and molybdenum[25] complexes.

*Bromination and iodination.*Kirschning and coauthors have developed several experimental procedures for the stereoselective bromoacetoxylation or iodoacetoxylation of alkene based on the interaction of DIB with iodide or bromide anions.[26] The actual reacting electrophilic species in these reactions are the diacetylhalogen(I) anions, $(AcO)_2I^-$ and $(AcO)_2Br^-$, which can also be prepared as the polymer-supported variant.[27] A similar iodocarboxylation of alkenes using amino acid-derived iodobenzene dicarboxylates **21** selectively affords the respective amino acid esters **22** in moderate yields (Scheme 3.12).[28]

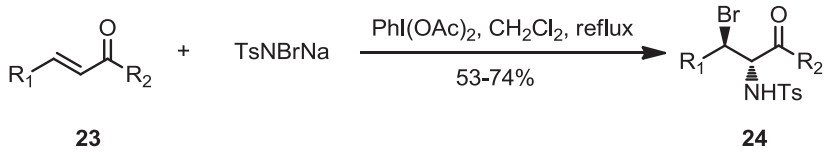


21 **22**

X = CH_2 or O; R = Me, CH_2Ph, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$

Scheme 3.12. Iodination of alkenes.

A new and convenient procedure for the aminobromination of electron-deficient olefins using Bromamine-T as nitrogen and bromine source promoted by (diacetoxyiodo)benzene was developed by Xia, Wu, and Wang.[29] This metal-free protocol is highly efficient and affords the vicinal bromamines with excellent stereoselectivities (Scheme 3.13).



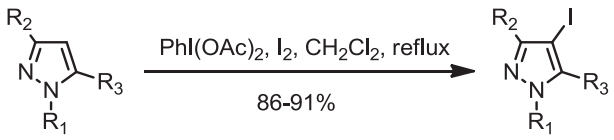
23 **24**

R_1 = 3,4-$Cl_2C_6H_3$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, Ph, etc,
R_2 = Ph, 4-ClC_6H_4, OMe, NEt_2, etc.

Scheme 3.13. Aminobromination.

Iodine in combination with [bis(acyloxy)iodo]arenes can be used for the oxidative iodination of aromatic and heteroaromatic compounds.[15] A mixture of iodine and BTI in acetonitrile or methanol iodinates the aromatic ring of methoxy substituted alky aryl ketones to afford the products of electrophilic monoiodination in 68-86% yield.[30] 1-Iodoalkynes can be prepared in good to excellent yields by the oxidative iodination of terminal alkynes with DIB, potassium iodine, and copper(I) iodide.[31] A solvent-free, solid state oxidative halogenations of arenes using DIB as the oxidant has recently been reported.[32]

Substituted pyrazoles can be iodinated to the corresponding 4-iodopyrazole derivatives by treatment with iodine and DIB or polymer-supported DIB at room temperature (Scheme 3.14).[33]



25 **26**

R_1 = H, Ph, 2,4-$(NO_2)_2C_6H_3$, 4-ClC_6H_4
R_2 = Me or Ph; R_3 = Me or Ph

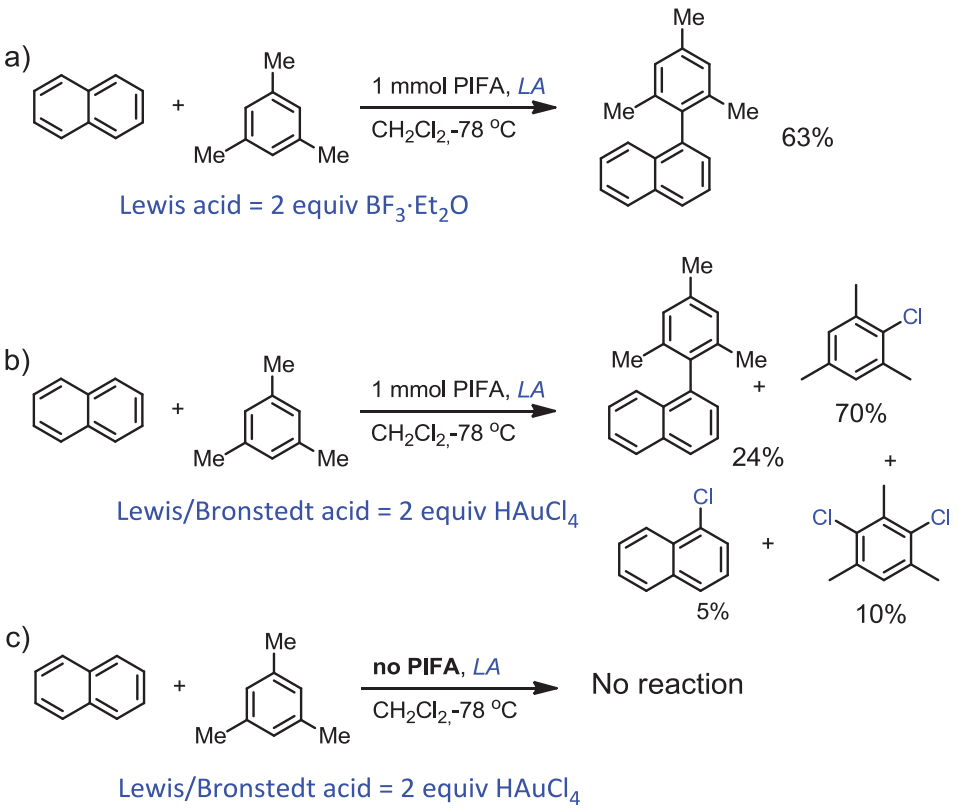
Scheme 3.14. Iodation of substituted pyrazoles

Various dihydropyridone derivatives can be efficiently iodinated by the treatment with N-iodosuccinimide (NIS) in the presence of [hydroxy(tosyloxy)iodo]benzene.[34]

The DIB/I_2 system can be used for the oxidative decarboxylation/iodination of carboxylic acids. Juaristi, Iglesias-Arteaga, and coauthors have utilized this reaction in the efficient syntheses of enantiopure 1-benzoyl-2(S)-tert-butyl-3-methylperhydropy - rimidin-4-one[35] and 2-substituted-5-halo-2,3-dihydro-4(H)-pyrimidin-4-ones.[36]

3.2. Results and discussion: Halogenation using PIFA and several halide sources

As was already discussed in Section 1.5 (the Group's precedents in Hypervalent Iodine Chemistry), the group's early work on transformation promoted by iodine(III) reganets centered on the oxidative coupling between arenes and substituted benzenes, following the work by Kita and coworkers.[37] Briefly, the method consisted in submitting the arene substrate mixture to a combination of phenyliodine (bis)trifluoroacetate (PIFA) and $BF_3{\cdot}Et_2O$ (Scheme 3.14a). The role played by the latter Lewis acid remains somewhat elusive, although the group's recent work provides evidence for an abstraction (full or partial) by the BF_3 species of one of the trifluoroacetate ligands from the hypervalent iodine centers, leading to a more electrophilic species and a stronger oxidant (Figure 3.1).[38] Indeed, no coupling takes place in the absence of a Lewis acid. The trifluoroborane reagent, however, is used in stoichiometric quantities, probably due to its consumption as an acid-base complex with the trifluoroacètic acid produced in the reaction.To test the scope of other potential activator we tested, among other additives to replace BF_3, tetrachloroauric acid, $HAuCl_4{\cdot}3H_2O$, first in stoichimoetric amounts (Scheme 3.14b). The reaction afforded a 24% GC yield of the expected mesitylnaphthalene product, along with the 1-chloromesitylene (70% GC) and smaller amounts of other chlorination products. The same reaction failed in the absence of PIFA (Scheme 3.14c).



Scheme 3.14. Attempted coupling of naphthalene and mesitylene with various Lewis acids.

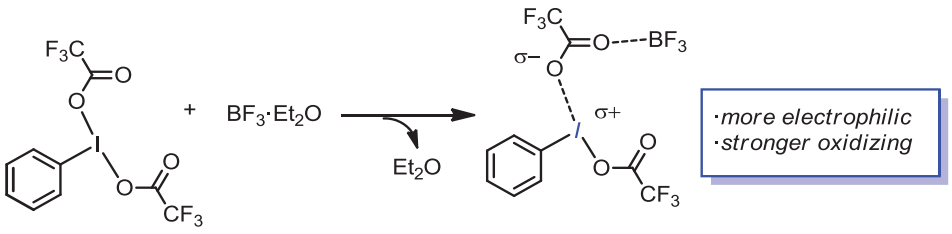
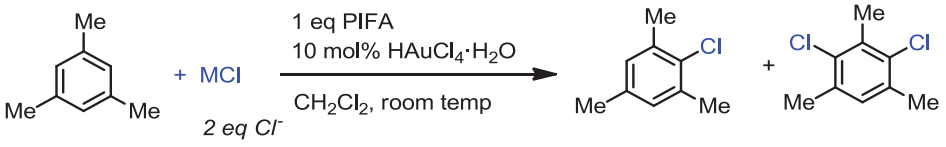


Figure 3.1. Proposal for Lewis Acid activation mechanism of the iodine(III) reagent

Suspecting that the efficient halogenation of mesitylene may constitute a gold-accelerated electrophilic substitution, with $HAuCl_4$ also serving as the halide source, we proceeded to submit mesitylene to catalytic amounts of $HAuCl_4$ in the presence of stoichiometric amounts of a range of chloride salts (Table 3.1).

Table 3.1. Chlronination of mesitylene using chloride ion and the chlorine source



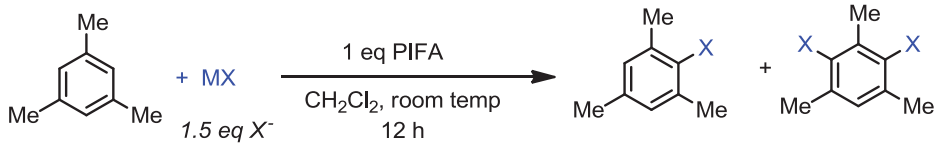
Run	MCl	% Conversion	MesCl (% GC)	$MesCl_2$ (% GC)
1	NaCl	100	50	40
2	$MgCl_2$	95	45	30
3	TBACl	80	40[a]	12
4	TBABr	40	35[b]	--

[a]Small amount of MesBr was also detected.
[b] The yield corresponds to MesBr.

As seen in Table 3.1, both inorganic chlorides employed, NaCl and $MgCl_2$, worked well, albeit with some of the overchlorination product observed (entries 1 and 2). In both cases, as expected, the hypervalent iodine reagent was fully consumed producing stoichiometric amounts of iodobenzene. The use of the more soluble tetrabutylammonium chloride did not improve the reaction performance (entry 3). In this case, small amounts of the bromination product, MesBr, were detected and rationalizedasstemming from the TBABr impurities present in the commercial chloride samples. Indeed, the use of TBABr (entry 4) led to approx. 35% GC yield of MesBr.

We initially speculated that the process might represent a gold-catalyzed halogenation of arenes. Indeed, the year this work was initiated (2010), Wang *et al.* reported the gold(III)-catalyzed bromination of arenes using *N*-bromosuccinimide (NBS) as an electrophilic source of halide.[39] In their work, the role of the Lewis acid catalyst consistint in increasing that electrophilicity even further through the binding of gold to one of the NBS oxygen atoms. Nevertheless, the hypothesis of gold catalysis in our work was subsequently discarded, since the halogenation could be carried simply by combining PIFA with a variety of chloride sources in the absence of any catalyst or additive. Aiming to reduce the formation of dichloromesitylene, the amount of chloride in further studies was reduced from 2.0 eq to 1.5 eq. As shown in Table 3.2, both NaCl and $MgCl_2$ performed well, affording >90% of MesCl after 12 h at room temp (entries 1 and 2), with only small amounts of $MesCl_2$. Interestingly, no product was observed the somewhat less reactive PIDA was used in place of PIFA (entry 3). Gratifyingly, the use of KBr led to a facile conversion of mesitylene to 1-bromomesitylene, albeit contaminated with some di-brominated product (entry 4). In this case, the bromination regiochemistry (that is, aromatic *vs* benzylic) was confirmed by spiking the GC sample with authentic 1-bromomesitylene. Finally, the use of NaI led to a rather clean, but somewhat sluggish iodination (entry 5), with the red color of the reaction mixture suggesting the formation of at least some molecular iodine.

Table 3.2. Chlorination of mesitylene using the PIFA/MCl combination.



Run	MX	% Conversion	MesX (% GC)	$MesX_2$ (% GC)
1	$MgCl_2$	98	90	<3
2	NaCl	97	92	<3
3	NaCl[a]	0	--	--
4	KBr	100	85	9
5	NaI	70	60	--

[a]The diacetate reagent $PhI(OAc)_2$used instead of PIFA.

Finally, we briefly tested a fluoride source in hopes of obtaining aryl fluorides. Unfortunately, the use of either CsF or the more soluble TBAF did not lead to any conversion of mesitylene. We noticed that a combination of CsF and PIFA in CH_2Cl_2 resulted in a thick suspension, which is likely the sparingly soluble $PhIF_2$.

The finding that no catalyst was required was somewhat disappointing, given the loss of the possibility to influence the reaction through catalyst design. Nevertheless, the process attracted our attention, given that the halogenation normally requiring an electrophile (*N*-halosuccinimide, molecular X_2), in our hands proceeded with a formal anionic halide. A priori, this *umpolung* from Cl^- to an electrophilic formal Cl^+ would take place within the coordination sphere of iodine(III), through generation of the know $PhICl_2$ (Figure 3.2a). The second possibility is the formation, and subsequent of a diaryliodonium halide intermediate, a manifold discussed in Section 1.4.2 (see Schemes 1.17 and 1.18 in Chapter 1). This second possibility, however, appears unlikely. In fact, the mesityl group in diaryliodonium tends does not engage easily in substitution, favouring, instead, the participation of the "other" aryl group in the formation of the Ar-Nu product.[40] Thus, in this case chlorobenzene, and not chloromesitylene, would be expected as the main product. Further mechanistic studies are discussed in the next section.

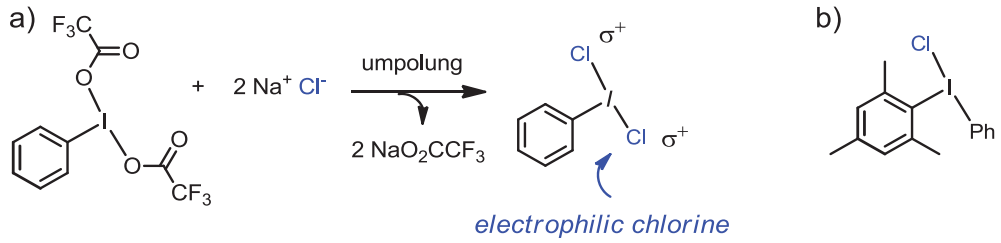
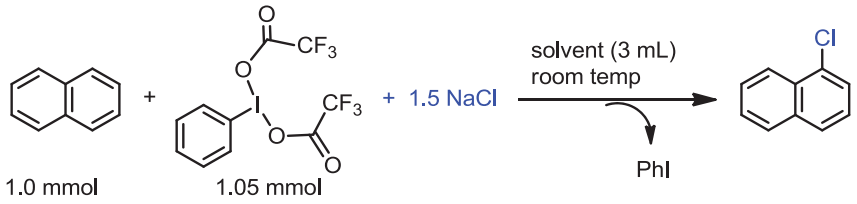


Figure 3.2. Chlorine atom umpolung through binding to a trivalent iodine(III) center.

The concept of converting a nucleophilic anion into a formally electrophilic cation could offer a conceptually interesting solution to a number of synthetic process, by allowing, through the use of iodine(III), to employ a wide variety of the readily availabel anionic nucleophiles (halides, azides, cyanides, etc. etc) as electrophilic reagents. Based on these preliminary results, as given the state of the art in this research area, we proceededtostudy the chlorination of the more challenging naphthalene substrate with PIFA and sodium chloride (Scheme 3.15).



Scheme 3.15. Chlorination of naphthalene using PIFA/NaCl combination.

The course of the reaction was followed by mass gas chromatography using $C_{11}H_{24}$ as the internal standard. Best results (66%)were achieved using a stochiometric amount of PIFA (1.05 eq), an excess of NaCl (1.5 equiv) in CH_2Cl_2 as solvent, at room temperature after 16 hours. Similar results were obtained using CH_3CN. As seen in Table 3.3, however, the use of other polar solvents, including the ethanol, did not improve the outcome. In all cases, the chlrorination took place in the 1 position, as confirmed by the ^1H NMR of the product; none of the 2-chloronaphthalene product was detected.

Table 3.3. Solvents screen in the *umpolung* chlorination of naphthalene.

	CH_2Cl_2	CH_3CN	THF	C_2H_5OH
Yield	66%	64%	33%	29%

Only marginal improvement in yield (68%) was achieved using a finely ground NaCl powder (coffee grinder). We also briefly revisited the possibility of accelerating the reaction through the use of a 5 mol% loading of transition metal and /or Lewis acid catalyst, including $Pd(OAc)_2$, $AuCl_3$, $FeCl_3$, $Eu(OTf)_3$, $Yb(OTf)_3$, $BF_3{\cdot}Et_2O$ (Table 3). The obtained results are summarized in the Table 3.4, and clearly show the failure of this approach.

Table 3.4. Catalyst screening in halogenation reaction of naphthalenes

Cat	--	$Pd(OAc)_2$	$AuCl_3$	$FeCl_3$	$Eu(OTf)_3$	$Yb(OTf)_3$	$BF_3{\cdot}Et_2O$[a]
Yield	66	41%	2%	6%	60%	--	--

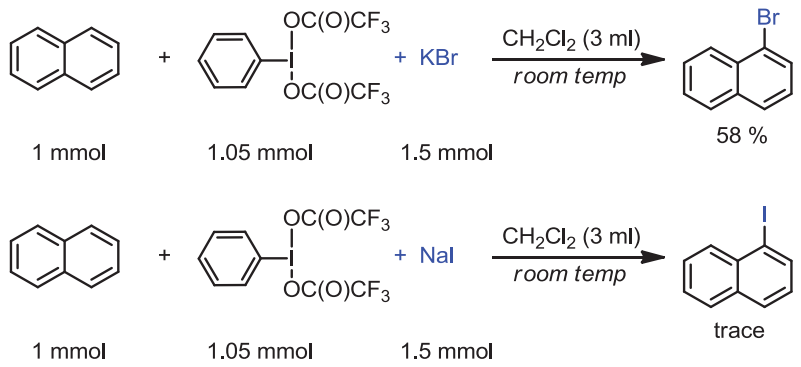
[a]10 mol% $BF_3{\cdot}Et_2O$ was added to the reaction.

Similarly, an increase in temperature led to a very poor reaction performance (Table 3.5), possible due to the thermal instability of the putative $PhICl_2$ intermediate and an unproductive formation of PhI and Cl_2 (see Section 3.3 for a more detailed discussion).

Table 3.5. Halogenation reaction of Scheme 1 at different temperatures

Temp, ^oC	% GC yield
0	69
25	64
60	17

Unfortunately, attempts to extend the methodology to bromination and iodination of naphthalene were only partially successful (Scheme 3.16). Thus, conducting the reaction under optimized conditions in the presence of KBr led to a 60% yield of 1-bromonapthalene. However, only trace amounts of iodonapthalenes were obtained using NaI. At this point we concluded that further work would be needed for this process to be become competitive. We, wondered however, whther other substrate clases would also be amenable to such *umpolung* halogenation.



Scheme 3.16. Attempted bromination and iodination of naphthalene.

We then went on to test the halogenation of other substrates like β-dicarbonyl compounds.The conditions of thehalogenations of naphthalene (NaCl + PIFA)were applied to ethyl 2-oxocyclohexanecarboxylate as substrate. Unfortunately, theonly a 32% GC yield of the target 1-chloro-2-oxocyclohexanecarboxylate was obtained.In light of this, we chose the test the more active titanium tetrachloride. In concrete, by reaction with PIFA and Titanium(IV) Chloride 2-acetyl-2-chlorocyclohexanone, ethyl 1-chloro-2-oxocyclohexanecarboxylate and ethyl 1-chloro-2-oxocyclopentanecarboxylate were obtained (Figure 3.3).

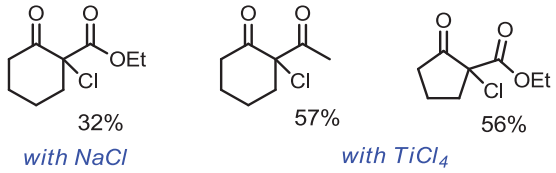
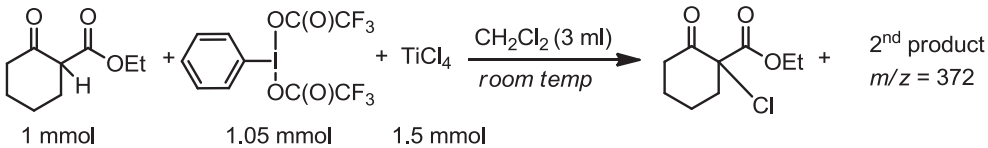


Figure 3.3. Some examples of the *umpolung* chlorination of β-dicarbonyl substrates.

Interestingly, during the optimization of the chlorination of the ethyl 2-oxocyclohexanecarboxylate (Scheme 3.17),the formation of the expected α-chloroketoester was accompanied by the appearance of a large amounts of second product, as clearly observed on the GC trace (Figure 3.4).



Scheme 3.17. Chlorination reaction of β-ketoester

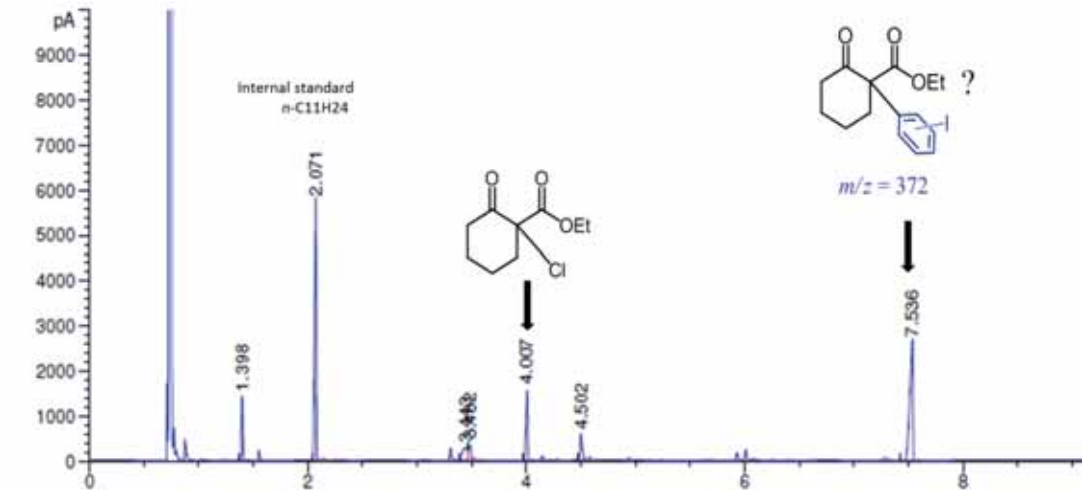


Figure 3.4. GC spectrum corresponding to reaction of Scheme 17

This new species had the molecular weight of 372 (by GC-MS), which was consistent with the incorporation of a C_6H_4I group (*i.e.* a –PhI fragment) to the substrate ketoester. From this reaction mixture, this substance was isolated in a 30% yield and was identified by NMR as the α-(1-iodophenyl)2-oxocyclohexanecarboxylate, with the iodine atom incorporated *ortho* to the newly formed C-C bond. Given the interesting features of the new chemical process that this product represents, the scope and mechanism of this transformation will be discussed in the next chapter.

As for the *umpolung* halogenation result, we felt that any further improvement in the efficiency of the process will liley be conditioned by the understanding of the reaction mechanism. Thus, some preliminary mechanistic investigation is presented in the next section. At this time, however, we considered it more urgent to priorize our efforts in the newly discovered arylation reaction (Figure 3.4), given that it might give access to the hitherto unexplored classes of substances. Indeed, the arylation product isolated from the reaction in Scheme 1 had never been reported prior to this work. As a consequence, further halogenation work will be carried out by other members of the group in the future.

3.3. Studies on the mechanism of chlorination reaction with PIFA

Given the presence of the fluorine atoms in the hypervalent iodine reagent used in these studies, ^{19}F NMR was chosen as ahighly convenient tool for studying the reaction mechanism. As reference, the ^{19}F NMR spectra of phenyliodine bis(trifluoroacetate) and the trifluoroacetic acid were recorded (reference to internal hexafluorobenzene, not shown). As expected, the spectrum of PIFA showed, in addition to the main PIFA

resonance at -74.5 ppm, small amounts of the trifluoroacetic acid (-76.3 ppm) likely due to the hydrolysis of the hypervalent iodine reagents (see section 1.3.2).

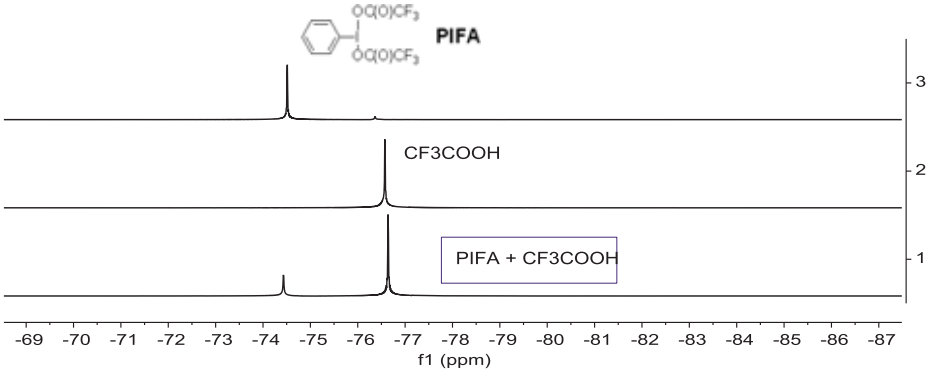
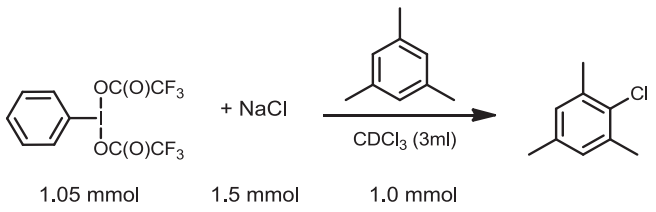


Figure 3.5. Comparison of the ^{19}F NMR spectra of PIFA and trifluoroacetic acid (C_6F_6 as the internal standard).

Next, the model chlorination of mesitylene (Scheme 3.18)was followed by ^{19}F NMR in $CDCl_3$ (Figure 3.5). First, PIFA and NaCl (1:1.5) were mixed in $CDCl_3$ andstirred in a 5mL flask for 7hours (a quantity of an insoluble solid remained throught the reaction). With this test, we expected to detect the putative products of the ligand exchange between PIFA and NaCl, namely either the known $PhICl_2$(indirectly through NaO_2CCF_3 liberation) (see Figure 3.2a) or the mixed ligand species $PhI(Cl)(O_2CCF_3)$. However, a^{19}F-NMR analysis of an aliquot taken directly from this mixture (Figure 3.5, compare a and b) showed the descrease in the intensity of the PIFA resonance and the concomitant riseof the concentration of CF_3COOH/CF_3COONa, with no other ^{19}F resonance present.Mesitylene (1 equiv.*vs* PIFA) was then added to the solution leading to the complete disappearence of the PIFA resonanceafter 1 hour. According to the GC analysis, the mixture contained a fill equivalent of PhI, along with some chloromesitylene product and unreacted mesitylene.



Scheme 3.18. Chlorination of mesitylene

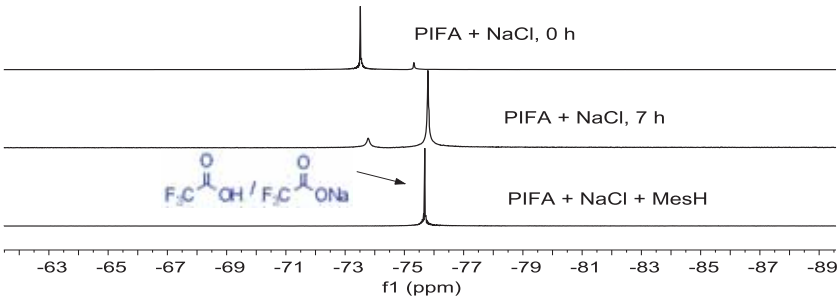


Figure 3.6. ^{19}F-NMR of PIFA, NaCl with mesitylene

At the same time we carried out some ^{1}H-NMR experiments of a mixture of PIFA and NaCl (1:1.5) (0h, 3h and 7h). If we compare the spectrum of PIFA (Figure 3.7) with the one corresponding to the mixture of PIFA and NaCl we can notice that PIFA disappeared with the consequent formation of other compounds coming from the substitution of trifluoroacetate ligand by chlorine.Indeed through comparsion of the ^{1}H NMR spectrum of the reaction mixture with that of an authentic sample of $PhICl_2$, it can be deduced that, upon contact with NaCl, the starting $PhI(O_2CCF_3)_2$is transformed, first, into an intermediate species, and then, after 7 h. In all likelihood, the intermediate species observed after 3 hours is the mixed ligand $PhI(Cl)(O_2CCF_3)$ (Figure 3.8).

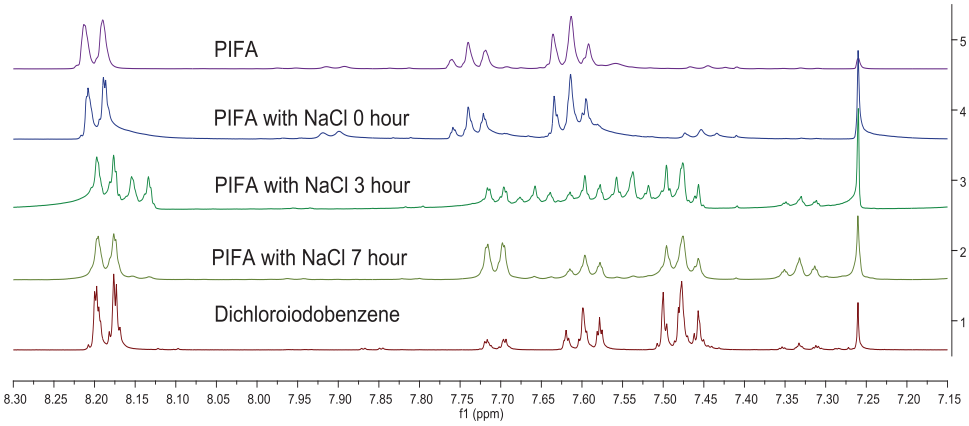


Figure 3.7. ^{1}HNMR of a mixture of PIFA and NaCl at different times.

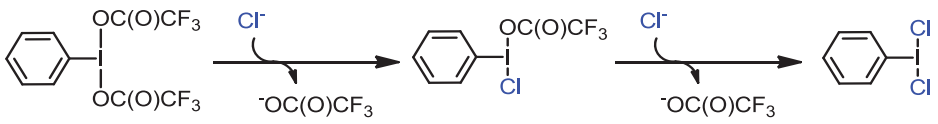


Figure 3.8. Sequential ligand exchange from PIFA to $PhICl_2$.

Then after 7 hours mesitylene(1 equiv)was added to the solution mixture. As shown in Figure 3.9 compoundsboth chlorinated species disappeared, with a concomitant appearance of iodobenzene (and chlorinated mesitylene derivatives). So, we surmise that these are the real intermediates of the mechanism for the chlorination reaction of mesitylene (Scheme 3.18).

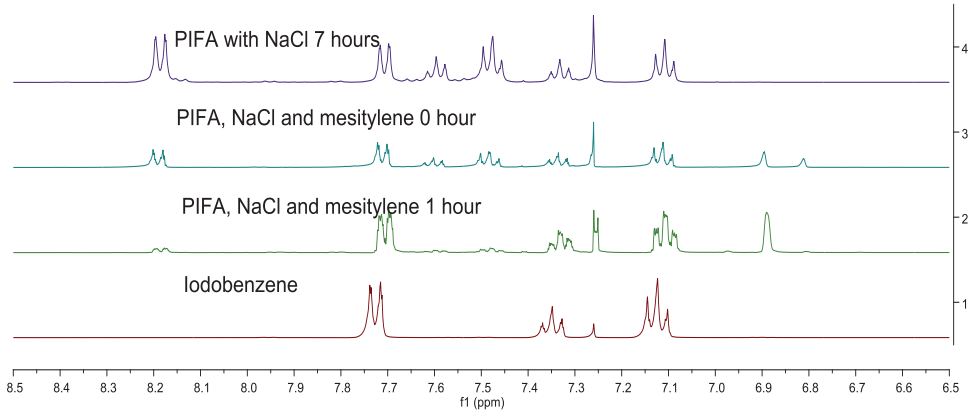
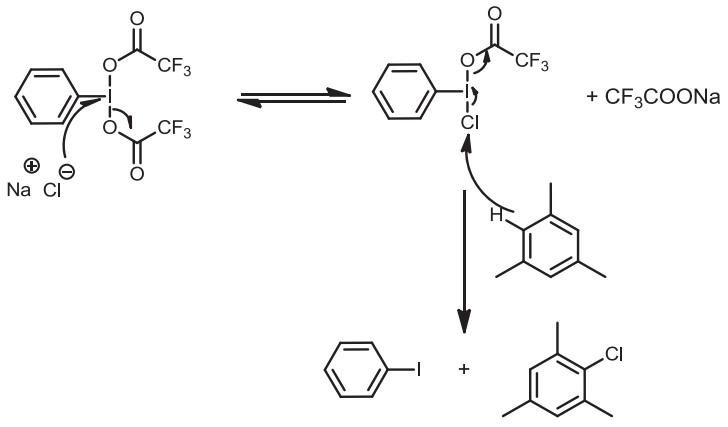


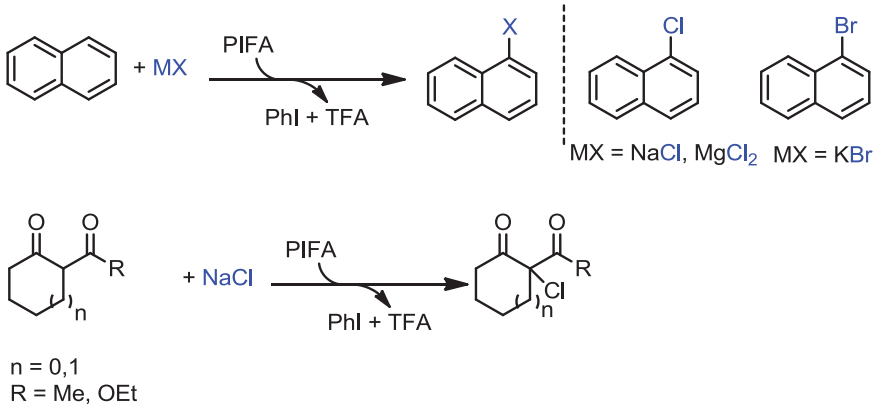
Figure 3.9. ^{1}HNMR of a mixture of PIFA, NaCl and mesitylene at different times

So, we propose a mechanistic hypothesis for this reaction consisting of a first displacement of one trifluoroacetate ligand from PIFA by chlorine atom, followed by a reaction of mesitylene with chlorine and displacement of the second trifluoroacetate which is consequent with the formation of CF_3COOH and iodobenzene (scheme 3.19).



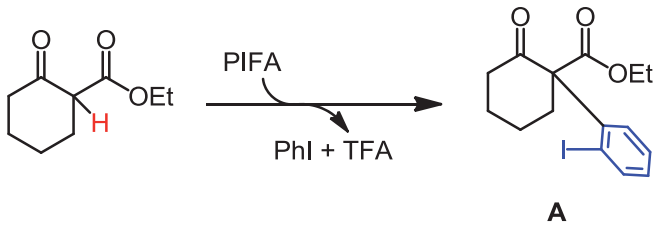
Scheme 3.19. Proposed Mechanism of Chlorination of mesitylene.

As a conclusion of this part we have explored the halogentation of mesitylene and naphthalene as examples of arene compounds and a β-dicarbonyl compounds in the presence of PIFA and employing the appropriate metal halide.



Scheme 3.20. Halogentation of arenes and β-dicarbonyl compounds

Also, we have found the presence of an interesting arylated compound A. In the next chapter we will study this new arylating process promoted by PIFA (scheme 3.21).



Scheme 3.21.

3.4. Experimental section

3.4.1. *General remarks*

Nuclear Magnetic Resonance (NMR) recorded at the *Servei de RessonanciaMagnetica Nuclear* of the *Universitat Autonoma de Barcelona*. 1H-NMR and ^{13}C-NMR spectra were recorded using Bruker instruments (DXP-250, DXP-360 and AVANCE-III 400). Chemical shift (δ) are given in ppm using the residual non-deuterated solvent as internal reference. ^{19}F-NMR spectra were recorded using Bruker instrument (AVANCE-III 400).

Thin-Layer Chromatography (TLC) was performed using 0.25 mm plates (Alugram Sil G/UV_{254})

Flash Chromatography was performed under nitrogen pressure on a *Macherey-Nagel GmbH & Co KG* silica gel which had a particle size of 230 – 400 mesh and pore volume of 0.9 mL/g.

Gas Chromatography (GC) was performed with an Agilent Technologies 7890A instrument equipped with an *Agilent HP-5* (30m x 0.32m x 0.25 um) capillary column. Unless otherwise stated, instrument methods used to monitor catalytic tests are: *Normal* 75 T_0 =75 °C, t_0 = 0.5 min, 25 °C/min T_f = 240 °C, t_f = 4 min. Sometimes longer method was used: Long 75 T_0 = 75 °C, t_0 = 0.5 min, 25 °C/min T_1 = 240 °C, t_1 = 2min, 10 °C/min, T_2 = 280 °C, t_2 = 5 min (*long*).

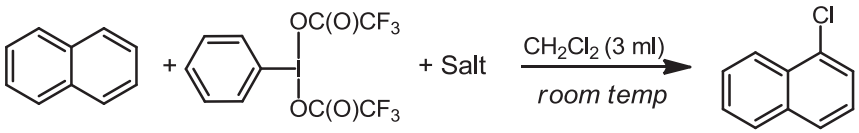
Other details: When required, experiments were carried out using standard vacuum and Schlenk techniques under N_2 or Ar atmosphere using dry solvents which were distilled and cannula or syringe transferred.

Commerical reagents were directly used as received. Na_2SO_4 and $MgSO_4$ used to dry the organic layers were anhydrous.

Dry solvents were prepared using standard methods: CH_2Cl_2 and CH_3CN were distilled over CaH_2. Commercial dry DMF from *Sigma-Aldrich* was used without further purification. In some experiments, dry solvents were obtained from two instruments: PureSolv (Innovative Technologies: THF, CH_2Cl_2, Pentane).

3.4.2. *Halogenation of Arene*

General procedure:

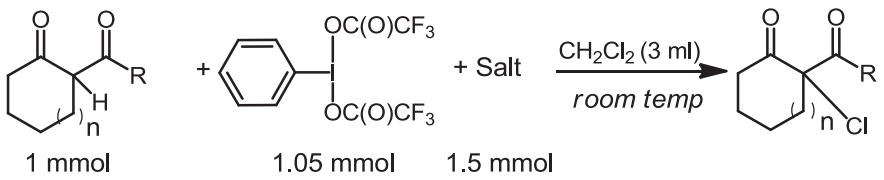


1 mmol 1.05 mmol 1.5 mmol

The chloride salt (Sodium Chloride or Magnesium chloride, 1.5 mmol) was added to a stirred solution of the appropriate starting substrate (1 mmol) in CH_2Cl_2 (3 mL). PIFA (1.5 mmol) was added in one portion to the above solution. The reaction was lasted overnight. $C_{11}H_{22}$ as internal standard was added to above solution. GC and GC-MS were used for analysis the yield.

3.4.3. *Halogenation of β-dicarbonyl substrates*

General procedure:

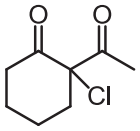


1 mmol 1.05 mmol 1.5 mmol

n = 0, 1
R = Me, OEt

The chloride salt (sodium chloride or titanium(IV) vhloride, 1.5 mmol) was added to a stirred solution of the appropriate starting substrate (1 mmol) in actonitrile (2 mL). PIFA (1.5 mmol) was added in one portion to the above solution. The reaction was left stirring overnight. At this time, TLC analysis showed the disappearence of the starting substrate. The reaction mixture was then diluted with diethyl ether (15 mL) and washed with water (20 mL). The aqueous layer was extracted with ether (10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

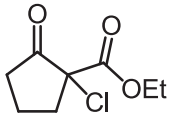
2-acetyl-2-chlorocyclohexanone



AcOEt: Hexane 1:10 (R_f = 0.5). White oil, 99mg, yield: 57%.

^{1}H NMR (360 MHz, $CDCl_3$) δ 2.29 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.08 (s, 1H), 1.71 – 1.56 (m, 1H).

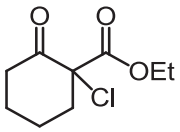
Ethyl 1-chloro-2-oxocyclopentanecarboxylate



AcOEt: Hexane 1:10 (R_f = 0.3). White oil, 106mg, yield: 56%.

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.2 Hz, 1H), 2.75 (ddd, *J* = 14.4, 10.8, 7.2 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.46 – 2.31 (m, 1H), 2.23 – 2.06 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 2H).

Ethyl 1-chloro-2-oxocyclohexanecarboxylate

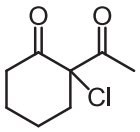


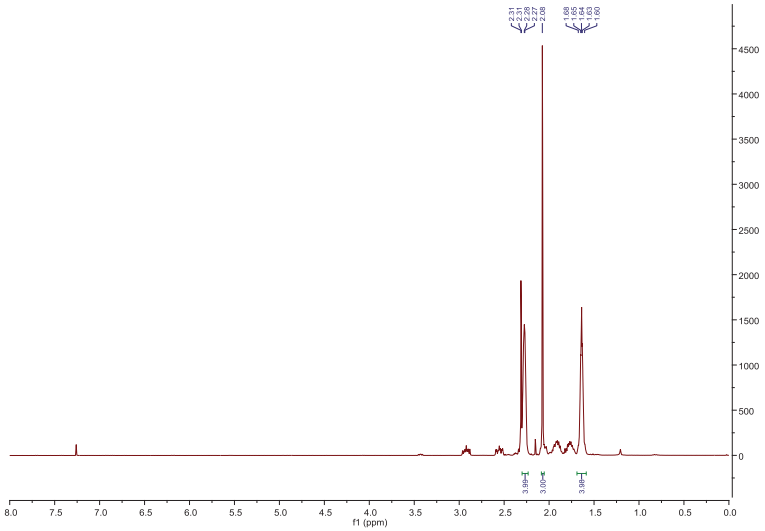
AcOEt: Hexane 1:10 (R_f = 0.8). White oil, 61mg, yield: 30%.

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.2 Hz, 2H), 2.91 – 2.75 (m, 2H), 2.44 (ddd, *J* = 21.6, 10.8, 7.2 Hz, 1H), 2.30 – 2.07 (m, 2H), 2.02 – 1.81 (m, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

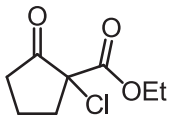
3.5. Spectral data.

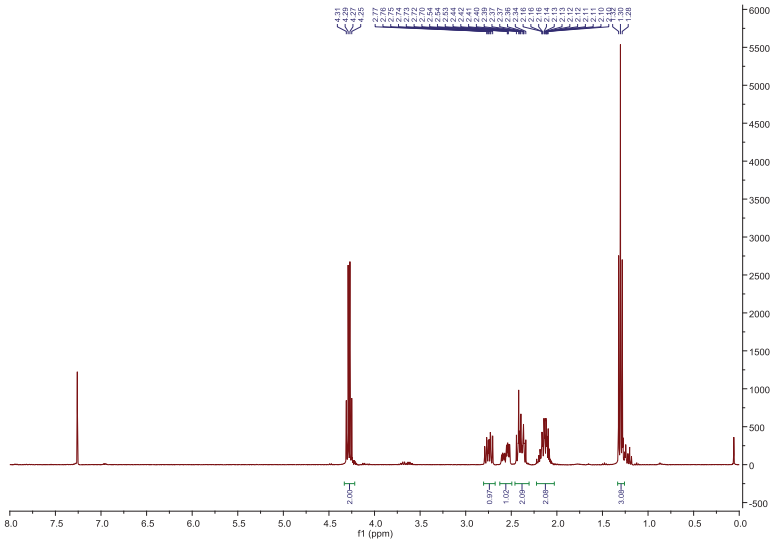
2-acetyl-2-chlorocyclohexanone



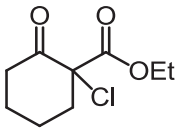


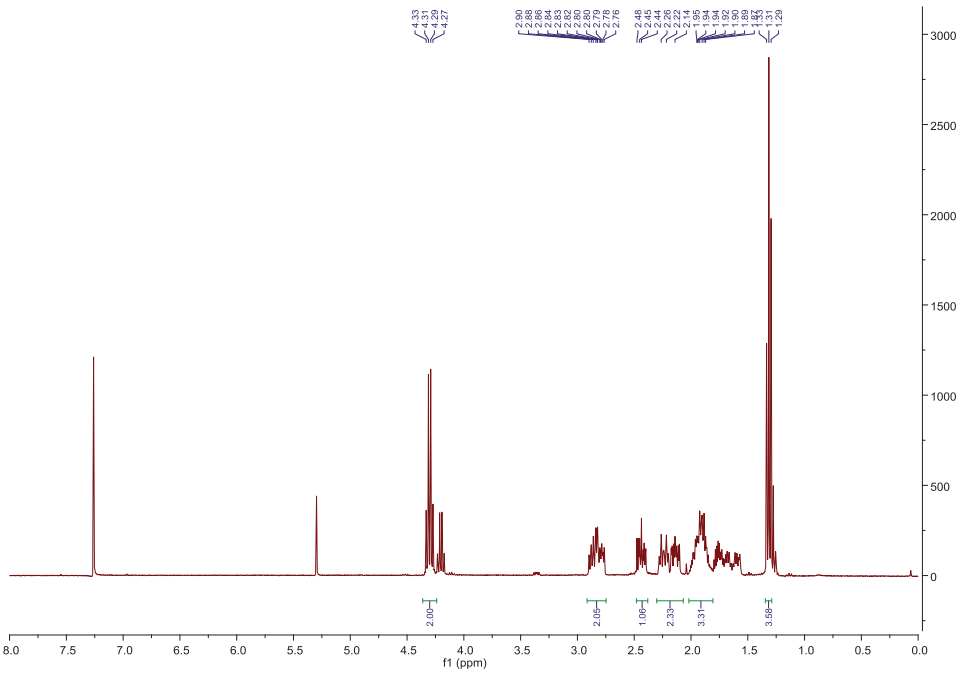
ethyl 1-chloro-2-oxocyclopentanecarboxylate





Ethyl 1-chloro-2-oxocyclohexanecarboxylate





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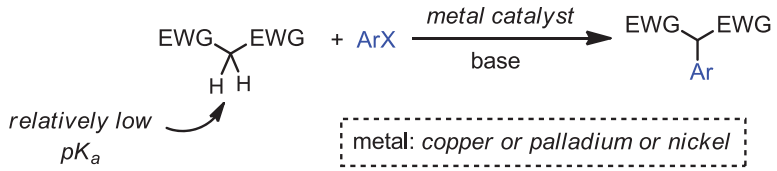
4. HYPERVALENT IODINE REAGENTS IN THE α-ARYLATION OF ACTIVATED KETONES

4.1. Introduction

4.1.1. *Precedents in metal-catalyzed α-arylation of substrates containing activated methylene compounds.*

Since the 1980's, the α-arylation of ketones has constituted an important class of carbon-carbon bond-forming processes. Closely related to this class of transformations, the arylation of substrates bearing two electron-withdrawing moieties linked to a methylene group has attracted much attention because it provides an easy access to important classes of biologically active natural/synthetic products.[1] The values for pK_a of the methylene CH unit in these substrates, significantly below that of a "normal" carbon-hydrogen, have represented a particulalry important parameter to be considered in the choice of experimental conditions, includingin transitionmetal catalysis. In this chapter, the overview of the literature data on the transition metal-catalyzed arylation of the dicarbonyl and alkyl cyanoacetate compounds has been subdivided into two parts. In the first section the results of copper-catalyzed arylation processes will be discussed. The second part is concerned with the literature on the palladium and nickel-catalyzed arylation. This area has been the subject of several reviews, most recently by Johanssen and Colacott.[2]



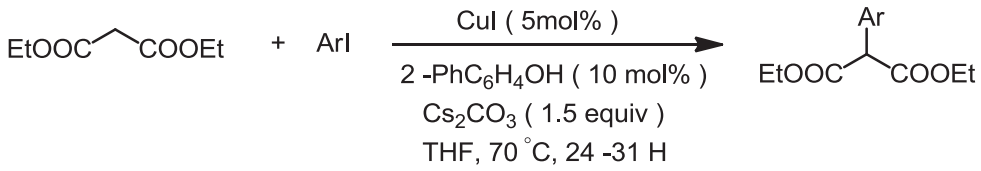
Copper-catalyzed arylations

In the 1970s, McKillop *et al*. established that C-H acids such as β-ketoesters, can be C-arylated in good to excellent yields by reaction with a variety of haloaromatic carboxylic acids in the presense of NaH and a catalytic amount of CuBr.[3]Despite this observation, up until the 1980s and even 1990s, most of such processescontinued to employ stoichometric amount of copper salts in a classical Ullmann-type fashion.[4]

In a pioneering 1993 publication, Miura *et al.* described a synthetically interesting procedure in which a catalytic amount of the air stable copper(I) iodide(5 mol%) was employed in the coupling between ethylcyanoacetate and iodobenzene, albeit at

somewhat elevated temperature (120 °C) and using 2 equiv of the arylating agent.[5] Importantly, the authors showed that CuI alone is capable of catalytic turn-over. It was, however, subsequent publications from several groups that showed that milder conditions could be achieved by using an appropriate ancillary ligand to modulate the reactivity of the copper center. Thus, a mild, general method for the arylation of malonates was described by Hennessy and Buchwald in 2002.[6]The method involved the treatment of a molar excess of the dicarbonyl substrate with aryl halide in the presence of Cs_2CO_3 and catalytic amount of CuI and the 2-phenylphenol as additive(Table 4.1). Imprtantly, the reaction proceeded at 70 °C, a far cry from the previously required 120 °C. The exact role played by 2-phenylphemol in the reaction was not elucidated, but the most likely scenario, confirmed by later work from this and other groups, is the formation of the reactive copper(I)-phenolate species as the active catalyst. Indeed, in the absence of any additive the arylation proceeds to only 80% conversion.

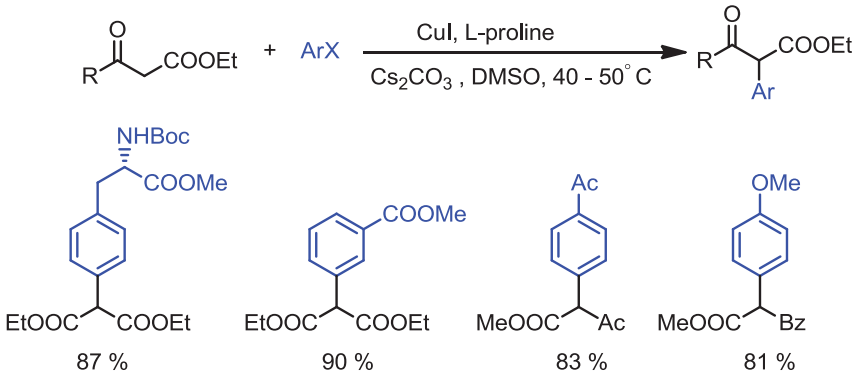
Table 4.1. CuI/2-phenylphenol-catalyzed arylation of diethyl malonate with aryl halides (*Hennessy and Buchwald, 2002)*



Entry	Ar	Yield (%)
1	1-naphthyl	96
2	2-*i*-PrC_6H_4	84
3	4-ClC_6H_4	94
4	3-pyridyl	73
5	3-$CF_3C_6H_4$	89
6	2,4-$(Me)_2C_6H_3$	87

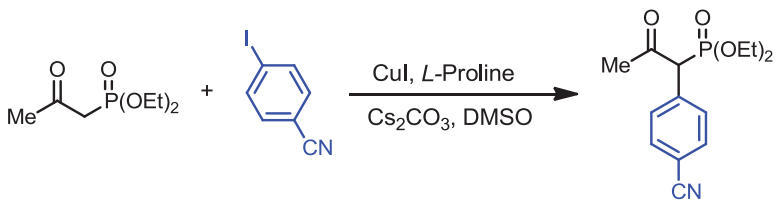
The importance of the supporting ligands in the CuI-catalyzed arylation of activated methylene compounds, demonstrated by Buchwald and He, was

subsequently confirmed in several later publications. An interesting example is the use of the simple *L*-Proline (first established as efficient ligands in the related copper-catalyzed amination) by the groups of Jiangand Ma[7]. Thus, *L*-Proline has been used as an ancillary ligand for the arylation of several ketoesters, with reactions at temperatures as low as 40°C (Scheme 4.1).[8]



Scheme 4.1. CuI/L-proline-catalyzed intermolecular arylation of activated methylene compounds.

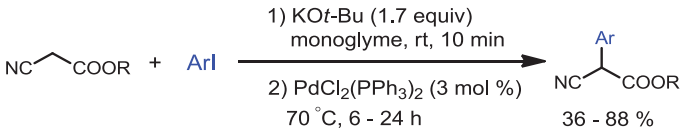
Building on the reactivity of the bulky phenols in copper-catalyzed processes (see above), the the group of Tanimori introduced BINOL as an efficient ligands for the arylation reactions.[9] In 2007, Kwong*et al*. developed the concept of the proline-type ligands by employing 2-pinacolinic acid as an ancillary ligand in the copper-catalyzed α-arylation of malonates.[10] Parkinson demonstrated that in the case of the ethylacetoacetate as substrate, the CuI-catalyzed arylation reaction in the absence of additional ligandsin DMSO at 80°C to obtain mixtures of affords a mixture of ethyl 2-arylacetoacetates and its decarboxylation product, ethyl arylacetates.[10b]Other substrate classes have also been transformed under similar condition. As an example, Rout *et al* reported the CuI/Proline-catalyzed arylation of β-ketophosphonates(Scheme 4.2).[11]



Scheme 4.2. Copper-catalyzed arylation of ketophosphonates

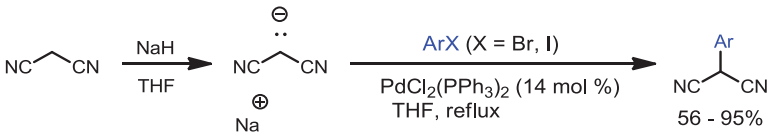
Pd- and Ni-catalyzed arylations

The development of the arylation of the active methylene compounds with Ni and Pd has taken place in parallel to the discovery of the copper-based protocols, with the first examples of the palladium-catalyzed arylations dating back to 1980s. In 1984, Takahashi *et al*. synthesized a variety of alkylarylcyanoacetates in modest-to-good yields by treatment of alkyl cyanoacetates with KO*t*-Bu in monoglyme, followed by addition of aryl iodides and a catalytic amount of $PdCl_2(PPh_3)_2$. (Scheme 4.3)[12]



Scheme 4.3. $PdCl_2(PPh_3)_2$-Catalyzed Arylation of Alkyl Cyanoacetates with Aryl Iodides

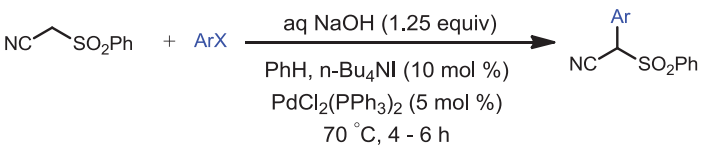
Similar reaction conditions were subsequently employed for the arylation of ethyl cyanoacetate with dihaloarenes.[13]Catalytic amounts of $PdCl_2(PPh_3)_2$ were also used to prepared arylmalonitriles in moderate-to-excellent yields by trearment of the sodium salt of malononitrile with aryl iodides in THF (Scheme 4.4).[14]



Scheme 4.4. $PdCl_2(PPh_3)_2$-Catalyzed Synthesis of Arylmalononitriles.

In 1993, α-aryl-α-cyanosulfones were prepared under mild conditions with good yields by $PdCl_2(PPh_3)_2$-catalyzed coupling reactions between α-cyanosulfones and aryl halides in benzene in the presence of aqueous NaOH and a phasetransfer catalyst (Table 4.2).[15]

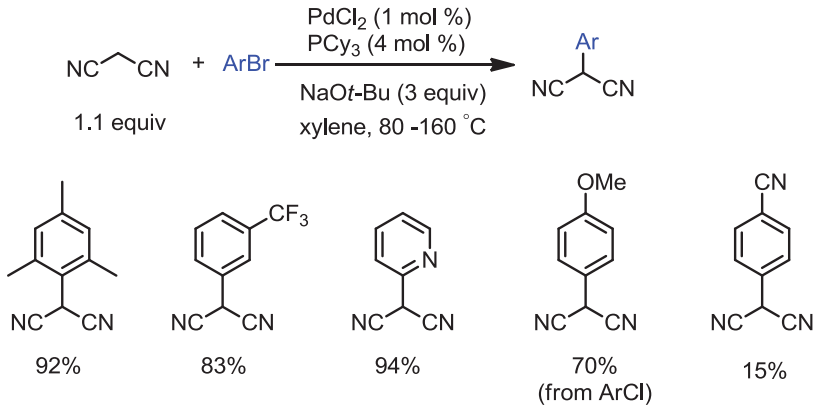
Table 4.2. Pd-Catalyzed Arylation of Phenylsulfonylacetonitrile under Phase-Transfer Conditions



entry	Ar	X	Yield (%)
1	Ph	Br	72
2	Ph	I	90
3	4-MeC_6H_4	Br	70
4	4-MeC_6H_4	I	91
5	4-BrC_6H_4	Br	68

In 1999, Kawatsura and Hartwig reported that the use of either DTBPF or P(*t*-Bu)$_3$ in combination with Pd(dba)$_2$ and Pd(OAc)$_2$, respectively, allows mild arylation of dialkylmalonates.[16] An important issue in the arylation of the substarte bearing an activated CH_2 group (unlike the CH substrates) is the possibility of double arylation, often leading to important selectivity issue, and the formation of the mixtures of the mono- and the bis-arylated products. In principle, the introduction of the first aryl group makes the remaining CH group even more acidic. Nevertheless, good selectivities in mono-arylation can be achieved due to the increased steric hinderance (and a relative kinetic inertness) of themonoraylated species.In 2002, the influence of various bases on the yield and selectivity in the palladium-catalyzed mono-α-arylation of diethylmalonate with chloro-, bromo-, and iodobenzene was investigated by Aremandia *et al*., who found that $Ba(OH)_2$ gives excellent results for reactions performed in DMA at 100 °C in the presence of 2 mol % Na_2PdCl_4.[17] In the same year, the α-monoarylation of diethyl malonate, di-*tert*-butyl malonate, and ethyl cyanoacetate with sterically hindered and unhindered aryl bromides and chlorides was performed in high yields by Beare and Hartwig using a catalyst system composed of Pd(dba)$_2$ and P(*t*-Bu)$_3$, Q-Phos, or (1-Ad)P(*t*-Bu)$_2$ as the supporting ligand.[18]

In 2006, Schneider et al. developed a convenient method for the synthesis of arylmalononitriles (including hindered ones) in high yields consisting of the reaction of malononitrile with aryl halides in xylene in the presence of NaO*t*-Bu and a catalyst system composed of $PdCl_2$ and PCy_3 (Scheme 4.5).[19]

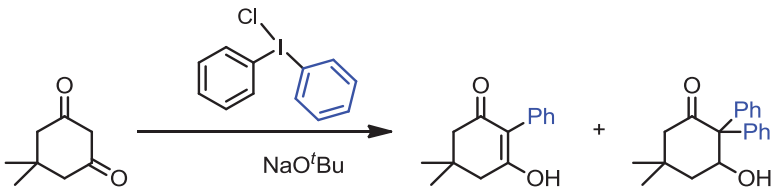


Scheme 4.5. $PdCl_2/PCy_3$-Catalyzed Coupling of Malononitrile with Aryl Halides.

4.1.2. *Precedents in α-arylation of substrates containing activated methylene compounds using hypervalent iodine reagents*

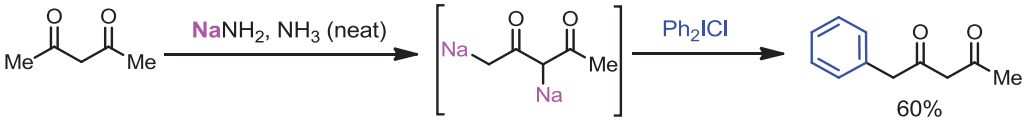
Diaryliodonium salts and other hypervalent iodine reagents provide a means by which arylation can be achieved without the need for toxic or expensive transition-metal reagents.[20]

In 1960s, Beringer et al. reported the first arylation using diaryliodonium salts (scheme 4.6). Phenylation of a cyclic 1,3-dione with diphenyliodonium chloride was achieved in 22% yield, together with 23% of the diarylated product. The reaction required a stoichimtric amount of base (presumably to generate the reactive enolate anion) and used *tert*-butanol was used as solvent



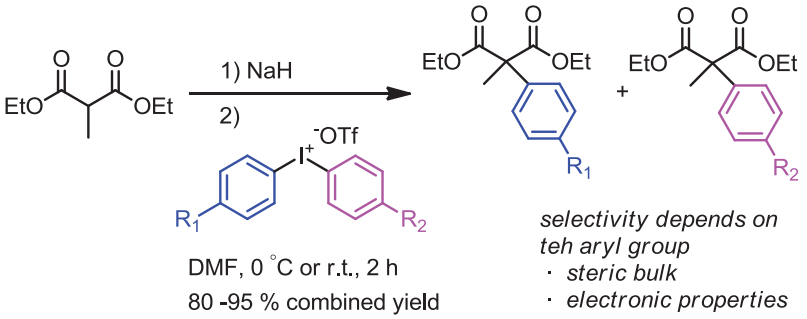
Scheme 4.6. The first reported arylation of a diketone with a aryliodonium salt (Beringer *at al.*)

The arylation of diones was further investigated by Hampton and co-workers using $NaNH_2$ base in liquid ammonium. Under these conditions, the authros were able to conduct the monoarylation of 2,4-pentanedione (*i.e. acetylacetone)*on a multigram scale[21] The process is unique in that it allows, through double deprotonation, to install the aryl group at the less acidic 1-position of the diketones (Scheme 4.7).



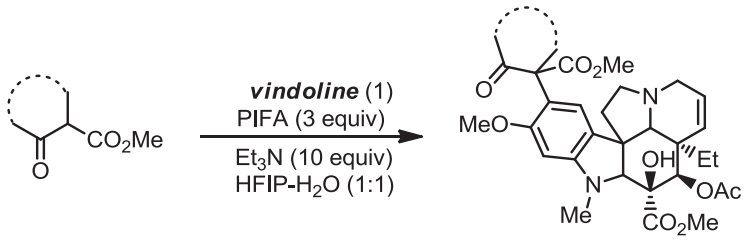
Scheme 4.7. Selectiove monoarylation of pentanedione at the 1-position using Ph_2ICl

In 1999, a highly efficient arylation of malonates was reported by Oh et al.[22] In this extensive study, the preference for transfer of the electron-deficient aryl moiety of an unsymmetrically diaryliodonium salt was demonstrated (Scheme 4.8). More, recently, a comprehensive study of the factors affecting the selectivity in aryl transfer from the diaryl-λ^3-iodonium salts was reported by Olofsson *et al.* The importance of this study stems from the fact that one of the aryl groups is necessarily lost as ArI during the process. Thus, in cases where a "valuable" aryl group is to be transferred, one must usually contend with using half of the groups as sacrificial ArI, leading to the search of a convenient and cheap dummy group, one that would always remain bound to the iodine atom, and would thus favour the transfer of the other group. This endeavor, however, has not been satisfactorily resolved, given the complexity of the factors governing the selectivity of the process.



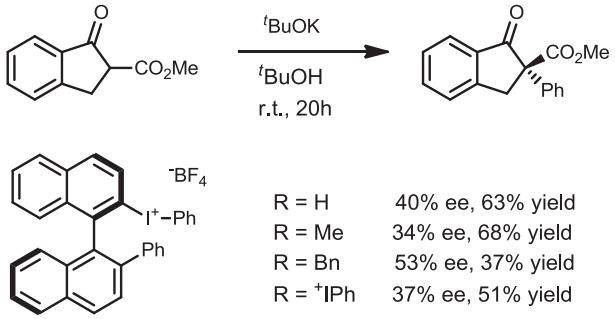
Scheme 4.8. Chemoselectivity in aryl group transfer from a diaryliodonium salts.

More recently, Boger and co-workers reported the regioselective intermolecular coupling reaction of the alkaloid *vindoline* with a large range of substrates including -ketoesters, -diketones, -ketoaldehydes, -ketonitriles, malononitriles and –cyanoesters (Scheme 4.9). This transition-metal free PIFA promoted intermolecular sp^3/sp^2 coupling was conducted in the presence of an excess of triethylamines and using a mixture of hexafluoroisopropanol and water as reaction medium.[23] The process does not proceed through the vindoline-based diaryliodonium intermediate, but rather through a SET radical intermediates. In fact, the putative (phenyl)(Vindolinyl)iodonium was indeed observed in some cases, but proved to be a dead-end structure.



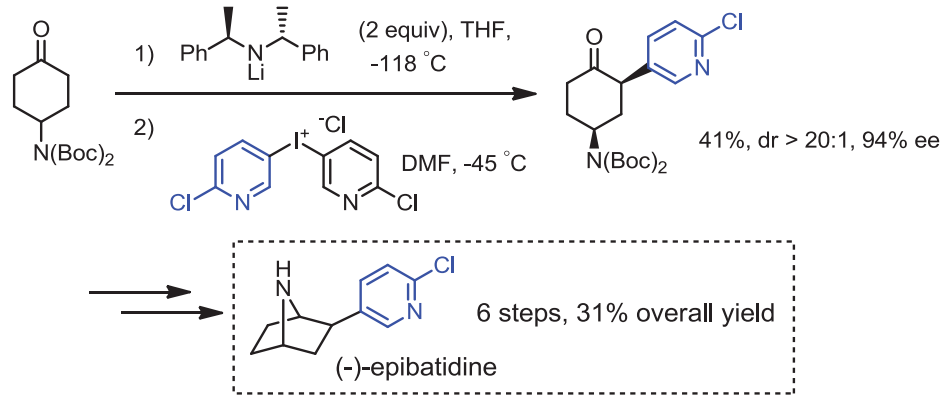
Scheme 4.9. Coupling reaction of vindoline.

To date, only two asymmetric arylation reactions have been reported. In 1999, Ochiai *et al.* utilized chiral diaryliodonium salts based on a binaphthyl core in the arylation of -ketoesters (Scheme 4.10).[24]



Scheme 4.10. Asymmetric arylations using chiral iodonium salts

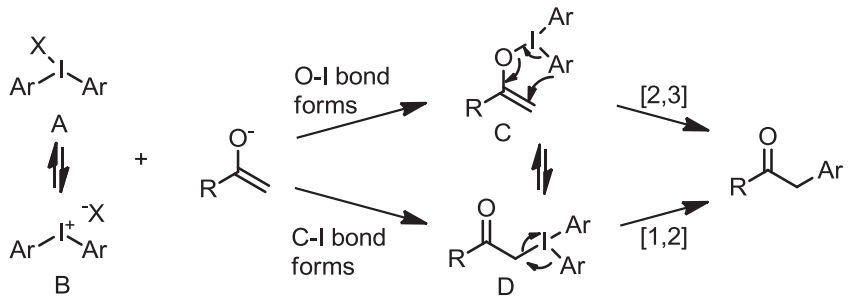
The second example employs a chiral base to desymmetrize 4-substituted cyclohexanones *prior* to arylation (Scheme 4.11). This strategy was used by Aggarwal and Olofsson in an elegant synthesis of (-)-epibatidine.[25]



Scheme 4.11. Asymmetric arylations using Simpkins' base and $(Het)_2ICl$.

Some mechanistic aspects of this arylation reaction have already been discussed in Section 1.4.2. A priori for an trivalent iodine Ar(L)INu species, the for mation of the Ar-Nu product could take place through a fomal reductive elimination path, the a nucleophilic atac on the *ipso* carbon atoms of the arene group (with reductive loss of Ar-I), or by SET mechanisms. Diaryliodonium salts are generally believed to react by reductive elimination pathway, delivering the equatorial aryl moiety to the axially installed nucleophile.

In the reaction with enolates several intermediates have been proposed. The enolate could react with neutral **A** or cationic **B**. Either pathways could give intermediates **C** or **D** with oxygen or carbon bonded to iodine. These intermediated could equilibrate rapidly or form the product through different reductive elimination mechanisms, [2,3] rearrangement or [1,2] rearrangement. Computational calculations by Norrby (in collaboration with Olofsson) favour the [2,3] rearrangement pathway over the [1,2] for the α-arylation of various types of enolizable carbonyl compounds (Scheme 4.12), which partially explains the difficulty in achieving an enantioselective aryl delivery (loss of stereoinformation in the O-enolate).[26]

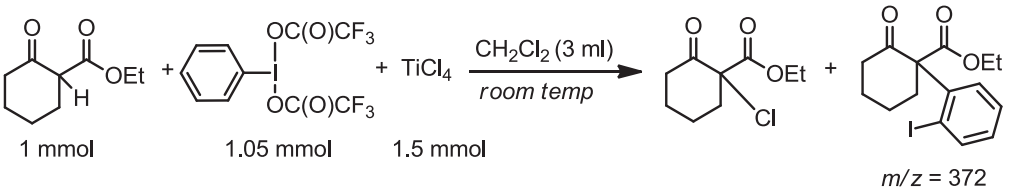


Scheme 4.12. Possible intermediates in the arylation of enolates

4.2. Results and discussion

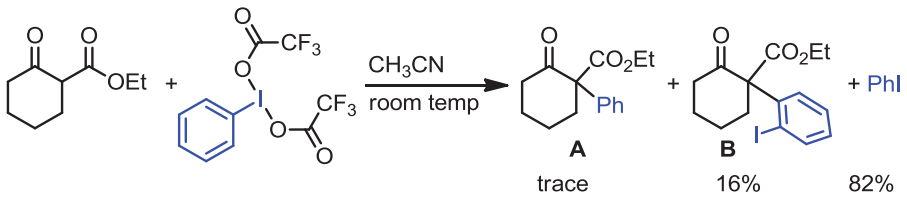
4.2.1. *Preliminary screening and mechanistic proposal*

As discussed at the end of Chapter 3 (section 3.3) the oxidative chlorination of the ethyl 2-oxocyclohexanecarboxylate in the presence of PIFA was accompanied by the appearance of non-negligible large amounts of a second product identified as the α-arylated ketoester. Specifically, the new species was the α-(1-iodophenyl) 2-oxocyclohexanecarboxylate, with the iodine atom incorporated *ortho* to the newly formed C-C bond. The presence of the iodine atom was confirmed, among other techniqes, by the GCMS analysis of the product and by the characteristic C-I resonances at 99.7 ppm in the ^{13}C NMR.



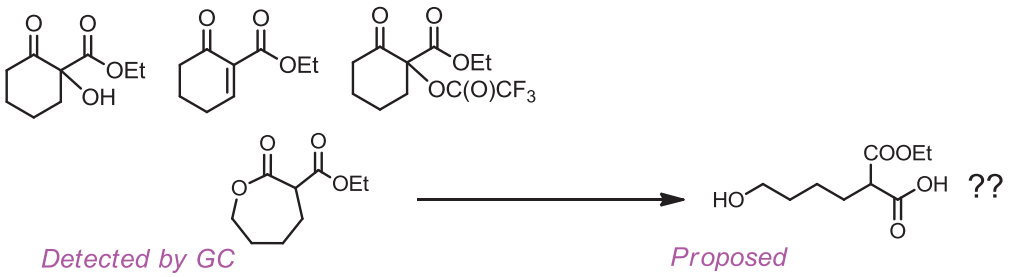
Scheme 4.13. Indentification of the new α-arylation byproduct from an attempted α-chlorination.

Additional experiments revealed that moderate amounts of this new species can be achieved simply by mixing the ketoester substrate, ethyl 2-oxocyclohexanecarboxylate, with PIFA at room temperature (Scheme 4.14).It is interesting to note that only traces of the more conventional phenylated species **A** were observed, with iodobenzene accounting for the remainder of the hypervalent iodine reagent. Interestingly, the reaction concluded with the full consumtion of the ketoester and the generation of iodobenzene (82%) as a byproduct.



Scheme 4.14. Arylation of the β-diketone **1a** with phenyliodine bis(trifluoroacetate).

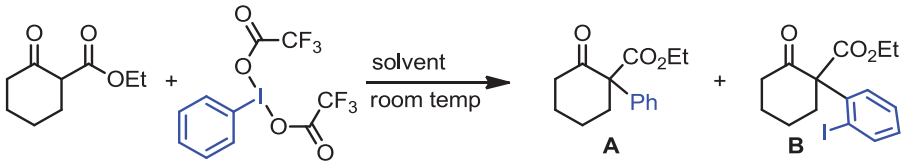
The fate of ketoester has proved elusive, with only small amounts of other products detected by GC. We have obtained some evidence that for the oxidative ring opening of the cyclohexanone moiety might take place, through the initial α-oxidation of the substrate or a Baeyer-Villiger type oxygen insertion processes (Scheme 4.15)



Scheme 4.15. Possible decomposition product to account for the disappearance of the ketoester substrate.

The selective (in terms of the Ph group) formation of the product **B** (in Scheme 4.14) suggested that the arylation in this case proceeds by a mechanism distinct from that operating with the diaryliodonium salts and represented in Scheme 4.12. Indeed, the use the basic medium necessary for the arylation by Ph_2IX afforded, in the case of PIFA, none of the arylated products (Table 4.3, entry 1). A solvent screen under neutral conditions revealed that the yield of **B** is favoured by a polar medium (entries 3-5), and particularly by the use of a 1:1 CH_3CN/CF_3CO_2H mixture (entry 6). The yield could be further improved by employing a stoichiometric trifluoroacetic anhydride additive (entry 7). Under these conditions, the reaction was complete in 2 h at room temperature and afforded a 52% of the arylated **B**. Although trace amounts of the phenyl-containing **A** were observed in some cases, these were attributed to the eventual loss of halogen from **3a**and not the direct phenylation via the classical mechanism. No product was observed using triflic anhydride as additive (entry 8). The improvement in yield with the addition of the trifluoroacetic anhydride was attributed to its ability to react with traces of water. Indeed, only 8% yield of **A** was achieved when water was added to the reaction mixture (entry 9)

Table 4.3. Screening of conditions in the arylation of 2-oxocyclohexanecarboxylatewith PIFA.[a]

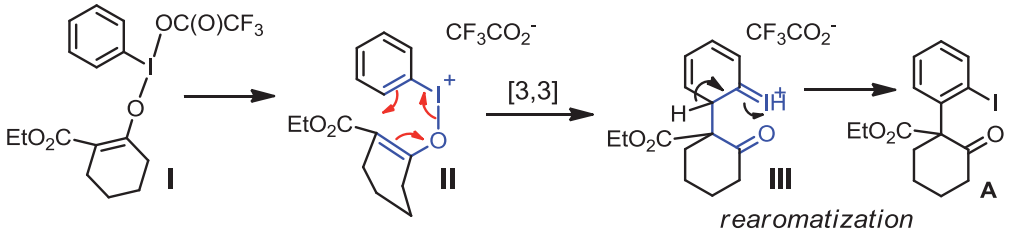


Entry	Solvent	Additive	%**2a**[b]	%**3a**[b]
1	*t*BuOH	KO*t*Bu		
2	Cyclohexane		<1	21
3	CH_2Cl_2		<1	24

4	CH_3CN		1	30
5	CF_3CO_2H		1	34
6	CH_3CN-CF_3CO_2H		2	48
7	CH_3CN-CF_3CO_2H	$(CF_3CO)_2O$	3	**52**
8	CH_3CN-CF_3CO_2H	$(CF_3SO_2)_2O$		
9	CH_3CN-CF_3CO_2H	H_2O		8

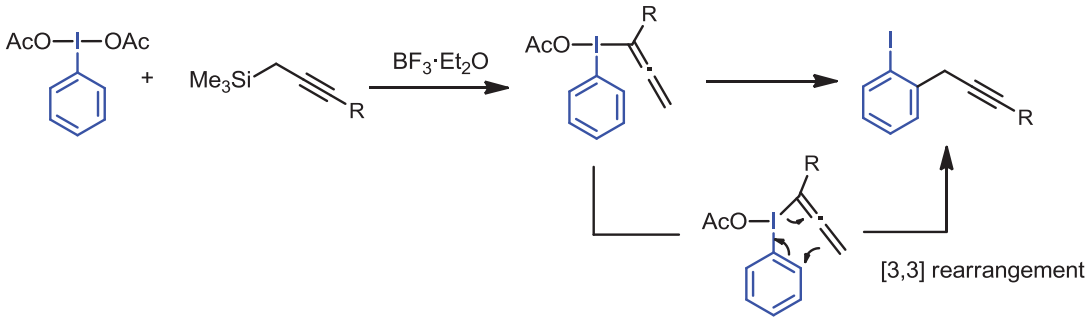
[a] Using 1.0 mmol **1a**, 1.3 mmol PIFA in 4 mL of solvent at room temp.; [b] GC yield corrected *vs* internal *n*-$C_{11}H_{24}$

We hypothesized that the reaction likely proceeds via initial displacement of one of the trifluoroacetates to form an iodonium *O*-enolate **I**, which, upon anion dissociation (to give **II**) and a [3,3] sigmatropic rearrangement, followedby rearomatization,would yield the arylated species **A** (Scheme 4.16).Aclosely related process involving an arylative sulfoxide Claisen rearrangement was recently disclosed in an elegant work from the Maulide laboratory.[27]Thus, as was the case of the sulfoxide, the key to the facile [3,3] rearrangement of the putative iodonium *O*-enolate in this case is likely the positive charge build up at the bridging iodine atom in the intermediate cationic species **II** (*i.e.* constituting a charge-accelerated hetero-Claisen process).[27b]



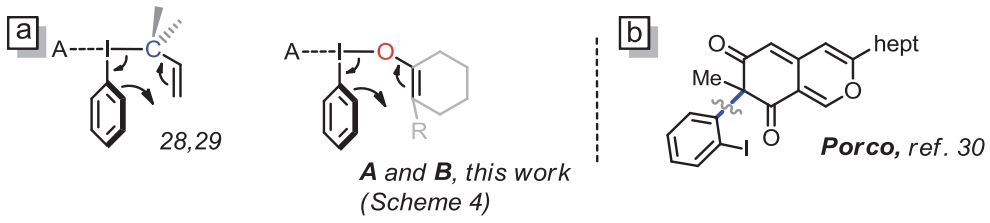
Scheme 4.16. A proposed arylation of ketoesters through an iodonium Claisen reaction.

This mechanistic proposal is, in principle, supported by some literature precedents. Thus, the term *reductive iodonio-Claisen rearrangement*(RICR) was coined in the early 1990's by Ochiai and coworkers, who studied the rearrangement of the*in situ* generated propargyl and allenyliodanes (Scheme 4.17).[28]



Scheme 4.17. Ochiai's early exemple of an iodonium Claisen process.

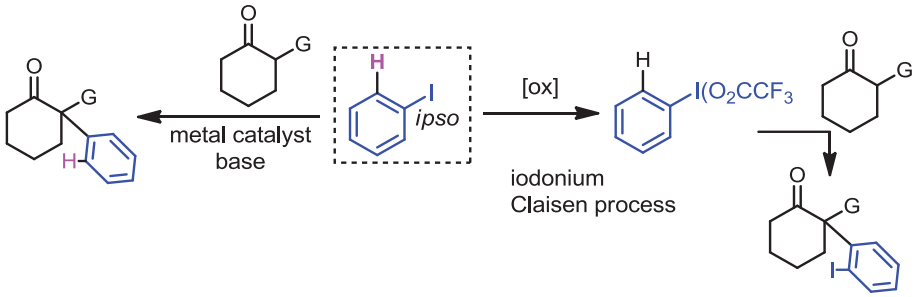
Thus, the reaction of the phenyliodine diacetate with propargylsilanes afforded, in the presence of $BF_3{\cdot}Et_2O$, an iodoarene bearing a propargy group *ortho* to the iodine. The authors concluded that: "*Although the intermediate allenyl(ary1)iodinanes have not been isolated and detected by NMR experiments, our results clearly indicate [..] a reductive iodonio-Claisen rearrangement at low temperature, yielding o-propargyliodoarenes. … Claisen rearrangements involving atoms of group 17 have never been reported*." The concept was recently applied by Khatri and Zhu to the synthesis of complex *o*-allyliodoarenes.[29]Interestingly, however, while the Claisen precursors invoked in these aforementioned processes contain two C-ligands bound to the central hypervalent iodine (ignoring the third weakly bound counterion, Scheme 18a, C-I-C motif), the iodine center in the intermediates **A**/**B** postulated in Scheme 4 bears both a carbon and a more labile O-enolate ligand (Scheme 4.18a, C-I-O motif). A rearrangement *via* a C-I-O intermediate is in line with the mechanism proposed by Porco *et al* for the formation of a side product (Scheme 4.18b) in the PIFA-mediated oxidation of a resorcinol derivative.[30]



Scheme 4.18. a) The C-I-C and the O-I-C ligand arrangement in the iodonio-Claisen precursor; b) a related arylated product proposed to form *via* [3,3] rearrangement.

Intrigued by the mechanistic and synthetic implications of the new α-arylation protocol, we set out to develop this methodology into anapproach complementary to both the classical arylation with diaryl λ^3 iodane, and the methods based on metal catalysts. Considering PIFA as a surrogate for iodobenzene, this complementary is

illustrated in Scheme 4.19. Thus, while the metal-catalyzed arylation ttakes place with the new C-C bond formed to the iodoarene *ipso* ipso position. In contrast, the new protocol offered the possibility to form that bond at the C atom *ortho* to the iodine, with the halogen atom serving as as pseudo-directing group (Scheme 4.19).



Scheme 4.19. The complementarity of the arylation protocols.

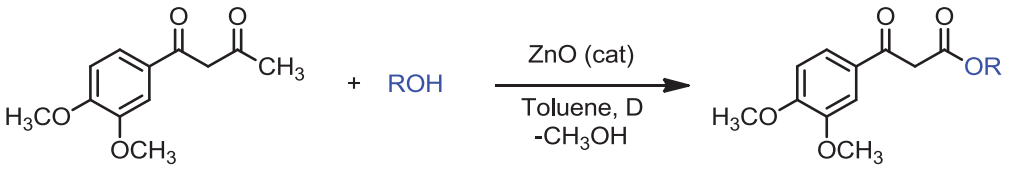
Thus, having achieved a moderate 52% yield in the arylation of ethyl 2-oxocyclohexanecarboxylate (Table 4.2, entry 7), we proceeded to probe the scope of this transformation starting with other ketoesters and the related β-diketone substrates.

4.2.2. *Arylation of β-ketoesters and β-diketone substrate*

Synthesis and properties of β-ketoesters. β-ketoesters are some of the most important building blocks in organic synthesis. The reactivity of this class of compounds allow for their rapid elaboration into more complex molecular structures. A key factor in the chemistry of β-ketoesters is their ability to serve as both nucleophilic and an electrophilic reagents. A classic method for the preparation of β-ketoesters is the reaction of diketene with alcohol.[31]Of the wide variety of other methods (beyond the scope of this overview), we will also mention the preparation of structurally general β-ketoesters *via* the acylation of Meldrum's acid at the intercarbonylic position, followed by the decarboxylative thermolysisin alcohols mediud.[32]

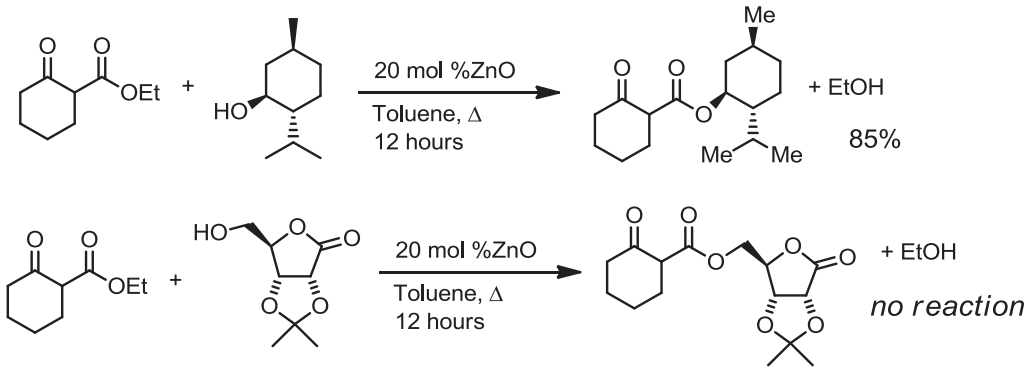
Transesterification reaction represents the electrophilic facet of the reactivity of β-ketoesters. Most of the methods of transesterification are equilibrium driven reactions where the excess of one of the reactants is required to achieve good yields. This equilibrium process can be catalyzed by a wide range of catalysts, including the recently described catalysis by zeolites[33] and naturalclays,[34] Mg-Al-hydrotalcites-like anionic clays,[35] montmorillonite K-10,[36] Nb_2O_5,[37] polyaniline salts,[38] B_2O_3/ZrO_2,[39] Zn[40]and $NH_2SO_3H/[C_3MIm]Cl$.[41]

In our own group, a new transesterification protocol was developed by Alex Pericas and co-workers[42]during the enantioselective synthesis of biologically active compounds. Thus, Pericas' doctoral work required the preparation of a wide series of analogs of 3-(3,4-dimethoxyphenyl)-3-oxopropanoate with a varying degree of the bulk of the OR substituent. After some experimentation, they found that this reaction could be efficiently mediated by catalytic amounts of ZnO (Scheme 4.20). Interestingly, the method was found to be highly selective towards the ketoester moiety, presumably due to the formation of the activated zinc chelate.



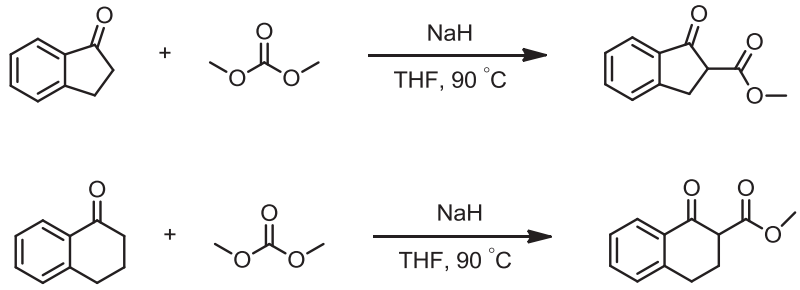
Scheme 4.20. Zinc-catalyzed transesterification developed in our group (Pericas *et al*, 2008).

Using these conditions, we went on to test the preparation of two new ketoesters by the reaction of the ethoxy substrate with the chiral menthol and the shugar-derived alcohol (Scheme 4.21). Thus, while the reaction with menthol produced 85% of the desired transesterification pproduct, only the starting material was recovered in an attempted transfesterification with the duranone-based nucleophile.



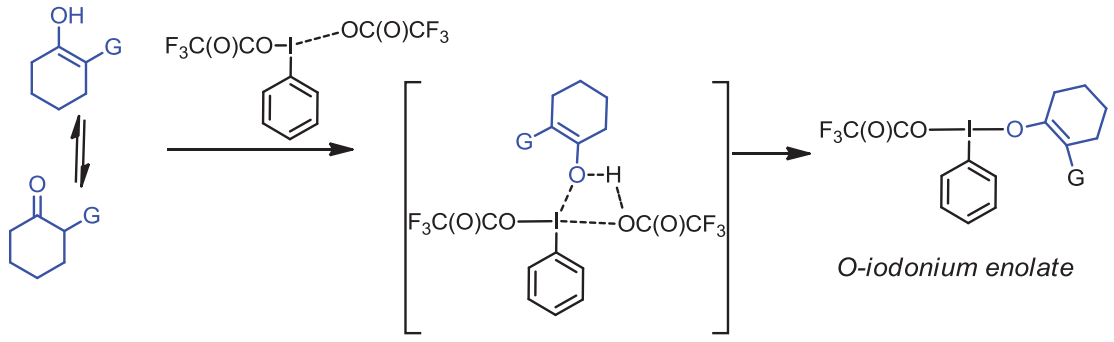
Scheme 4.21. Derivatives from ethyl 2-oxocyclohexanecarboxylate

As demonstrated by Xuequan Wang and coworker,[43] certain cyclic β-ketoesters can be produced efficiently through the simple acylation of ketones in the presence of a strong base using dimethylcarbonate as acylating agent. Using this method, we went on to prepare two new cyclic ketoester substrates through the acylation of indanone (Scheme 4.22,a) and tetralone (Scheme 4.22,b) in the presence of sodium hydride.



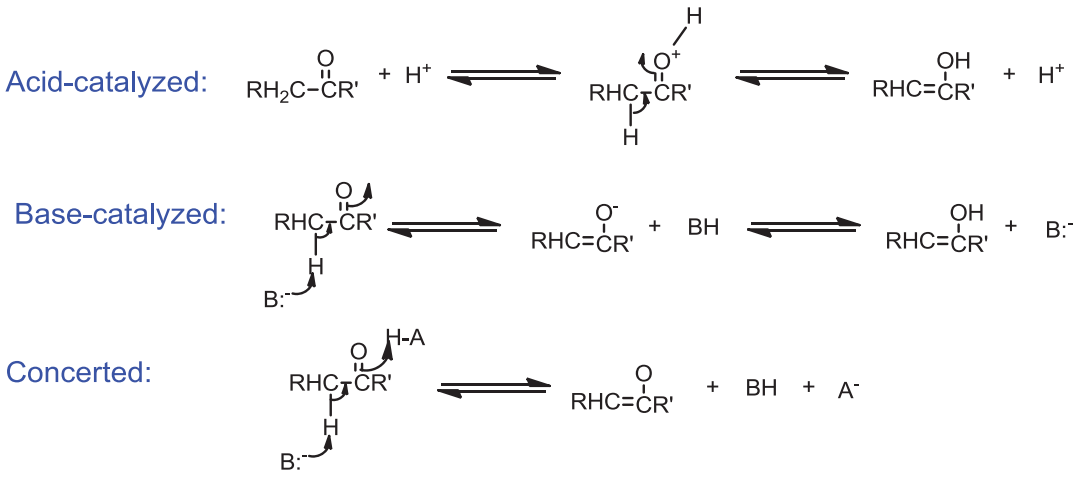
Scheme 4.22. α-acylation of the cyclic ketones.

As discussed above, the α-arylation transformation which is the subject of this doctoral dissertation likely proceeds through the formation of an O-iodonium enolate intermediate. The fact that the reaction takes place under acidic conditions suggests that the formation this species does not occur through the prior ketone deprotonation, as was the case with the classical Beringer-type arylation using diaryliodonium salts. Instead, it is highly likely that the iodonium enolate untermediate forms directly from the enol form of the substrate, a process that may be assisted by an acidic medium (Scheme 4.23).

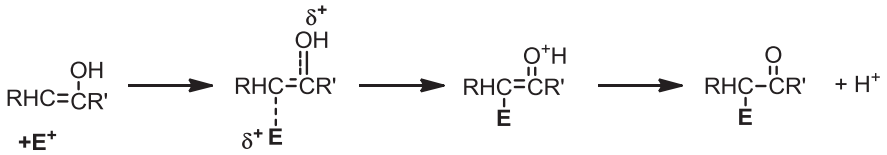


Scheme 4.23. The formation of the iodonium *O*-enolate.

Overall, the carbonyl compounds can act as carbon nucleophiles in the present of *acid catalysts*, as well as base. The nucleophilic reactivity of carbonyl compounds in acidic solution is due to the presence of the *enol tautomer*. The equilibrium between carbonyl compounds and the corresponding enol can be acid- or base-catalyzed and can also occur by a concerted mechanism in which there is concurrent protonation and deprotonation. As we will see shortly, the equilibrium constant is quite small for monocarbonyl compounds, but the presence of the enol form permits reactions that do not occur from the carbonyl form.



Like simple alkenes, enols are nucleophilic by virtue of their π electrons. Enols are much more reactive than simple alkenes, however, because the hydroxyl group participates as an electron donor during the reaction process. The oxygen is deprotonated and the strong C=O bond is formed, providing a favorable energy contribution (Scheme 4.24).



Scheme 4.24. The electrophilic character of an enol

Enols are not as rective as enolate anions, however. This lower reactivity reflects the presence of the additional proton in the enol, which decreases the electron density of the enol relative to the enolate. In MO terminologie, the –OH and $–O^-$ donor substituents both raise the energy of the π-HOMO, but the O^- group is the better donor.

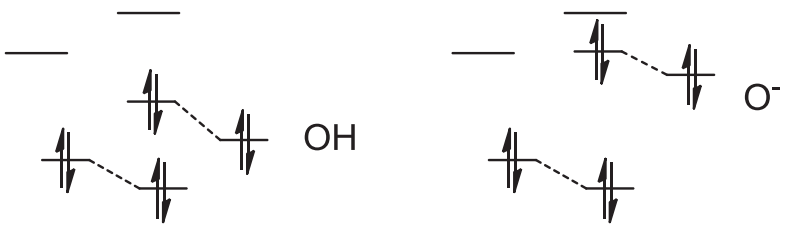
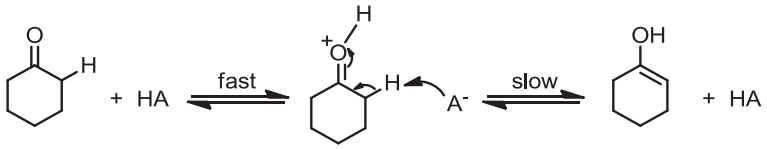


Figure 4.1. Orbital energy differences between *enol* and an *enolate*.

A number of studies of the acid-catalyzed mechanism of enolization have been done, and the case of cyclohexanone in illustrative. The reaction is catalyzed by various carboxylic acids and substituted ammonium ions. The effectiveness of these

proton donors as catalysts correlates with their pKa values. When plotted according to the BrØnsted catalysis law the value of the slope α is 0.74. When deuterium of tritium is introduced in the α-position, there is a marked decrease in the rate of acid-catalyzed enolization: $k_H/k_D \sim 5$. This kinetic isotope effect indicates that the C-H bond cleavage is part of the rate-determining step. The generally accepted mechanism for acid-catalyzed enolization pictures the rate-determining step as deprotonation of the protonated ketone (Scheme 4.25)



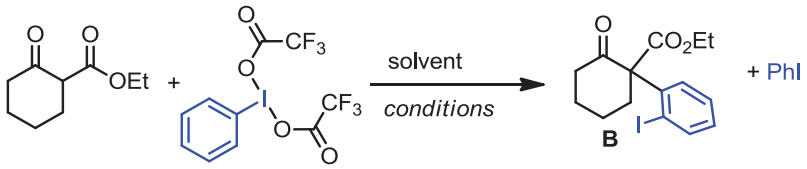
Scheme 4.25. Acid catalysis in cyclohexanone enolization.

There are extensive data on the equilibrium constant for enolization. In Table 4.4 some quantitavie information on the amount of enol present at equilibrium for some representative compounds has been collected. For simple aldehydes , the K_{enol} is the range 10^{-4} to 10^{-5}. Ketones have *smaller* enol content, with K_{enol} around 10^{-8}.

Table 4.4. Equilibrium Constants for Enolization of Some Carbonyl Compounds.

entry	Enolization equilibrium	*K* enol/keto
1		$4.2X10^{-7}$
2		$1.2X10^{-8}$
3		$3.3X10^{-8}$

With these parameters in mind, the efficiency of the test coupling between betweenethyl 2-oxocyclohexanecarboxylate and PIFA was examined under a range of conditions (Scheme 4.26).



Scheme 4.26. The model coupling between a cyclic ketoester and PIFA.

As seen earlier, the choce of solvent had a profound effect on the reaction performance. This screening was conducted using an excess of PIFA (1.5 equiv) and at room temperature. After a specified, period of time, the yield of both the product **B** and iodobenzene was measured by Gas Chromatography, employing *n-u*ndecane as internal standard and employing a correction factor to compensate for differences in response factor. As shown in entries 4-6 of Table 4.5 (see above), yields above 30% could be achieved with both CH_3CN and trifluoroacetic acid, with optimal results reached with a mixture of these two solvents. A more detailed look at these changes is presented in Table 3 and Figure 2, showing the results with the three solvent systems tested under two different concentration: 0.5 M and 0.25 M (with respect to the ketoester substrate).

Table 4.5. Dependence of the arylation efficiency on solvent and concentration.

Run		CH_3CN (mL)	CF_3COOH (mL)	GC Yield, %[a]
1	**2** mL reaction volume	2	0	17
2		1	1	**41**
3		0	2	26
4	**4** mL reaction volume	4	0	11
5		2	2	**40**
6		0	4	27

[a]Only the yield of the arylation product is given

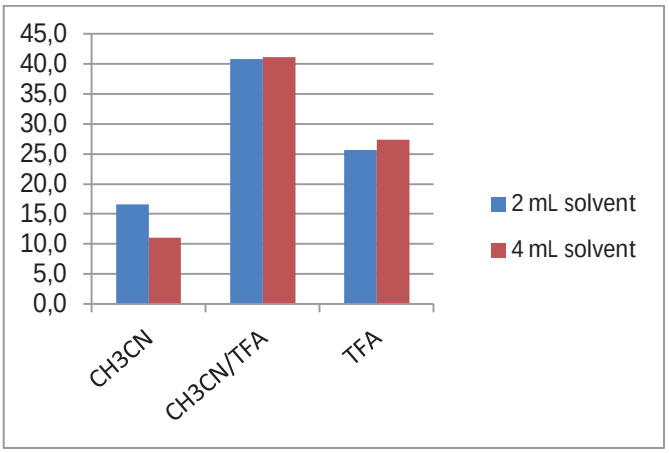


Figure 4.2. Dependence of the arylation efficiency on solvent and concentration

As seen in Figure 4.2, the reaction performance was found to be fairly insensitive to the concentration. In both cases, however, best results were achieved using a mixture of acetonitrile and trifluoroacetic acid. Additional experiments were then conducted by varying the ratio of these two solvents. It was found that reactions conducted with a solvent ratio close to 1:1 performed margibally better than those with a large excess of one of the solvent (Table 4.6, Figure 4.3).

Table 4.6. Arylation performance as afunction of %acetontrilie

Run	%CH3CN	GC Yield((%)
1	0	17
2	25	43
3	40	47
4	50	46
5	60	44
6	75	45
7	100	26

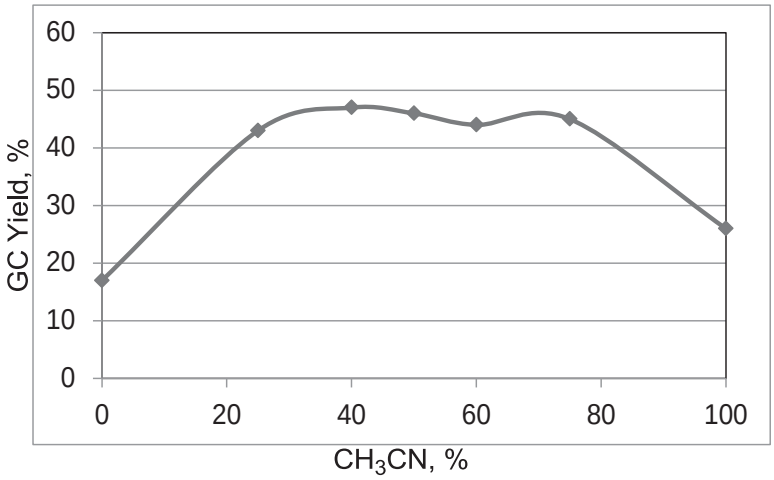


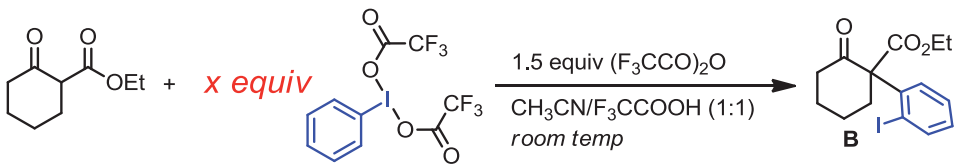
Figure 4.3. Arylation performance as a function of %acetontrilie**.**

Interestingly, the exact fate of the rest of the ketoester substrate remains unclear (with some accounted for by the oxidation products shown in Scheme 4.15). In contrast, all of the (ArI) moiety derived from PIFA could be accounted forby the arylated product **B**as well as iodobenzene, whose combined yields (as measured by calibrated GC runs) were always equal to the initial emount of PIFA employed (eq. 1). Thus, large amounts of iodobenzene have proved to be unavoidable from the unproductive reduction of PIFA.

$$mmol\ (\mathbf{B}) + mmol\ (PhI) = mmol\ (PIFA)_{init} \qquad (1)$$

The yield of the reaction could be improved to above 50% by using stoichiometric amounts (1-1.5 equiv) of the trifluoroacetic anhydride. This improvement might be due to the ability of this reagent to act as a water scavenger (i.e. a drying agent), producing only the trifloroacetic acid as by product. Hopwever, the possibility that this reagent is also involved in the coupling process cannot be discarded at this point. In the finaloptimization intent, we examined the effect of varying the equivalent of PIFA employed from 0.9 to 1.5 equiv (Table 4.7, Figure 4.4).

Table 4.7. Effect of the equiv. of PIFA on the yield in the arylation



		GC Yield, %		
Runs	Equiv PIFA	45 min	120 min	600 min
1	0.9	39.20	39.80	38.90
2	1.0	41.20	43.30	43.30
3	1.1	45.30	45.80	45.40
4	1.2	47.20	47.40	47.10
5	1.3	46.80	47.00	47.10
6	1.5	47.40	46.90	46.70

[a]Yields are given with respect to the ketoester substrate even for the run with 0.9 equiv. PIFA.

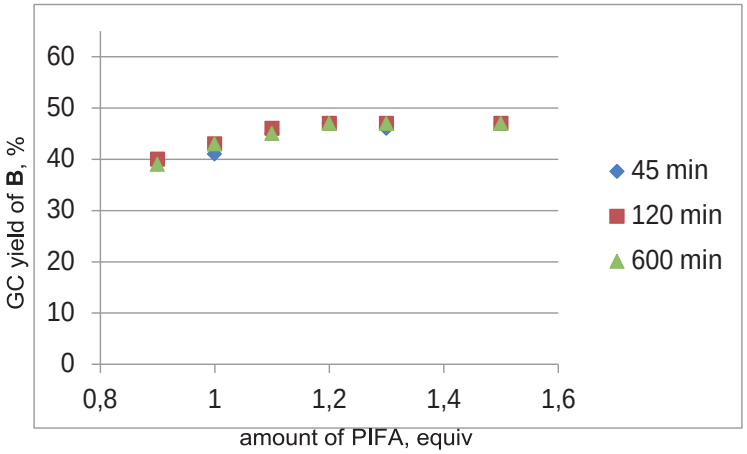
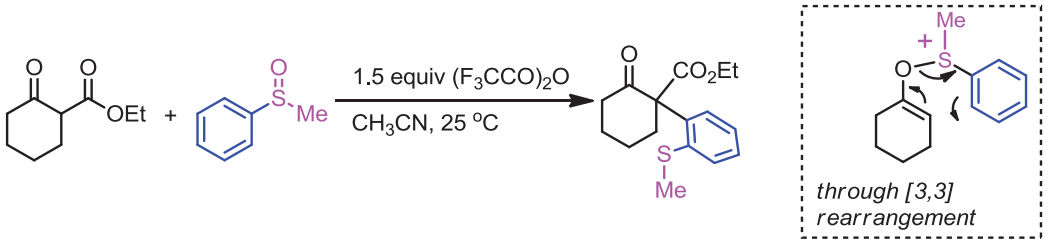


Figure 4.4. Effect of the equiv. of PIFA on the yield in the arylation

Optimal yields could be achieved using an excess of PIFA as low as 1.1-1.3 equivalents. The study also showed that the eaction was extremely rapid (albeit not high yielding), with no further evolution observed after the first 45 minutes of the reaction. From this point on, the standard reaction conditions adopted in this work consist of using a 1:1 mixture of acetonitrile/trifluoroacetic acid as solvent, trifluoroacetic acid anhydride (1.5 equiv) as additive and employing 1.1-13 equiv of the hypervalent iodine reagent. In virtually all cases, the reaction will be conducted at room temperature.

Before proceeding to the next section, it should be noted that the conditions established for this transformation are very close to those employed by Huang and Maulide in a closely related process: the α-arylation of ketoesters using arylsulfoxides (Scheme 4.27).[27a] These similarities may serve as another indicator that the two processes likely proceed through the same mechanism, namely the charge-accelerated [3,3] sigmatropic rearrangement.

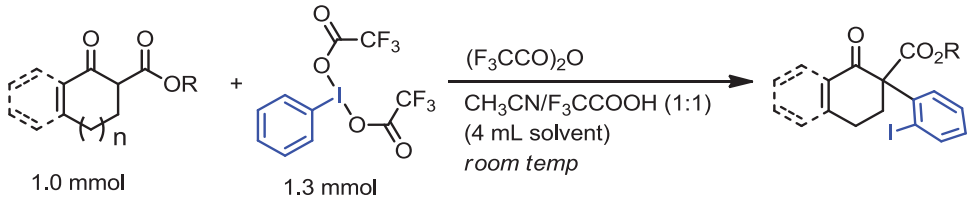


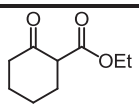
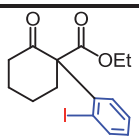
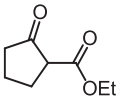
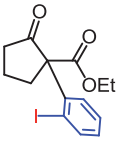
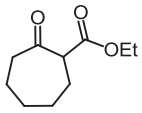
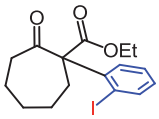
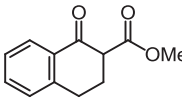
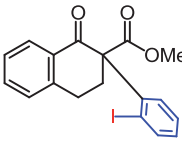
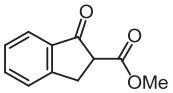
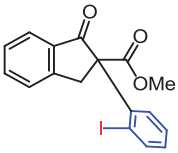
Scheme 4.27. α-arylation of ketoesters by Huang and Maulide.

4.2.3. *Substrate scope in the arylation of β-ketoesters, β-diketones and α-cyanoketones.*

In order to establish the generality of the α-arylation protocol suing PIFA as the arylating agent, several newly prepared diketones were tested. It was found that the protocol could be effective for a number of β-diketones, with yields, however, not exceeding 55%. Thus, 5, 6, and 7-membered cyclic β-ketoesters underwent smooth coupling in 2h at room temp (Table 4.8, entries 1, 2 and 3) affording the α-(iodoaryl) derivatives in approx. 50% yield. In the case of the benzofused ketoesters, the yields were found to be acceptable for the indanone -derived ketoesters, but quite low in the case of the 6-membered tetralone analogue (entrie 4 and 5).

Table 4.8. Results of Coupling between β-ketoesters and PIFA.



entry	Substrate	Product	Yield, %[a]
1			48%
2			52%
3			51%
4			28%
5			57%

[a]Isolated yield.

In all cases, the GC-MS analysis of the reaction, as well as the NMR analysis of the isolated product showed the incorporation of the iodophenyl unit with the iodine atoms installed *ortho* to the newly formed C-C bond, with no other regioisomers ever detected. The freshly run reaction mixtures were also free of the α-phenylated product (type **A** in Scheme 4.14), although a small GC peak for this product developed after prolonged storage, likely the result of the known tendency of aryl iodide to undergo photochemical protodeiodination. The final proof for the *ortho* regiochemistry was provided by the X-Ray Diffraction analysis of single crystal of the indanone-derived arylation product corresponding to entry 5 in Table 4.8. As illustrated in Figure 4.5, the iodophenyl group in the molecule (solid state) is found wiith the iodine atom rotated away from the 5-membered ketone.

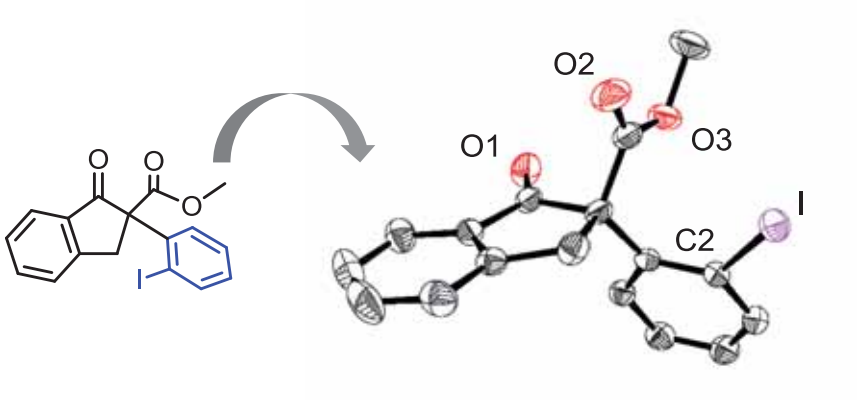
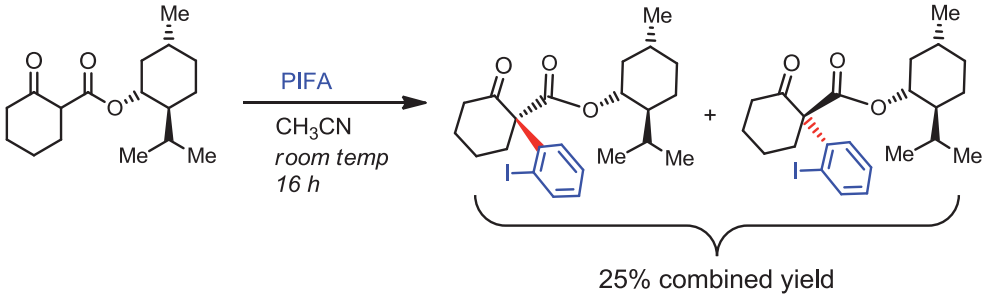


Figure 4.5. ORTEP diagram of the product corresponding to entry 5, Table 6, with H atoms omitted for clarity.

The new arylation process produces a quaternary carbon stereogenic center, and should, therefore, be amenable to stereoselective induction. Our brief foray into this field consisted in an attempt to perform a diastereoselective α-arylation in a using a chiral auxiliary. Thus, the menthol-derived ketoester prepared *via* a transesterification protocol (see Scheme 4.20) was subjected to PIFA; the test was conducted before the final optimized condition had been established, and so acetonitrile was still use as the only solvent. From the reaction mixture, a 25% yield of the arylayed product was isolated as an essentially equimolar mixture of the two diasteroisomers (Scheme 4.28).



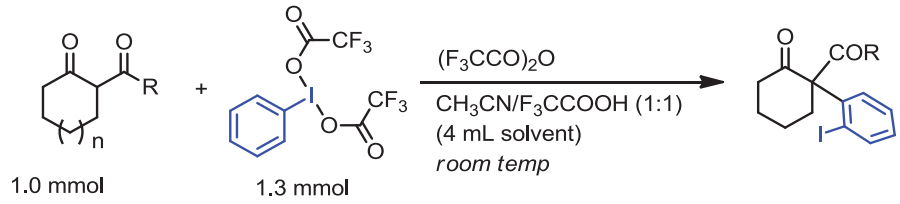
Scheme 4.28. Attempt at a disastereoselective α-arylation with PIFA.

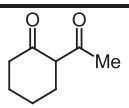
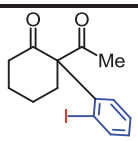
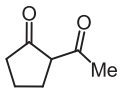
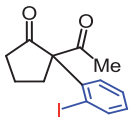
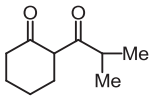
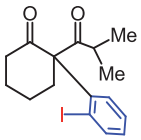
While the product may still be used to obtain a single arylketone enantiomer through diastereomer separation (and deprotection), the experiment showed that the menthyl group was a poor stereoinductor in for this reaction. For lack of time, this topic was not pursued furher.

The substrate scope was further expanded to β-diketones. Both the 2-acetylcyclohexanone and 2-acetylcyclopentanone underwent coupling in 2-4 hours to give the α-arylated species in yields around 40-50%. For the diketone

substrates,increasing the bulk to the isobutyryl group still allowed for the arylationto proceed in a 50% yield (entry 3).

Table 4.9. Results of Coupling between β-diketones and PIFA.



entry	Substrate	Product	Yield, %[a]
1			51%
2			37%
3			50%

[a]Isolated yield

Finally, several other substrate classes have been tested, all consisting in a cyclohexanone moiety bearing an electron-withdrawing group in the α position (Figure 4.6). Of these, only the cyanoketone proved to be suitable. Gratifyingly, however, for this substrate the reaction proved even more efficient than with the ketoesters, affording the desired α-arylated α-cyanoketone in a 72% yield (Scheme 4.29).

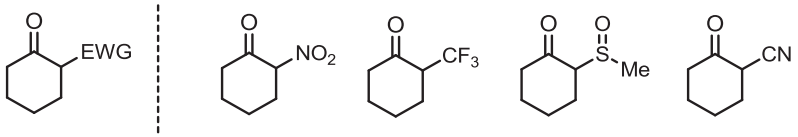
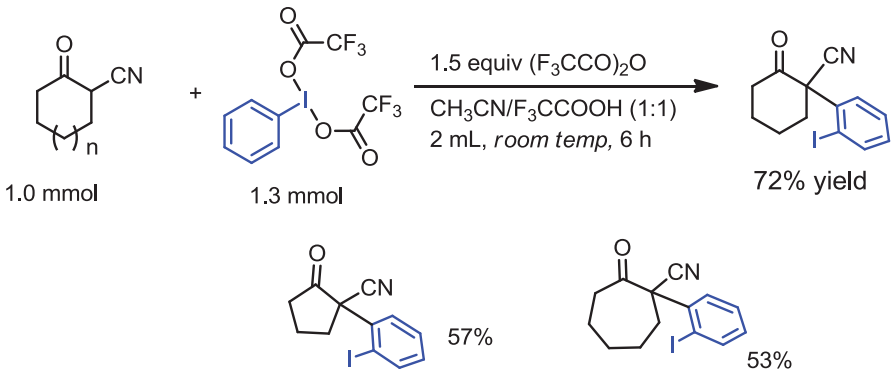


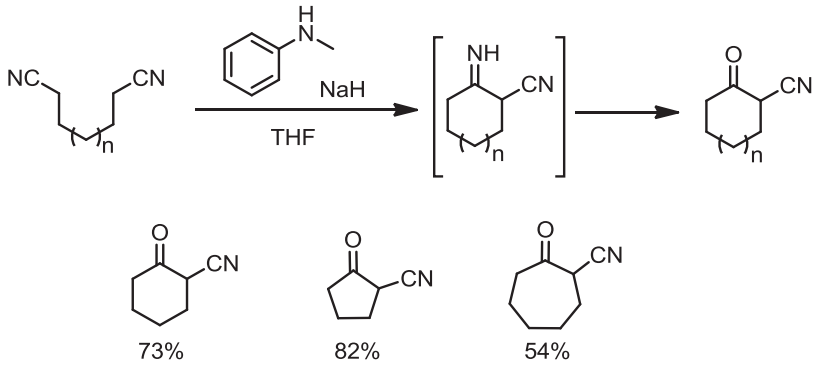
Figure 4.6. Some of the cyclic ketones tested as substrate for arylation with hypervalent iodine.



Scheme 4.29. Arylation of a cyclic cyanoketone.

Interestingly, the process proved cleaner, but significanty slower than with ketoesters of α-diketones. Thus, some starting cyanoketone was still detected after a 3 h interval, with the process requiring 6-7 hours to reach completion.

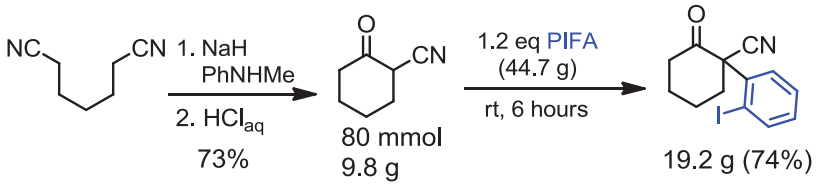
Encouraged by this precedent, and given the prohibitive price of the commercially available α-cyanocyclohexanone, we proceeded to synthesize larger quantities of this and the related 5- and 7-membered cyanoketones using the Thorpe-Ingold cyclization[44] of linear aliphatic α,ω-dinitriles (Scheme 4.30). The most convenient literature procedure[45] consisted in using a using sodium *N*-methylanilide (generated in situ from sodium hydride and *N*-methylaniline) as a base, followed by acid hydrolysis of the resulting enamine.



Scheme 4.30. Thorpe-Ziegler cyclization of alkanedicarbonitriles.

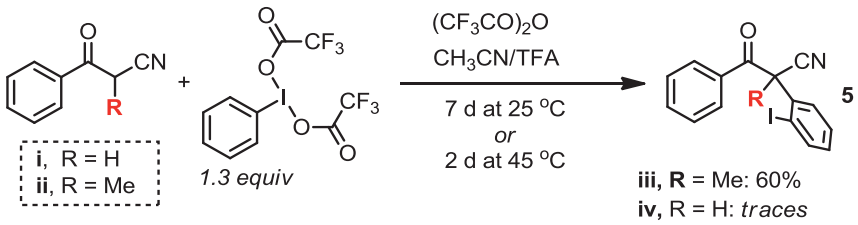
The new cyanoketone substrates were subsequently submitted to the optimized arylation protocol using PIFA as an iodoaryl transfer agent. The target α-arylcyanoketones were obtained in 58% and 53% yield for the 5- and the 7-membered cyclic substrates, respectively (Scheme 4.29). For the substrate derived from cyclohexanone, the arylation procedure was found amenable to laboratory scale-up.

Thus, In order to assess the synthetic potential of the 2-(*o*-I-aryl)-cyanoketones, the arylated product was prepared on a multi-gram scale in two steps via the Thorpe-Ziegler cyclization of 1,5-dicyanopentane followed by the newly developed α-arylation with PIFA (Scheme 4.31). Thus, 9.8 grams of 2-cyanocyclohexanone were submitted to a solution (CH_3CN/CF_3COOH) containing 44.7 grams of the phenyliodine bis(trifluoroacetate). After 6 houtrs and an appropriate work-up, the 19.2 grams of the target α-(2-iodophenyl)-2-cyanocyclohexanone were obtained, which represented a 74%.



Scheme 4.31. Multi-gram scale arylation of the cyclic α-cyanoketones.

Finally, we turned our attention to the arylation of an open chain cyanoketone with PIFA. Here, the viability of the formation of both a tertiary and a quaternary carbon centre was tested using the substrates **i** and **ii** (Scheme 4.32). Interestingly, while only decomposition products were detected for benzoylacetonitrile **i**, the use of 2-benzoylpropionitrile **ii** differing from **i** only by the presence of a 2-Me substituent led to a slow but clean arylation, which came to completion either after a week at room temperature or after 2 days at 45 °C and afforded, affording the target arylation product**iii** in 60% yield. The failure of **i** to undergo arylation is likely the result of a more favourable formation of the iodonium C-enolate and/or the formation of a known iodonium ylide species. Indeed, submitting a 1:1 mixture of **i** and **ii** to PIFA failed to produce any of the desired arylated product.

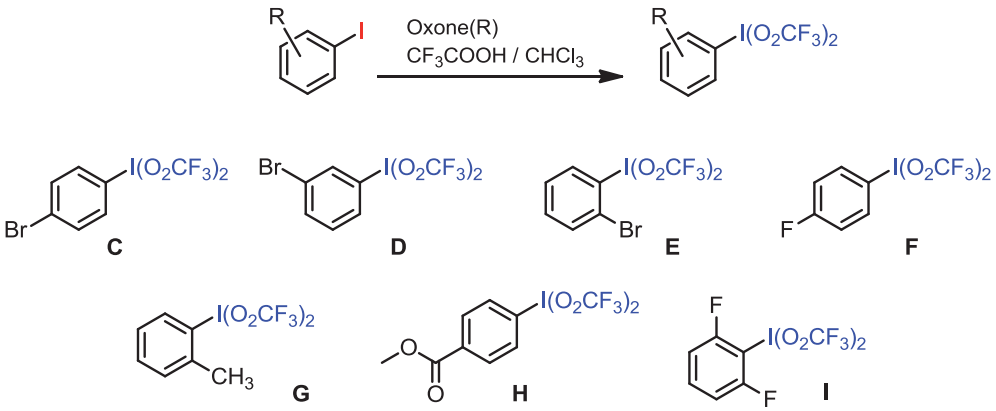


Scheme 4.32. Arylation of the open-chain α-cyanoketone

4.2.4. *Exploring the scope of the hypervalent iodine reagents*

The efficiency in the arylation of the cyanoketones, particularly α-cyanocyclohexanone led us to explore the introduction of the *o*-iodoaryl fragments

aother than the *o-iodophenyl* derived from PIFA. As demonstrated by Zhdankin and co-workers[46], [bis(trifluoroacetoxy)iodo] -perfluoroalkanes $C_nF_{2n+1}(OCOCF_3)_2$ (n=4, 6, 8, 10, 12) can be conveniently prepared by the oxidation of the corresponding perfluoroalkyl iodines with Oxone in trifluoroacetic acid at room temperature and (and can be subsequently convered to the stable [hydroxy(tosyloxy)-iodo]perfluoroalkanesby treatment with p-toluenesulfonic acid). This general and convenient procedure has been further extended to the synthesis of various [bis(trifluoroacetoxy)iodo]arenes, $ArI(OCOCF_3)_2$, affording high yields of the target λ^3-iodanes after crystyallization. Thus, following this procedure we went on to prepare several hypervalent iodoarene bis(trifluoroacetates), some for the first time (Scheme 4.33), obtaining the corresponding hypervalent derivatives in in 60-80% yield.

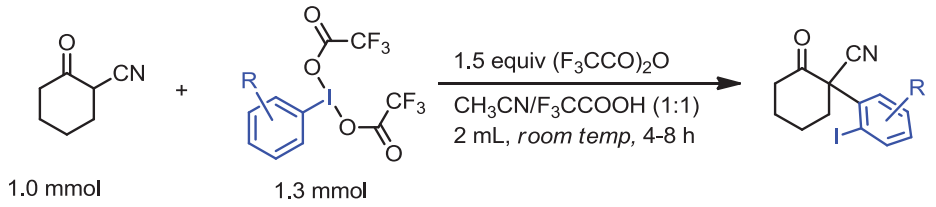


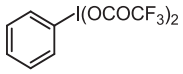
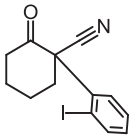
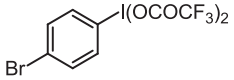
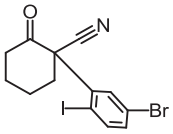
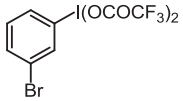
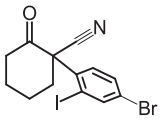
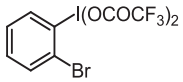
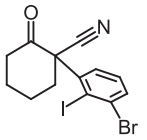
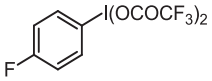
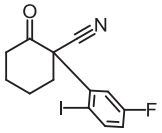
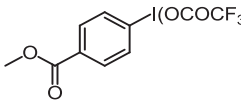
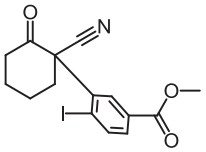
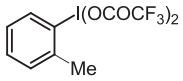
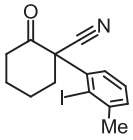
Scheme 4.33. Preparation of substituted aryliodine bis(trifluoroacetate) derivatives.

All reagents were obtained as colorless or pale-yellow crystalline solids. Compounds bearing a second halogen atom, namely **C-F**, proved fairly stable upon prolonged storage. In contrast, the *ortho*-Me derivative **G** was found to decompose within days at room temperature, going from a pale-yellow crystalline solid to a pungent red oil, consisting of a mixture of the α-carboxyiodobenzenes. The high instability of this derivative was attributed to the fact that a chemically labile benzylic CH_3 is brought into a close proximity of a highly reactive (i.e. highly oxidizing) iodine(III) center. Nevertheless, compound **G** could be stored at a low temperature for several months without significant decomposition. Finally, compound **I**, with the two *ortho* positions blockedwas prepared to be used in subsequent mechanistic studies.

The newly prepared hypervalent reagents were subsequently applied to the arylation of 2-cyanocyclohexanone (Table 4.10).

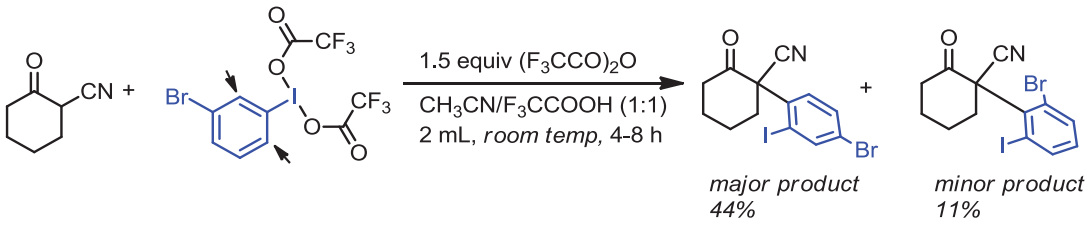
Table 4.10. Result of Coupling between 2-oxocyclohexanecarbonitrile and substituted hypervalent reagents.



entry	$ArI(O_2CCF_3)_2$	Time (h)	Product	Yield, %[a]
1		6		80%
2		6		76%
3		6		44%
4		6		64%
5		5		52%
6		7		76%
7		6		56%

[a]Isolated Yield

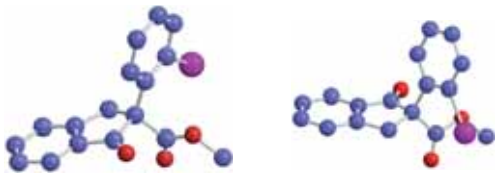
Interestingly, for the reaction corresponding to the arylation using the hypervalent reagent bearing a *meta* Br, both the TLC and the GC analysis of the reaction mixture showed a second product (Scheme 4.34), identified as the regioisomer with the new C-C bond formed at the aromatic 2 position between the iodine and the bromine. This second isomer was found to be fluxional by ^1H NMR due to the relatively slow rotation of the aromatic substituent around the highly hindered C-C bond.



Scheme 4.34. Aryl transfer from the *m*-bromophenyliodane.

Compared with the traditional arylation of enolates, the new arylation method has a very important advantage. The phenyl group is replaced by iodophenyl group. Two important evidences suppose the iodophenyl group was contained in the finally compound.

a) In ^{1}HNMR spectrum, there is four hydrogen peaks from iodophenyl group. Their position is between 6 ppm to 8 ppm, two doubling peaks, two tribling peaks. This means there is only four hydrogen in the iodophenyl group, one position was replaced by the other atom.
   In the ^{13}CNMR, the typical C-I peak can be found at 100ppm. Two spectrum suppose that iodophenyl group was remained.
b) We get the crystal of ethyl 2-(2-iodophenyl)-1-oxo-2,3-dihydro -1H-indene-2-carboxylate. From the X-ray crystallographic analysis, we can define the structure of arylation compound. Ethyl 2-(2-iodophenyl)-1-oxo-2,3 -dihydro-1H-indene-2-carboxylate is a chrial compound.



molecule 1 molecule 2

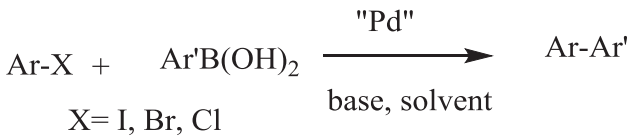
4.2.5. *The synthetic potential of the new α-aryl ketones.*

As we have mentioned before, this new method produces α-arylated carbonyl compounds having an iodine atom in the *ortho* position of the new formed Csp^3-Csp^2 bond. Thus, *a priori*, derivatization through this functional group seems an easy way to obtain different new compounds.

We are going to explain now, different methods used for the transformation of these intermediates in other products of interest.

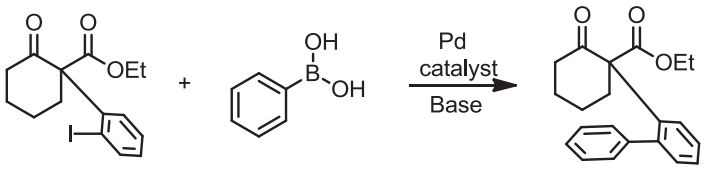
Suzuki-Miyaura cross-coupling reaction

The impact of Suzuki-Miyaura cross-coupling reaction (SMC, Scheme 4.35)[47] on academic and industrial research has been immense. Over the past two decades, it has become possibly one of the most efficient methods for the construction of biaryl or substituted aromatic moieties. Compounds that contain these substructures constitute important building blocks of polymers, ligands, a wide range of natural products such as alkaloids, and numerous biologically active pharmaceuticals. The key advantages of the SMC are the mild conditions under which it is conducted, the high tolerance toward function groups that is observed, the commercial availability and stability of boronic acids to heat, oxygen, and water, and the ease of handling and separation of boron-containing byproducts from the reaction mixtures. These desirable features make the SMC an important tool in medicinal chemistry as well as in the large-scale synthesis of pharmaceuticals and fine chemicals.



Scheme 4.35. General scheme for the Suzuki-Miyaura reaction

We started to study the reactivity of 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate with boronic acid (Scheme 4.36). We tested different palladium catalyst, different bases and different solvents as shown in the Table 4.10. We first selected the cheap and very useful $Pd(OAc)_2$ in the presence of triphenylphosphine as stabilizer of active palladium species and using Cs_2CO_3 as a base obtaining 52% yield of the coupling product. Then we changed the phosphine and SPhos was used (Figure 4.7). The palladium complexes of this organophosphorus compound normally exhibit high activity for Suzuki coupling reactions. The ligand has convenient handling characteristics since it is air-stable. In ours hands no reaction was obtained. Finally, we tested PEPPSI as palladium complex, that is known to catalyze various aminations and cross-coupling reactions including Suzuki coupling. Using 10 mol% of this catalyst and Cs_2CO_3 as a base we obtained 65% yield. We suppose that steric effects of the substrate are the responsible of this moderate yields.



Scheme 4.36. Suzuki-Miyaura of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate

Table 4.11. Suzuki-Miyaura reaction

Substrate (equiv)	$PhB(OH)_2$ (equiv)	Conditions	Solvent and T	Yield
1	1.5	$Pd(OAc)_2$ (4 mol%)	DMF/H_2O(95/5)	52%
		PPh_3 (12 mol%)	2 mL (100°C)	
		Cs_2CO_3 (1.5 equiv)		
1	1.5	$Pd(OAc)_2$ (1mol%)	Toluene	No reaction
		SPhos (12 mol%)	2 mL (100°C)	
		K_3PO_4 (2.0 equiv)		
1	1.5	PEPPSI (4 mol%)	Dioxane	60%
		Cs_2CO_3 (2.0 equiv)	2 mL (80°C)	
1	2.0	PEPPSI (10 mol%)	Dioxane	65%
		Cs_2CO_3 (2.0equiv)	2 mL (80°C)	

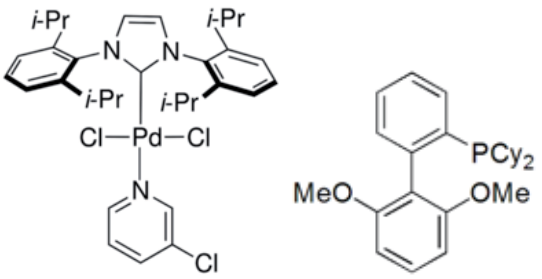
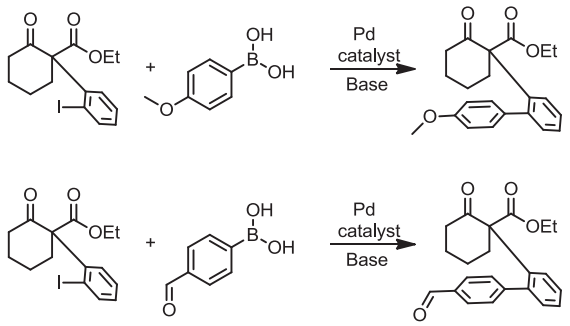


Figure 4.7. Structure of PEPPSI complex and SPhos ligand

The optimized conditions were applied to two other boronic acids: (4-methoxyphenyl)boronic acid and (4-formylphenyl)boronic acid (Scheme 4.37). Ethyl 1-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2-oxocyclohexanecarboxylate was obtained in 67% yield; and 33% yield was achieved for ethyl 1-(4'-formyl-[1,1'-biphenyl]-2-yl)-2-oxocyclohexane carboxylate.

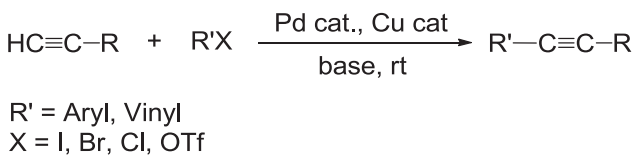


Scheme 4.37 Suzuki-Miyaura of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate with the other boronic acids.

In conclusion, the cross-coupling reaction of our α-arylated compounds with boronic acids processed highly efficiently, although the yields are not excellent probably due to steric effects.

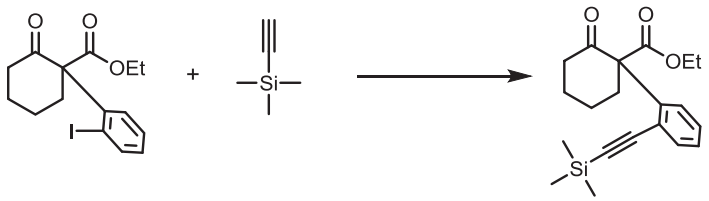
Sonogashira cross-coupling reaction

The Sonogashira reaction is a cross-coupling reaction between aryl or vinyl halides or triflates and terminal alkynes used in organic synthesis to form Csp-Csp^2 bonds (Scheme 4.38). It is a palladium-catalyzed reaction and normally is performed in the presence of copper salts as co-catalyts, which allows the use of milder reaction conditions. Thus, Sonogashira reaction can be carried out at room temperature, in aqueous media, and with a mild base, which has allowed its use in the synthesis of complex molecules. Its applications include pharmaceuticals, natural products, organic materials, and nanomaterials. It is also a key reaction for the synthesis of highly conjugated oligomers.[48]



Scheme 4.38. General scheme for the Sonogashira reaction

Our work started with the study of the reaction of ethyl 1-(2-iodophenyl)-2-oxocyclo hexanecarboxylate with ethylnyltrimethylsilane (Scheme 4.39).



Scheme 4.39. Sonogashira cross-coupling of 1-(2-iodophenyl)-2-oxocyclo hexanecarboxylate

We tested different conditions trying several solvents and catalysts. The results are shown in Table 4.11.

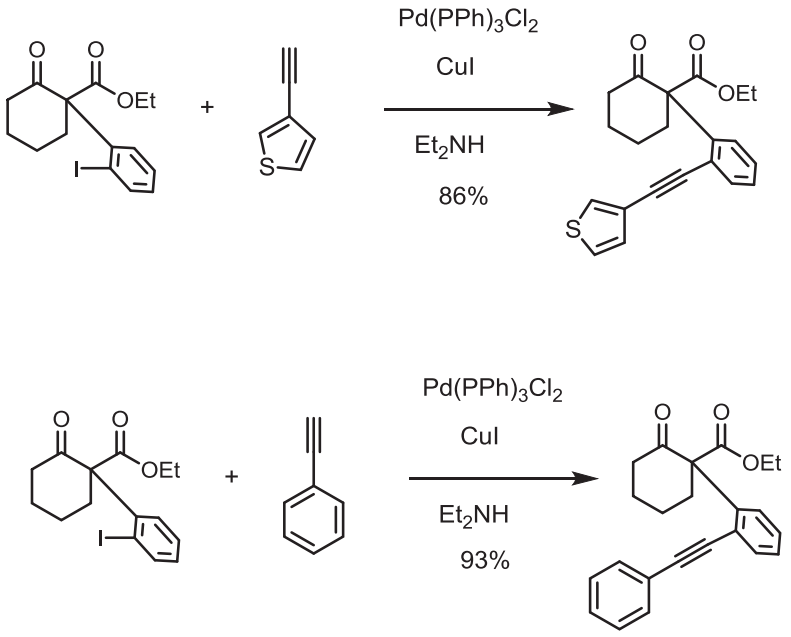
Table 4.12. Sonogashira cross-coupling of 1-(2-iodophenyl)-2-oxocyclo hexanecarboxylate

Run	Substrate (equiv)	Ethynyl trimethylsilane (equiv)	Catalyst and additives	Conditions	Yield
1	1	1.2	$PdCl_2$ (2 mol%) PPh_3 (2 mol%) CuI (1 mol%) Et_3N	CH_2Cl_2 r.t., 1h	42%
2	1	1.5	$PdCl_2$ (4 mol%) PPh_3 (4 mol%) CuI (2 mol%) Et_3N	CH_2Cl_2 r.t., 1h	61%
3	1	2	$PdCl_2$ (8 mol%) PPh_3 (8 mol%) CuI (4 mol%) Et_3N	CH_2Cl_2 40°C, 17h	60%
4	1	1.6	$Pd(PPh_3)_2Cl_2$ (4 mol%)	Et_2NH	70%

			CuI (2 mol%)	(0.3 M)	
				r.t., 36h	
5	1	1.8	$Pd(PPh_3)_2Cl_2$ (8 mol%)	Et_2NH	80%
			CuI (4 mol%)	(0.3 M)	
				45°C, 16h	
6	1	2.0	$Pd(PPh_3)_2Cl_2$ (8 mol%)	Et_2NH	90%
			CuI (4 mol%)	(0.1 M)	
				45°C 16h	

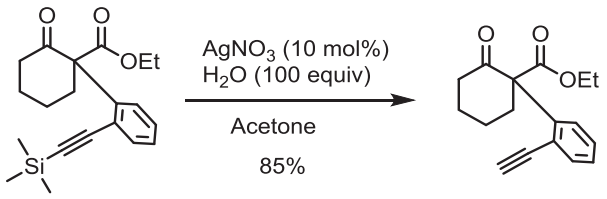
First reactions were carried out using $PdCl_2$ as catalyst, PPh_3 as palladium ligand, CuI as co-catalyst and Et_3N as base in CH_2Cl_2. After several preliminary reactions a maximum of 60% yield was obtained (run 3 of table 4.11). Then we changed the palladium source using $Pd(PPh)_3Cl_2$ and Et_2NH as base and solvent. After some reactions, 90% of ethyl 2-oxo-1-(2- ((trimethylsilyl)ethynyl)phenyl)cyclohexanecarboxy - late was obtained (run 6, table 4.11).

These last optimized conditions were then applied to two other alkynyl compounds, such as 3-ethynylthiophene and ethynylbenzene (Scheme 4.40). Thus, a really high yield of 86% of ethyl 2-oxo-1-(2-(thiophen-3-ylethynyl)phenyl)-cyclohexanecarboxylate was obtained when 3-ethynylthiophene was used. In the case of ethyl 2-oxo-1-(2-(phenylethynyl)phenyl)cyclohexanecarboxylate the yield was even higher up to 93%.



Scheme 4.40. Sonogashira reaction with 3-ethynylthiophene and ethynylbenzene.

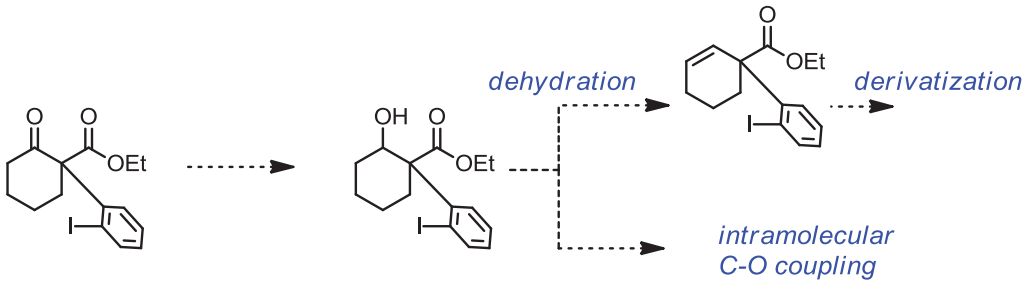
Several methods for the synthesis of 1-alkynes involve the preparation of 1-(trimethylsilyl)-1-alkynes followed by protiodesilylation of these silyl-protected compounds.[49] In general the protiodesilylation reaction can be effected with a large molar excess of a fluoride ion donor, typically $KF{\cdot}2H_2O$ in DMF or methanol,[50] NH_4F in methanol[49a] or tetrabutylammonium fluoride (TBAF) in THF,[49c,49i,51] or with a molar excess of an oxygenated base in a protic solvent such as K_2CO_3 in methanol,[49d, 52] $CaCO_3$ in methanol,[53] KOH in methanol[54] or sodium methoxide in methanol.[55, 56] However, these procedure sometimes suffer from selectivity problems under basic conditions.[49k,57,58] For instance, the reaction provides the alkene instead of the corresponding 1-alkyne.[49k] To avoid this problem, Adriano Carpita and coworkers explored a new procedure for deprotecting 1-(trimethylsilyl)-1-alkynes involving the use of a catalytic amount of $AgNO_3$ in acetone and water. Under these conditions, 85% of ethyl 1-(2-ethynylphenyl)-2-oxocyclohexane -carboxylate can be obtained from ethyl 2-oxo-1-(2-((trimethylsilyl)ethynyl)phenyl) –cyclohexanecarboxylate (Scheme 4.41).



Scheme 4.41. Conversion of a trimethylsilyl alkyne to a terminal alkyne

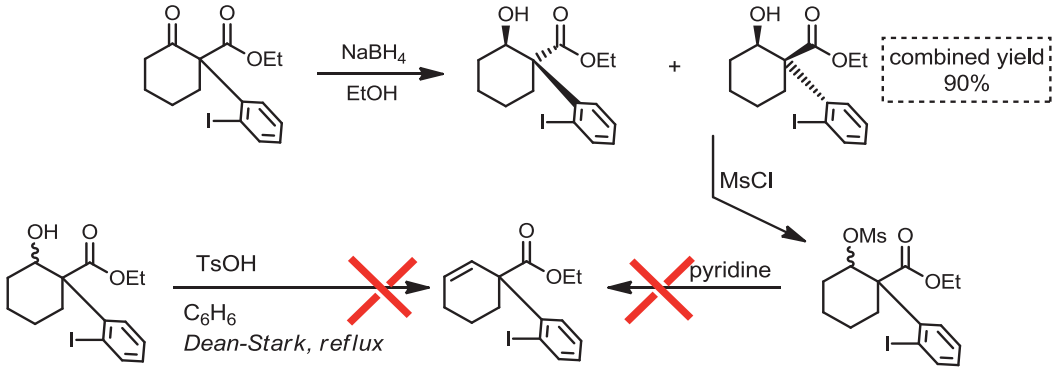
Further derivatization of the α-(2-iodoaryl) ketones

Having established the viability of involving the iodoarenemoitety in intermolecular coupling, we began to study transformation that would take advantage of pairs of functional groups present in the substrate, aiming to access polycyclic structures. Thus, as a previous step, the reduction of the ketone moiety was performed. In addition to the prospect of using the newly formed hydroxyl in intramolecular cross-coupling, we also envisaged that the reduced species might also be dehydrated into a synthetically useful cyclohexene derivative (Scheme 4.42).



Scheme 4.42. Prposedderivatization of theethyl 1-(2-iodophenyl)-2-oxocyclohexanecar – boxylate.

Indeed, reduction of the model ketoesters with $NaBH_4$ afforded a 90% yield of the target alcohol as a 1:3 mixture of the [OH, Ar] cis/trans stereoisomers, as gauged by the ^1H NMR (Scheme 4.43). Although some improvement in the stereoselectivity could be achieved at a lower temperature, additional work will be required in order to achieve a truly selective reduction, and, perhaps, to find methods for the selective synthesis of both stereoisomers. So far, we have been unable to convert the resulting alcohol into a cyclohexene, neither through direct dehydration not through an elimination from an O-activated species (Scheme 4.43).



Scheme 4.43. Reduction of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate

We next addressed the possibility of using the newly prepared arylated iodine-containing species in the formation of heterocyclic structures, particularly oxindole-based heterocycles. This work was inspired by the structure of (+)-Gelsemine, a major alkaloid component of the vines of *Gelsemiumsempervirens*. The compound was first isolated in 1876. Its intriguing structure was elucidated in 1959 by NMR spectroscopy and X-ray crystallographic analysis. To date, seven members of the gelemium alkaloid family have been characterized. These oxindole alkaloids have a hexacyclic architecture and seven carbon stereocenters, including two quaternary stereocenters compacted into a small cage. The challenging structure of gelsemine has been the target of extensive synthetic efforts around the world; within the last two decades a number of total syntheses were reported by the research groups of Johnson, Speckamp, Fukuyama, Hart, Overman, and Danishefsky. Among these total syntheses, there was only one asymmetric total synthesis accomplished by the Fukuyama group. Furthermore, none of these total syntheses has sufficiently illustrated the possible biosynthetic pathway of the gelsemine family.

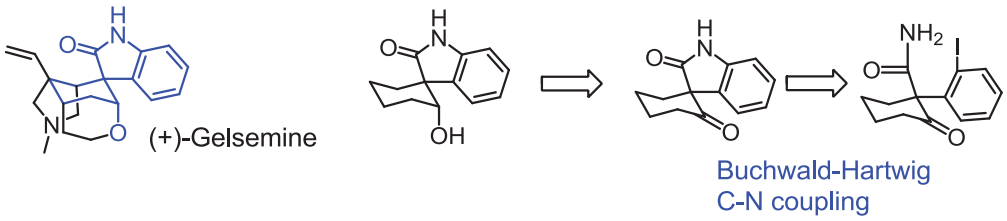
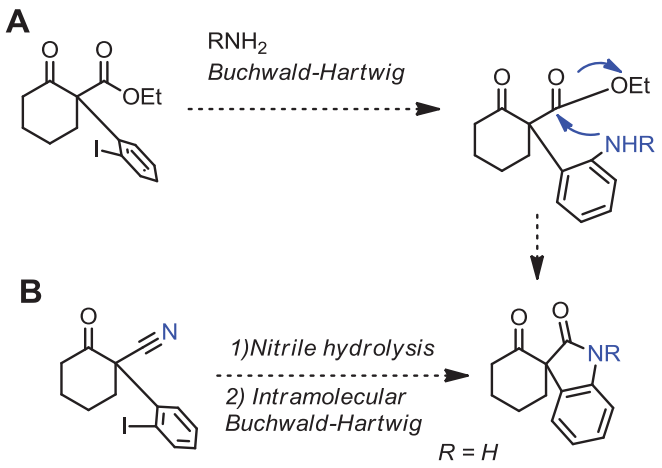


Figure 4.8. The structure of (+) Gelsemine (with the spiroxindole fragment highlighted) and a retrosynthetic proposal for the synthesis of the oxindole fragment from an α-(2-iodophenyl) ketone.

Interestingly, at the core of Gelsemine we find an oxindole skeleton sharing a carbon atom with a cyclohexanone ring, that is, a spiroxindole. We realized that this motif could be envisaged as stemming from the cyclization of an amide derivative of the arylatedketoesters (or ketonitriles), through an intramolecular C-N coupling between the amide NH_2 group and the aromatic iodine (Figure 4.8).

Our initial strategy consisted in performing a Pd-catalyzed Buchwald-Hartwigamination of the iodoarene moiety. The resulting aromatic amine is expected to undergo an intramolecular addition to the electrophilic carbonyl moiety of the ester, displacing the methoxy group and forming an oxindole; giving the highly favoured formation of a 5-membered ring, the cyclization would be expected to take place spontaneously under the conditions of the Buchwald-Hartwig cross-coupling (Scheme 4.44, **A**).



Scheme 4.44. Two approaches to the spiroxindole.

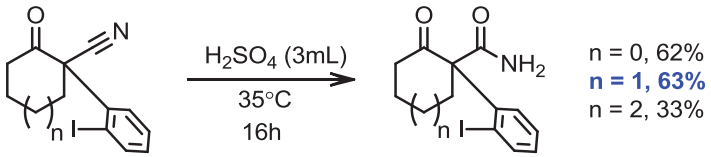
Unfortunately, attempts to carry out a palladium-catalyzed coupling between a model α-(2-iodophenyl) substrates provided very little of the desired C-N coupling product employing $Pd(OAc)_2$ in combination with BINAP or S-Phos as the catalyst system and NaO*t*Bu as base. We concluded that this intertness of the aryl iodide is due to the steric hinderance of the iodine group due to the bulky *ortho* substituent. It is interesting to note that the *orho* steric bulk, while not an issue in the case of the Pd-catalyzed C-C coupling (see above), becomes highly detrimental for the more challenging, and thus more sensitive, C-N coupling reaction.

We, therefore, attempted an alternative approach, consisting in converting an α-arylatedcyanoketone to an amidoketone through the hydrolysis of the nitrile group (Scheme 4.44, **B**). We found that this hydrolysis to be challenging under a variety of conditions, providing at best low yield of the target amide even upon storing in concentrated hydrochloric acid (Table 4.12, entry 1-5). As an acceptable solution, synthetically useful yields of the amide could be obtained via the hydrolysis of the nitrile in concentrated sulfuric acid at 35 °C. Although the conversion is not complete under these conditions, stopping the reaction after 16 hours, nevertheless, was found necessary to avoid the overhydrolysis of the amide product to the corresponding carboxylic acid (Scheme 4.45).

Table 4.12. The screening of conditions for amide hydrolysis

Run	Conditions	Outcome
1	2.5mol% CuI; NH_3(1.25 mL), H_2O 100°C, overnight	No product

2	10mol%TBAB; $NaOH_{aq}$; H_2O_2 (4 equv) Toluene (2 mL), 100°C overnight	No product
3	HCl(30%), r.t. overnight	Traces
4	H_2SO_4 (3 mL), r.t. overnight	30%
5	H_2SO_4 (3 mL), r.t. 3days	30%
6	**H_2SO_4 (3 mL)** **35°C, 16h**	**63%**



Scheme 4.45. Hydrolysis of the α-(2-iodoarene)cyanoketones.

The structure of the ketoamide obtained via this route was confirmed through a single crystal X-Ray structural determination. As expected, the 6-membered ring adopted a chair conformation, with the carboxamide group occupying an axial position, and the iodoarenegroup, an equatorial. The arene group is disposed in a way that the iodine atom is pointing away from the carboxamide group. (Figure 4.9). Under the same conditions, the corresponding 5- and 7-membered cyclic analogues were obtained in 62% and 33% yields, respectively.

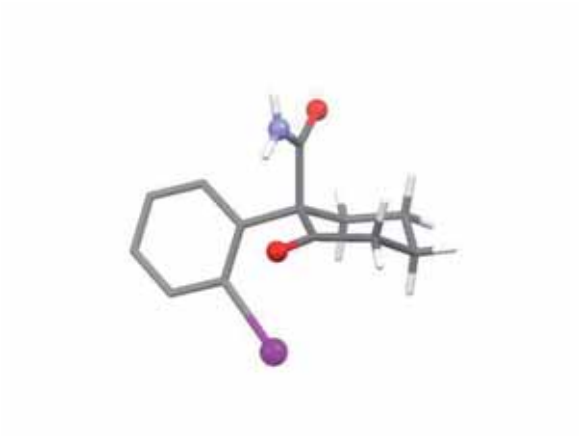
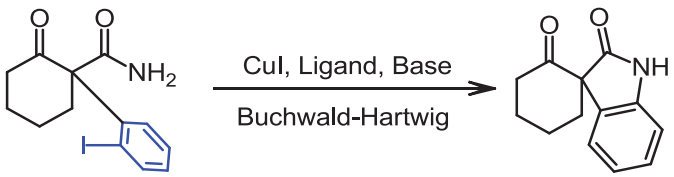


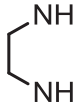
Figure 4.9. X-Ray crystal structure of the arylated β-ketoamide obtained through nitrile hydrolysis.

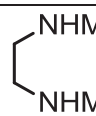
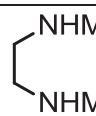
With the amide at hand, we proceeded to establish conditions required for the intramolecular C-N coupling between the amide nitrogen and the iodoarene. In general, perhaps some of the best conditions for the arylation of amide are those described by Buchwald and co workerusing a combination CuI with a chelating diamine; we were hopeful that in our case the C-N coupling would be further favoured by the formation of a 5-membered cycle. Thus, the 6-membered ketoamide was subjected to conditions of the Buchwald variant of the (copper-catalyzed) Goldberg coupling (Scheme 4.46, Table 4.13).



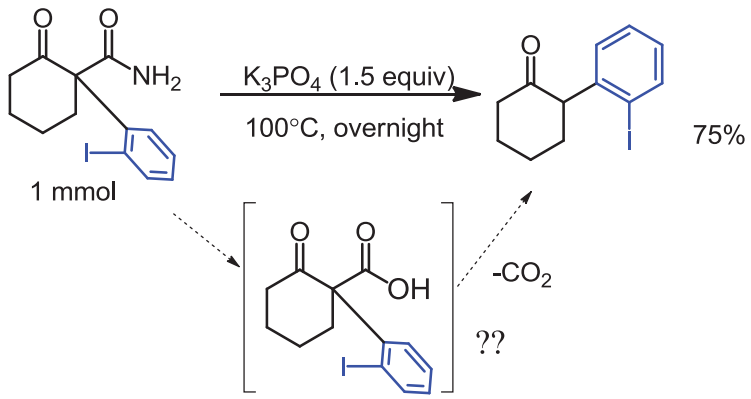
Scheme 4.46. C-N Cross Coupling of Amide.

Table 4.13. Optimization of the C-N Cross Coupling of Amide

Run	Ligand	Conditions	Outcome	Comment
1		5 mol% CuI; 10 mol% **L** 1.3 equivK_3PO_4; dioxane 1 mL 110°C 24 hours	No product	
2	--	10 mol% CuI 1.5 equivK_3PO_4; DMF2 mL 100°C 16 hours	20%	By-prod.

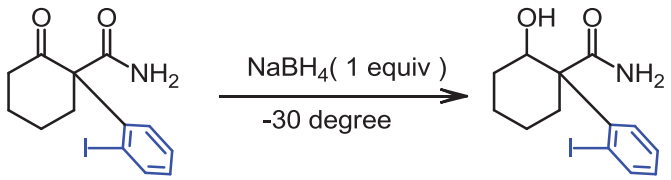
3	--	**no catalyst** 1.5 equiv K_3PO_4, DMF 2 mL 100°C, 16 h	No product	
4	--	10 mol% CuI 1.5 equiv Et_3N, DMF 2 mL 100°C,16 hours	No product	
5		CuI 10mol%, 20 mol% **L** Et_3N 2 equiv, DMF 2 mL 100°C,16 hours	<30%	By-prod
6		CuI 10mol%, 20 mol% **L** $NaHCO_3$ 2 equiv, DMSO 1 mL 100°C,16 hours	15%	By-prod

N,N'-dimethylethylenediamine was chosen as a ligand for this copper-catalyzed process. Dioxane proved ineffective as a solvent (Table 4.13, entry 1). Nevertheless, the use of the more polar DMF and DMSO did indeed small amounts of the target spiroxindole (entries 2,5 and 6). The possibility of the product formation via the non-catalyzed Nucleophilic Aromatic Substitution (S_NAr) was ruled out, as the control experiment in the absence of copper afforded none of the cyclized species (entry 2). Inevitably, the use of K_3PO_4 as base led to the formation of non-negligible amounts of a second product. Through GC, GC-MS and NMR analysis, this side product was identified as the 2-(2-iodophenyl)cyclohexanone, apparently stemming through the decarboxylation (or decarboxyamidation) of the substrate. This side reaction does not require a catalyst; indeed, the same compound was obtained in a 75% yield simply by heating the substrate in the presence of potassium phosphate (Scheme 4.47). As a preliminary hypothesis, we envisage an initial base-promoted conversion of the amide to a carboxylate, followed by a thermal decarboxylation. Unfortunately, attempt to reduce this process by using a milder organic base (Et_3N) afforded nne of the target product (nor side-product, entry 4).



Scheme 4.47. By product of C-N Cross Coupling

Since the decarboxylation process is highly favoured in β-dicarbonyl systems, we thought to overcome the tendency of the substrate to lose CO_2 by converting the keto C=O group to a hydroxyl OH. Thus, using the standard $NaBH_4$ reduction (previously used for the reduction of the ketoester, Scheme 4.43), the target 2-hydroxy-1-(2-iodophenyl)cyclohexane-carboxamide was obtain as a trans:cis = 2:1 mixture in an overall 93% yield (Scheme 4.48). the structure of the major *trans* stereoisomer was determined by an single crystal X-Ray crystallographic analysis (Figure 4.10). Once again, the aryl group was found to occupy an equatorial position in the cyclohexane ring, with the OH group taking up an equatorial position on an adjacent carbon atom. Surprisingly, the compound does not present significant intramolecular hydrogen bonding, that is often found in compounds with vicinal H-donor/acceptor groups (*i.e.* OH and NH_2).



Scheme 4.48. Conversion of the β-ketoamide to a β-hydoxyamide

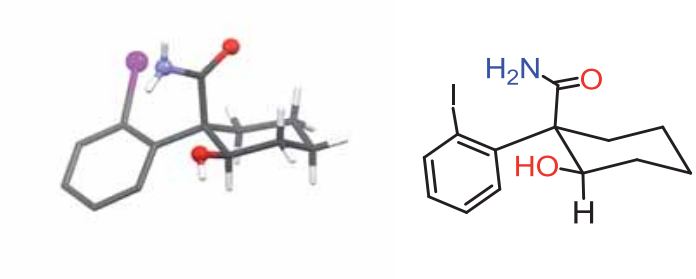
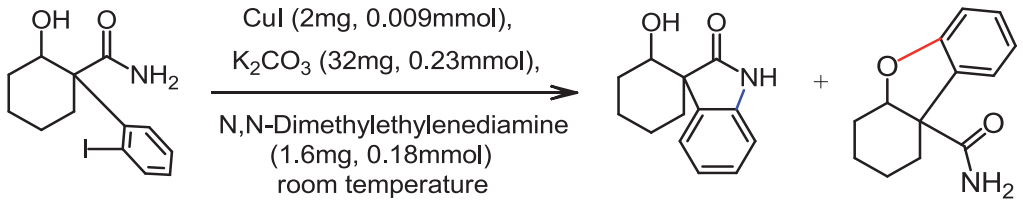


Figure 4.10. X-Ray crystal structure of the arylated β-hydoxyamide obtained through ketone reduction.

The substrate was then submitted to the cyclizative copper-catalyzed C-N coupling protocol established for the closely related ketoamide. Thus, the substtrate was stirred in DMF in the presence of copper iodide, K_2CO_3 and N,N'-Dimethylethylenediamine at room temperature. The analysis of the reaction mixture revealed that while the target spiroxindole did indeed form, another product also form in the reaction, this time corresponding to the competing coupling between the alcohol OH group and the aryl iodide. Incidentally, the formation of this hydroxynebzofuran species also constitutes the formation of a 5-membered ring, and is thus also favoured. Up to now, we have not found an effective way to optimizing the yield of the C-N cross process above 40% (Scheme 4.49).



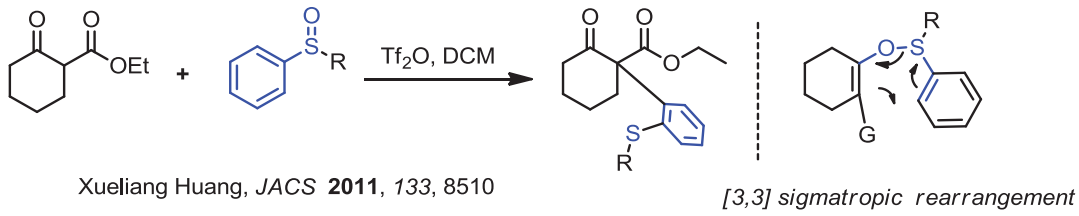
Scheme 4.49. C-N Cross Coupling of Alcohol.

The formation of both the spiro-oxindole (via C-N coupling) and the tetrahydo-benzofuran species (via C-O coupling) has sofar precluded further improvement in the yield of the spriroxindole target. Nevertheless, the possibility of both copper-catalyzed processes will be further studied with the aim of developing methods to selectively obtain either of the heterocycles in a selective fashion from the same precursors.

4.2.6.*Mechanistic studies of the arylation using PIFA and related species..*

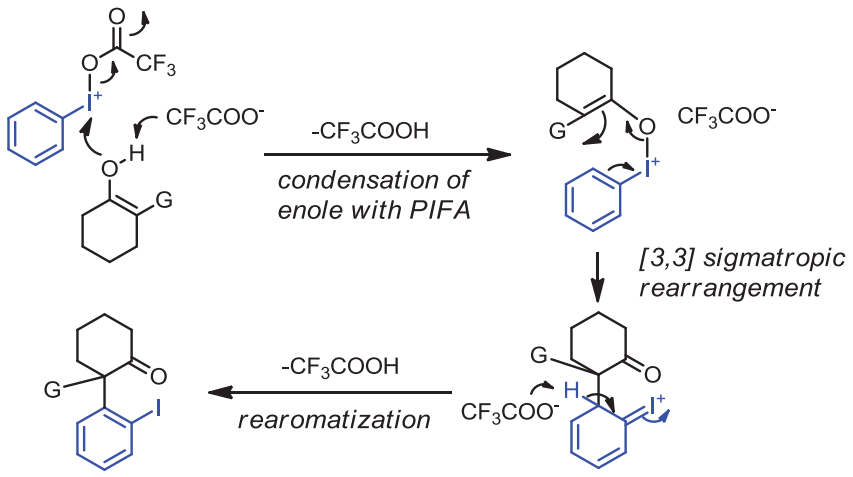
As discussed in previous sections, the formation of the new C-C bond leading to the α-(2-iodophenyl) ketone product could not be explained by the classical mechanism established for the related aryl transfer from the diaryl λ^3-iodanes. Unlike the reaction at

hand, this latter transformation proceeds with the transfer of a phenyl group, and is belived to proceed via the [1,2] rearrangement of an intermediate iodonium enolate (see Section 4.2.1). A likely explanation for the transfer of the 2-iodoaryl group observed in our arylation with PIFA could be found in the a the similar transformationreported by Huang and Maulide.[59] Specifically, the report describes a novel sulfoxide-mediated α-arylation of carbonyl substrates, in which the (now reduced) sulfur atom is retained o*rtho* to the newly formed C-C bond. This reaction proceeds under very mild conditions at room temperature and does not require any transition-metal catalyst (Scheme4.50). The exclusive formation of the *ortho*regiosomer was rationalized by the formation of a sulfonium enolate intermediate and a subsequent [3,3] sigmatropic rearrangement. Furthermore, the authors argue that the extremely mild conditions required for this transformation are due to the positive charge of the sulfur atom, leading to the *charge-accelerated Claisen reaction*.



Scheme 4.50. [3,3] sigmatropic rearrangement

We, therefore, propose an analogous mechanism, this time consisting in the [3,3] rearrangement of an intermediate iodonim*O*-enolate, also known as the *reductive iodoniumClaisen rearrangement* (RICR, Scheme 4.51).



Scheme 4.51. Mechanistic hypothesis for the iododoniumClaisen

Given that the process is a formal C-H bond functionalization of the aromatic ring *ortho* to the C-I bond, determining the kinetic isotope effect for this process would indicate whether the breaking of the C-H bond is involved in a rate-determining step.

As a brief background, the Isotope effects: a special type of substituent effect that has proved very valuable in the study of reaction mechanisms and involves the replacement of an atom by one of its isotopes. Isotopic substitution has most often involved replacing protium by deuterium (or tritium), but the principle is applicable to nuclei other than hydrogen. The quantitative differences are largest, however, for hydrogen, given that the atomic mass of ^{2}H is twice that of ^{1}H. Isotopic substitution has no effect on the qualitative chemical reactivity of the substrate, but it often has an easily measured effect on the rate at which reaction occurs. Particularly importantare the *primary kinetic isotope effects*, those in which a bond to the isotopically substituted atom is broken in the rate-determining step. We will use C-H bonds as the specific topic of discussion, but the same concepts apply for other elements.

Any C-H bond has characteristic vibrations which impart some energy to the molecule in its normal state. This energy is called the *zero-point* energy. The energy associated with these vibrations is related to the mass of the vibrating atoms. Because of the greater mass of deuterium, the vibrations associated with a C-D bond contribute less to the zero-point energy than do those of the corresponding C-H bond. For this reason, substitution of protium by deuterium lowers the zero-point energy of a molecule. The energy difference due to this vibration disappears at the transition state. The transition state has the same energy for the protonated and deuterated species. Since the deuterated molecule had the lower zero-point energy, it necessarily has a higher activation energy to reach this same transition state, and will occur at a rate lower than the protio substrate.

Just how large the rate difference is depends on the nature of the transition state. The maximum effect occurs when the hydrogen being transferred is bound about equally to two other atoms at the transition state. The calculated maximum for the isotope effect k_H/ k_D involving C-H bonds is about 7 at room temperature. It should also be noted that although even higher isotope effect (up to 40!) have been documented on occasions, these are believed to involve proton tunneling (quantum effects) and are beyond the scope of this overview.

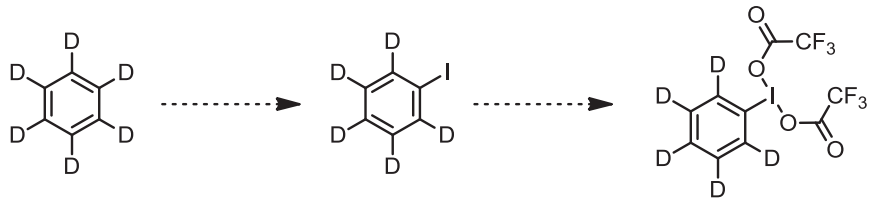
When bond breaking is more or less than half complete at the transition state, the value is less and can be close to 1 if the transition state is very reactant-like or very

product-like (i.e. very *late* or *early*). Primary isotope effects can provide two very useful pieces of information about a reaction mechanism. First, the existence of a substantial isotope effect, that is, if $k_H/ k_D$is 2 or more, is strong evidence that the bond to the isotopically substituted hydrogen atom is being broken in the rate-determining step. Second, the magnitude of the isotope effect provides a qualitative indication of where the transition state lies with respect to product and reactant. A relatively low primary isotope effect implies that the bond to hydrogen is either only slightly or nearly completely broken at the transition state. That is, the transition state must occur quite close to reactant or to product. An isotope effect near the theoretical maximum is good evidence that the transition state involves strong bonding of the hydrogen to both its new and old bonding partner.

Isotope effects may be observed even when the substituted hydrogen atom is not directly involved in the reaction. Such effects are called *secondary kinetic isotope effects*. Secondary isotope effects are smaller than primary ones and are usually in the range of k_H/ k_D= 0.7 – 1.5. Secondary isotope effects may be normal (k_H/ k_D> 1) or inverse (k_H/ k_D< 1). They are also classified as α, β, etc., depending on whether the isotopic substitution is on the reacting carbon or farther away. Secondary isotope effects result from a tightening or loosening of the C-H bond at the transition state. The strength of the bond may change because of a hybridization change or a change in the extent of hyperconjugation, for example. If sp^3–hybridized carbon is converted to sp^2 as reaction occurs, ahydrogenbound to the carbon will experience decreased resistance to C-H bending. The freeing of the vibration for a C-H bond is greater than for a C-D bond because the C-H bond is slightly longer and the vibration therefore has a larger amplitude. This will result in a normal isotope effect.

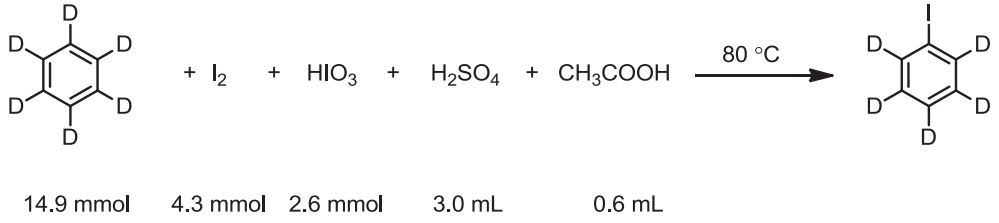
Often.rather than by measuring individual rate constants isotope effect are measured by a competition between H and D. In the simplest case, an equimolar mixture of the H- and the D- substrates is subjected to the reaction conditions to determine the so-called *intermolecular KIE*. In addition, for compound that present two (or more) equivalent hydrogen positions (such the two H *ortho* to a substituent), replacing one with a deuterium will allow to measure an *intramolecular KIE* simply by quantifying the ration of the D/H products.

Thus far we have synthesized PIFA-d_5 in order to measure the *intermolecular KIE*. Our synthetic proposal consisted in converting deuterated benzene to PhI-d_5 and subsequently oxidizing this iodoarene to the corresponding hypervalent derivative (Scheme 4.52).



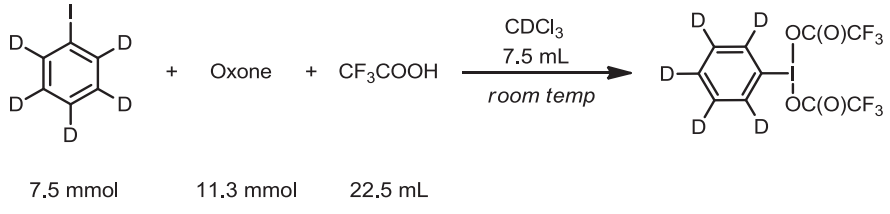
Scheme 4.52. Syntehtic proposal to accessPIFA-d_5.

Iodobenzene-$d_5$was prepared from the readily available benzene-d_6. *Thus, b*enzene-d_6 was monoiodinated by the method of Wirthe and co-workers[30]by a treatment with iodic acid, iodine, acetic acid- d_4 deuterium oxide and sulfuric acid to gives iodobenzene-d_5. Mass spectrometry indicates a purity of >98.5% C_6D_5I (Scheme 4.53).



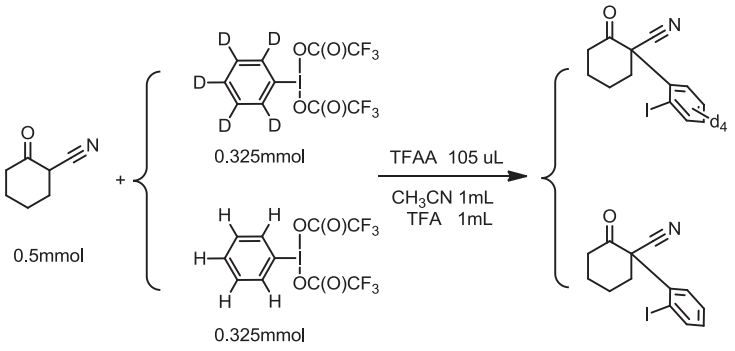
Scheme 4.53. Synthesis of iodobenzene-d_5

Given the small scale of the reaction, the separation of of the iodobenzene from the unreacted benzene by distillation of chromatography was found to be complicated. For this reason, we proceeded to use the PhI/PhH mixture directly in the next step (Scheme 4.54), affording the fully deuterated PIFA as a white solid after single recrystallization. The compound was found to be >98% isotopic purity, and was essentially devoid of signals in the ^{1}H NMR. The compound, however, was characterized by ^{13}C NMR, which showed the multipletsariding from the C-D coupling



Scheme 4.54. Synthesis of PIFA-d_5

With the perdeuteratedphenyliodinebis(trifluoroacetate) (PIFA-d_5) in hand we we tested this reagent in an intermolecular competition with the non deuterated PIFA (*e.g.* PIFA-d_5) using the model arylation of α-cyanocyclohexanone(Scheme 4.55).



Scheme 4.55. Cyanoketone worked with PIFA-d_5 and normal-PIFA

Thus, the reaction using equimolar amounts of PIFA-H_5 and PIFA-d_5 under otherwise standard conditions was allowed to proceed to approx. 20% conversion, and then the product was isolated. The ratio of the *protio* and the *deutero* products was then determined in the ^{1}H NMR by comparing the integration of the aliphatic resonances of the cyclohexanone moiety (common to both isotopomers) with those of the aromatic region which only contains the *protio* species Figure 4.9). As a reference, the integration the *axial*H atom (**H^b**) α to the ketone unit was set to 1H, giving, for the fully product an integration of 1H for each of the aromatic protons. From the experimental integration of 0.49H for the H *ortho* to the iodine atom, the ratio of the two isotopomers was found to be 1:1 within experimental error, and a KIE = 1.0, thus showing no measurable reactivity difference between the C-H and the C-D bonds in this process. Further experiments are underway to further narrow down the mechanistic proposal.

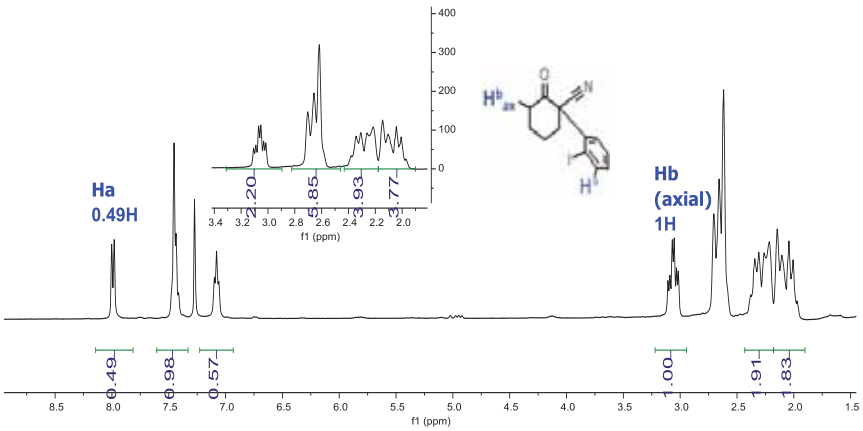


***Figure 4.*11.** A fragment of the ^{1}H NMR spectrum of the isotopomeric mixture of the arylatedcyanocyclohexanone.

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4.3. Experimental section

4.3.1. *General remarks*

Nuclear Magnetic Resonance (NMR) recorded at the *Servei de RessonanciaMagnetica Nuclear* of the *Universitat Autonoma de Barcelona*. H-NMR, C-NMR spectra were recorded using Bruker instruments (DXP-250, DXP-360 and AVANCE-III 400). Chemical shift (δ) are given in ppm using the residual non-deuterated solvent as internal reference.

Infra-red spectroscopy (IR) spectra were recorded with a Bruker Tensor 27 spectrometer using a Golden Gate ATR module with a diamond window. When necessary, IR spectra were recorded using KBr pellets using a Thermo Nicolet IR2000 spectrometer.

Mass-spectrometry (MS) Low- and High-resolution mass spectra were obtained by direct injection of the sample with electrospray techniques in a Hewlett-Packard 5989A and *micro TOF-Q* instruments respectively. These analyses have been performed by the *Servei d'Analisi Quimica (SAQ)* of the *Universitat Autonoma de Barcelona*.

Element Analysis (EA) of C and H were performed by the *Serveis Cientifico-Tecnics* of the *Universitat de Barcelona (SCT-UB)*. The percentages of C and H were determined by combustion using a EA-1108 C.E. elemental analyser of Thermo Scientific using BBOT as internal standard.

Thin-Layer Chromatography (TLC) was performed using 0.25 mm plates (Alugram Sil G/UV_{254})

Flash Chromatography was performed under nitrogen pressure on a *Macherey-Nagel GmbH & Co KG* silica gel which had a particle size of 230 – 400 mesh and pore volume of 0.9 mL/g.

Gas Chromatography (GC) was performed with an Agilent Technologies 7890A instrument equipped with an *Agilent HP-5* (30m x 0.32m x 0.25 um) capillary column. Unless otherwise stated, instrument methods used to monitor catalytic tests are: *Normal* 75 T_0 =75 °C, t_0 = 0.5 min, 25 °C/min T_f = 240 °C, t_f = 4 min. Sometimes longer method was used: Long 75 T_0 = 75 °C, t_0 = 0.5 min, 25 °C/min T_1 = 240 °C, t_1 = 2min, 10 °C/min, T_2 = 280 °C, t_2 = 5 min (*long*).

Melting points were determined using a Koffler-Reichert apparatus.

Powder X-Ray Diffraction (PXRD) experiments were performed by Xavier Caballero at the Universitat Autonoma de Barcelona using an instrument with a X-Ray source.

Others:

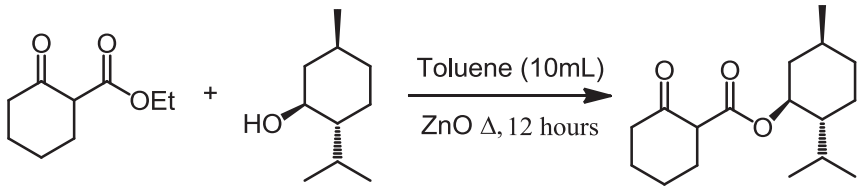
When required, experiments were carried out with standard with vacuum and Schlenk techniques under N_2 or Ar atmosphere using dry solvents which were distilled and cannula or syringe transferred.

Commerical reagents were directly used as received. Na_2SO_4 and $MgSO_4$ used to dry the organic layers were anhydrous.

Dry solvents were prepared using standard methods: CH_2Cl_2, , CH_3CN were distilled over CaH_2. Commercial dry DMF from *Sigma-Aldrich* was used without further purification. In some experiments, dry solvents were obtained from two instruments: PureSolv (Innovative Technologies: THF, CH_2Cl_2, Pentane).

4.3.2. *Preparation of β-ketoester*

Preparation of (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-oxocyclohexane carboxylate

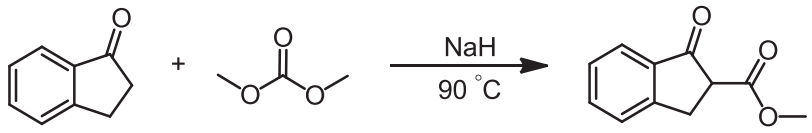


A round-bottom flask was charged with ethyl-oxocyclohexane carboxylate (5.88mmol, 1g), (-)-menthol (8.82mmol, 1.38g), zinc(II) oxide (1.18mmol, 0.10g, 20mmol%) and 10mL of toluene. The flask was fitted with a short-path distillation heat and heated, distilling the ethanol formed during the reaction. After 12 hours the TLC of the reaction mixture showed complete consumption of the β-ketoester. The reaction mixture was filtered through a plug of celite to remove the catalyst. The filtrate was concentrated under reduced pressure and the crude reside was purified by column

chromatography on silica gel, eluting with a mixture of AcOEt:Hexane = 1:9 (R_f = 0.8). White oil, 1.41g, yield: 85%.

^{1}H NMR (360 MHz, $CDCl_3$) δ 12.32 (s, 1H), 4.75 (td, *J* = 10.8, 3.6 Hz, 1H), 2.31 – 2.12 (m, 4H), 2.09 – 1.97 (m, 1H), 1.92 – 1.83 (m, 1H), 1.74 – 1.55 (m, 6H), 1.54 – 1.23 (m, 3H), 1.14 – 0.94 (m, 2H), 0.93 – 0.85 (m, 7H), 0.77 (d, *J* = 7.2 Hz, 3H).

Preparation of methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate

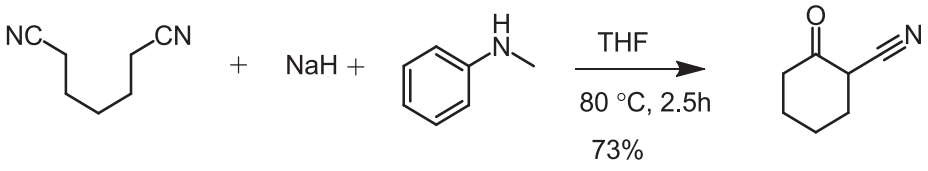


In a three-mecked ball (250mL) provided with mechanical stirring, is added NaH (2.06g, 63.92mmol) in dimethylcarbonate (35mL, 415mmol). To this mixture through an addition funnel, was added dropwise the solution of indanone (2.9g, 21.97mmol) in dimethylcarbonate and allow to react by mechanical agitation at 90 °C. After 3 hours, basified with NaOH 3% (40mL) and extract the unreacted indanone with ethyl acetate.

Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate and methyl 1-oxo-1,2,3,4-tetra - hydronaphthalene-2-carboxylate have already made by our group. So in this thesis, we won't provide any spectrum of them.

4.3.3. *Preparation α-cyano cycloalkanones*

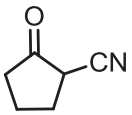
2-Cyanocyclohexanone



An oven-dried 3-neck 1-L flask was charged with a large stirbar and NaH (24.3 g @ 60% in oil, corresponds to 14.6 g oil-free, 607 mmol). A nitrogen inlet was added, and contents were flushed with nitrogen. At this point, the protecting oil was removed by stirring the contents with hexane (dry, 100 mL) for 15 min and then decanting the liquid via cannula. THF (300 mL, dry) and *N*-methylaniline were added. The flask was then fitted with a reflux condenser, and an addition funnel to which a solution of

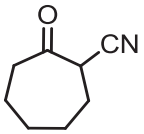
pimelonitrile (24.7 g, 202.2 mmol) in THF (150 mL) was transferred. This solution was added to the flask over a period of 20 minutes, and the reaction mixture was brought to reflux for 2.5 h, resulting in the formation of a thick paste. This mixture was cooled to 0 °C and was quenched by slowly adding H_2O (75 mL). The mixture was further acidified to a pH of 1 using diluted HCl. The resulting yellow solution was transferred to a separatory funnel, extracted with Et_2O and dried over $MgSO_4$. The oil obtained after evaporating the solvent was purified by vacuum distillation. Clear pale-yellow liquid, yield: 18.13 g, 73%. *^{1}H NMR in $CDCl_3$ shows that the product exists almost exclusively as the keto form*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (ddd, *J* = 11.2, 5.4, 1.0 Hz, 1H, CHCN), 2.60 (dtd, *J* = 14.2, 4.6, 1.3 Hz, 1H, C*H*HCO), 2.51 – 2.26 (m, 2H), 2.17 – 1.92 (m, 3H), 1.91 – 1.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5 (C=O), 116.7 (CN), 43.4 (CHCN), 40.7 (CH_2), 32.2 (CH_2), 26.9 (CH_2), 23.7 (CH_2).

2-oxocyclopentanecarbonitrile



Sodium hydride (1.80g, 45mmol, 60% w/w), cleaned previously with pentane anh., was suspended in THF anh. (22 mL) inside a schlenk. Under N_2 atm. was added *N*-methylaniline (4.87 mL, 45 mmol). After 5 min was added a solution of adiponitrile (1.71 mL, 15 mmol) in THF anh. (10 mL) dropwise by an addition funnel over 30 min. Dimroth refrigerant was coupled to the system and purged with N_2. The mixture was heated under reflux for 2.5h and then cooled to 0°C, at which time water (15 mL) was added dropwise and slowly to quench the reaction followed by addition of concentrated HCl to acidify the solution to around pH 1. The aqueous solution was extracted with ether (3X20 mL), and the combined extracts were washed with brine, dried, filtered and concentrated. The crude residue was subjected to purification by flash chromatography on silica gel, hexane/AcOEt = 7/3 (R_f = 0.3), yellow oil, 1.35g, 82.4%.^{1}H NMR (360 MHz, $CDCl_3$) δ 3.18 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.56 – 2.40 (m, 1H), 2.39 – 2.22 (m, 2H), 2.19 – 2.06 (m, 2H), 1.96 – 1.82 (m, 1H). ^{13}C NMR (91 MHz, $CDCl_3$) δ 207.4 (C=O), 116.8 (CN), 39.3 (CHCN), 36.6 (CH_2), 28.4 (CH_2), 21.0 (CH_2).

2-oxocycloheptanecarbonitrile

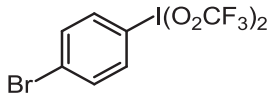


Following the procedure of 2-oxocyclopentanecarbonitrile. The reaction was quenched in 12 hours. hexane/AcOEt = 4/1 (R_f = 0.25), yellow oil.^{1}H NMR (360 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.63 – 2.55 (m, 2H), 2.14 – 2.03 (m, 1H), 2.02 – 1.89 (m, 1H), 1.87 – 1.75 (m, 2H), 1.75 – 1.61 (m, 3H), 1.61 – 1.48 (m, 1H).^{13}C NMR (91 MHz, $CDCl_3$) δ 203.54 (C=O), 117.6 (CN), 44.8 (CHCN), 44.7 (CH_2), 42.3 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 23.4 (CH_2).

4.3.4. *Preparation of hypervalent iodine reagents*

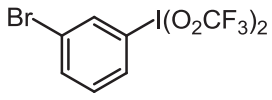
General Procedure. The aryliodonium bis(trifluoroacetates) were synthesized using Oxone® according to a method reported by Zhdankin and coworkers.[1] Briefly, a solution of the iodoarene and Oxone® (1.5 equiv persulfate) in a mixture of trifluoroacetic acid (3 mL/mmol ArI) and chloroform (1 mL/mmol ArI) was allowed to stir in a closed flask (under air) at until the disappearance of ArI by TLC. At this point, the solvent was evaporated to dryness and the residue was re-extracted with chloroform. After removing the salts by filtration, the solvent was once again evaporated to give the crude product as a microcrystalline solid. The pure product obtained by crystallization from a hot 30:1 cyclohexane/trifluoroacetic acid mixture.

p-Br-PIFA



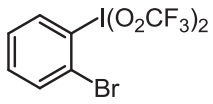
Following the General Procedure, the *p*-I-bromobenzene (1.351 g, 4.78 mmol) was allowed to react with Oxone® (2.200 g, 7.16 mmol) in a mixture of CF_3COOH (15 mL) and $CHCl_3$ (5 mL) for 5 h. White crystals, yield; 2.127 g, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (q, $J_{C\text{-}F}$ = 41.4 Hz, C=O), 136.7, 135.5, 129.4, 120.6, 113.0 (q, $J_{C\text{-}F}$ = 288.3 Hz, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.1.

m-Br-PIFA



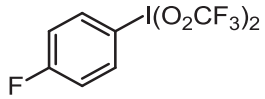
Following the General Procedure, the *m*-I-bromobenzene (1.26 g, 4.45 mmol) was allowed to react with Oxone® (2.05 g, 6.68 mmol) in a mixture of CF_3COOH (12 mL) and $CHCl_3$ (4 mL) for 6 h. Off-white crystals, yield: 1.194 g, 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (t, *J* = 1.9 Hz, 1H, *H*-2), 8.15 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H, *H*-3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (q, $J_{C\text{-}F}$ = 41.5 Hz, C=O), 137.3, 137.0, 133.5, 133.1, 124.9 ,122.0 ,112.9 (q, *J* = 288.3 Hz, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.1.

o-Br-PIFA



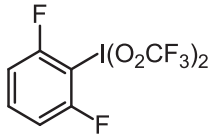
Following the General Procedure, the *o*-I-bromobenzene (1.350 g, 4.78 mmol) was allowed to react with Oxone® (2.200 g, 7.17 mmol) in a mixture of CF_3COOH (15 mL) and $CHCl_3$ (5 mL) for 20 h. White crystals, yield: 1.253 g, 51%.

p-F-PIFA



Following the General Procedure, the *p*-I-fluorobenzene (2.220 g, 10.0 mmol) was allowed to react with Oxone® (4.918 g, 16.0 mmol) in CF_3COOH (30 mL) and $CHCl_3$ (10 mL) for 2 h. White crystals, yield: 3.320 g, 74%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 – 8.17 (m, 2H), 7.43 – 7.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 (d, *J* = 258.8 Hz, C=CF), 161.1 (q, *J* = 41.4 Hz, C=O), 138.2 (d, *J* = 9.3 Hz), 119.8 (d, *J* = 23.3 Hz), 116.4 (d, *J* = 3.6 Hz, C-I), 112.8 (q, *J* = 288.3 Hz, CF_3); ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$) δ -73.2 (s, 6F, CF_3), -100.3 (tt, *J* = 7.9, 4.6 Hz, 1F, CF_{Ar}).

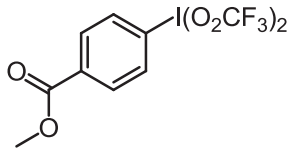
o-F-PIFA



Following the General Procedure, the 1,3-difluoro-2-iodobenzne (1.680 g, 7.0 mmol) was allowed to react with Oxone® (3.44 g, 11.2 mmol) in a mixture of CF_3COOH (20 mL) and $CHCl_3$ (6 mL) for 10 h. Colorless crystals, yield: 2.30 g, 70%. ^{1}H NMR (500

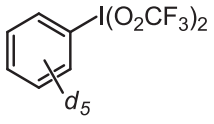
MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (tt, *J* = 8.5, 6.3 Hz, 1H), 7.37 – 7.28 (m, 3H); *the signals for the oxo dimer [ArI(TFA)]$_2$O (the minor component) integrate to 14%*; ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.71 (q, *J* = 41.8 Hz, C=O), 160.24 (dd, *J* = 259.4, 3.9 Hz, CF_{Ar}), 138.36 (t, *J* = 9.8 Hz, C *para* to I), 113.20 (q, *J* = 288.1 Hz, CF_3), 113.78 – 112.58 (m), 100.13 (t, *J* = 26.1 Hz, C-I); ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$) δ -73.35 (s, 6F), -92.94 (*pseudo* t, *J* = 6.1 Hz, 2F, CF_{Ar}).

p-(MeOCO)-PIFA



Following the a modification of the General Procedure, methyl *p*-iodobenzoate (2.096 g, 8.00 mmol) was allowed to react with Oxone® (4.912 g, 16 mmol) in a mixture of CF_3COOH (24 mL) and $CHCl_3$ (8 mL) for 8 h. The solvent was evaporated to dryness and the solid residue was extracted with several portions of hot chloroform (6 x 30 mL) and filtered. The combined chloroform extract was once again evaporated to dryness, redissolved in chloroform and filtered to remove traces of the inorganic salts. The volume was reduced to approx. 10 mL, and the solution allowed to cool first to room temp, then to -30 °C. Colorless crystals, yield; 1.808 g, 46%.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H) (*strong 2nd order effect for the aromatic AB*), 3.99 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.94 (CO_2Me), 161.10 (q, *J* = 41.5 Hz, $COCF_3$), 134.96 (CH_{Ar}), 134.77 (C_{Ar}), 132.89 (CH_{Ar}), 126.28 (C_{Ar}), 112.85 (q, *J* = 288.3 Hz, CF_3), 53.01 (Me). ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.11.

d$_5$-PIFA

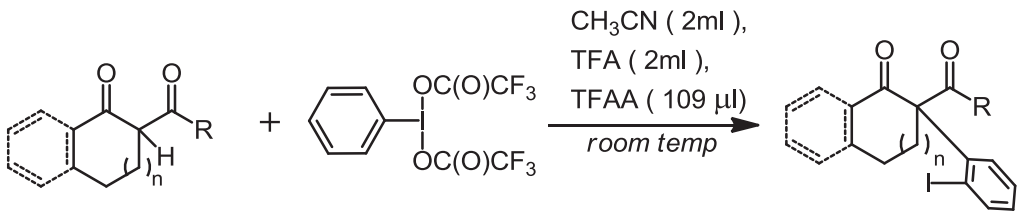


^{13}C NMR (91 MHz, $CDCl_3$) δ 161.2 (q, *J* = 41.0 Hz, C=O), 134.9, 133.4, 131.7, 113.00 (q, *J* = 289.4 Hz, CF_3).

4.3.4. *Arylation of enolate*

Arylation of β-ketone and β-ketoester

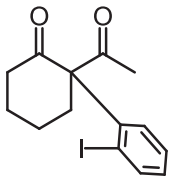
In General procedure A



n=0,1;
R=Me,OMe,OEt, iPr.

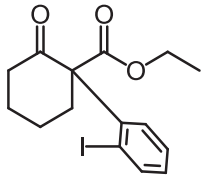
PIFA (560 mg, 1.3 mmol) was added in CH_3CN (2 mL) and CF_3COOH (2 mL) and TFAA (209 µL, 1.5 mmol) at room temperature in air atmosphere, the suitable of β-ketone or β-ketoester was added to the solution. The reaction progress was monitored by GC. The reaction was complete in 2 hours. The mixture was quenched with water (2 mL) and was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography.

2-Acetyl-2-(2-iodophenyl)cyclo hexanone



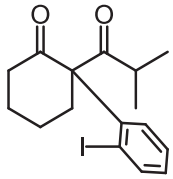
Following the general procedure A. Flash column chromatography:silica gel, AcOEt:Hexane 1:4 (R_f = 0.5). White oil, 174mg, yield: 51%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.02– 6.96 (m, 2H), 2.77 – 2.61 (m, 2H), 2.59 – 2.42 (m, 2H), 2.12 (s, 3H), 2.06 – 1.93 (m, 2H), 1.80 – 1.67 (m, 2H).^{13}C NMR (91 MHz, $CDCl_3$) δ 208.1 (C=O), 204.7 (C=O), 142.8 (CH), 142.2 (C), 129.7 (CH), 129.2 (CH), 128.5 (CH), 99.7 (C-I), 76.0 (C), 42.8 (CH_2), 34.9 (CH_2), 28.5 (CH_3), 26.0 (CH_2), 21.8 (CH_2).HRMS (ESI) m/z calcd for $C_{14}H_{15}IO_2$ $[M]^+$ 342.0009, found: 342.0018. Element analysis calce for $C_{14}H_{15}IO_2$: C 49.14%, H 4.42%, found: C 49.40%, H 4.43%. IR (ATR) v (cm^{-1}) 2929, 1714, 1686, 1460, 1408, 1159, 1115, 1006, 747.

Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate



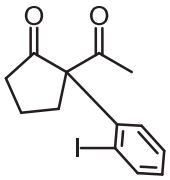
Following the general procedure A. Flash column chromatography: silica gel, AcOEt: Hexane 1:4 (R_f = 0.4). White oil, 180mg, yield: 48%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 4.35 – 4.20 (m, 2H), 2.83 – 2.57 (m, 4H), 2.05 – 1.97 (m, 2H), 1.86 – 1.94 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$) δ 205.1 (C=O), 170.4 (C=O), 142.4 (CH), 141.4 (C), 129.3 (CH), 128.9 (CH), 128.2 (CH), 99.5 (C-I), 70.1 (C), 62.3 (CH_2), 41.8 (CH_2), 36.4 (CH_2), 26.1 (CH_2), 22.3 (CH_2), 14.0 (CH_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}IO_3$ $[M]^+$ 372.0115, found: 372.0117. IR (ATR) v (cm^{-1}) 2938, 1711, 1461, 1234, 1206, 1011, 745.

2-(2-iodophenyl)-2-(isobutyryl)cyclohexanone



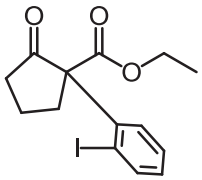
Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:4 (R_f = 0. 6). White oil, 185mg, yield: 50%. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 2.91 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.58 – 2.42 (m, 2H), 2.03 – 1.93 (m, 2H), 1.81 – 1.66 (m, 2H), 0.97 (overlap d, *J* = 3.6, 3.6 Hz, 6H).^{13}C NMR (91 MHz, $CDCl_3$) δ 211.1 (C=O), 208.5 (C=O), 142.8 (CH), 141.4 (C), 130.1 (CH), 129.2 (CH), 128.4 (CH), 99.9 (C-I), 76.4 (C), 43.3 (CH_2), 37.8 (CH_2), 35.9 (CH), 27.2 (CH_2), 22.2 (CH_3), 21.4 (CH_3), 21.2 (CH_2).HRMS (ESI) m/z calcd for $C_{16}H_{19}IO_2$ $[M]^+$ 370.0322, found: 370.0321. Element analysis calcd for $C_{16}H_{19}IO_2$: C 51.91% H: 5.17%, found: C: 51.52% H: 5.19%. IR (ATR) v (cm^{-1}) 2932, 2863, 1706, 1687, 1448, 1109, 761, 731.

2-acetyl-2-(2-iodophenyl)cyclopentanone



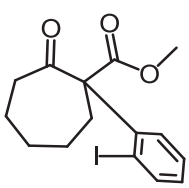
Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:9 (R_f = 0.4). White oil, 120mg, yield: 37%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 3.44 – 3.35 (m, 1H), 2.57 – 2.40 (m, 2H), 2.27 – 2.23 (m, 1H), 2.20 (s, 3H), 2.11 – 2.00 (m, 1H), 1.79 – 1.67 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 214.5 (C=O), 204.2 (C=O), 142.9 (C), 142.6 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 98.5 (C-I), 76.4 (C), 40.5 (CH_2), 34.9 (CH_3), 29.4 (CH_2), 19.3 (CH_2).HRMS (ESI) m/z calcd for $C_{13}H_{13}IO_2$ $[M]^+$ 327.9852, found:327.9859. Element analysis calcd for $C_{13}H_{13}IO_2$: C 47.58% H: 3.99%, found: C:48.36%, H: 4.09%. IR (ATR) v (cm^{-1}) 2922, 1730, 1701, 1461, 1360, 1192, 1110, 1006, 721.

Ethyl 1-(2-iodophenyl)-2-oxocyclopentanecarboxylate



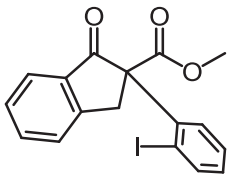
Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:9 (R_f = 0. 4). White oil, 186mg, yield: 52%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.98 – 6.94 (m, 4H), 4.30 – 4.15 (m, 4H), 3.20 (ddd, *J* = 14.4, 10.8, 7.2 Hz, 1H), 2.64 – 2.46 (m, 3H), 2.17 – 2.04 (m, 1H), 1.78 – 1.61 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$) δ 214.0 (C=O), 169.7 (C=O), 142.1(CH), 141.7(C), 129.0 (CH), 128.8 (CH), 128.2 (CH), 98.9 (C-I), 70.1 (C), 62.5 (CH_2), 39.6 (CH_2), 36.3 (CH_2), 19.5 (CH_2), 14.1 (CH_3).HRMS (ESI) m/z calcd for $C_{14}H_{15}IO_3$ $[M]^+$ 357.9958, found: 357.9963. IR (ATR) v (cm^{-1}) 2922, 1744, 1710, 1463, 1228, 1078, 1002, 747.

Methyl 1-(2-iodophenyl)-2-oxocycloheptanecarboxylate



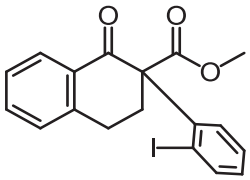
Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:9 (R_f = 0. 4). White oil, 190mg, yield: 51%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.22 – 3.17 (m, 1H), 3.01 – 2.96 (m, 1H), 2.79 – 2.73 (m, 1H), 2.18 – 2.12 (m, 1H), 1.84 – 1.72 (m, 5H), 1.59 – 1.47 (m, 1H).^{13}C NMR (91 MHz, $CDCl_3$) δ 208.4 (C=O), 171.9 (C=O), 142.4 (C), 142.3 (CH), 129.6 (CH), 128.7 (CH), 127.8 (CH), 98.3 (C-I), 71.7 (C), 52.9 (CH_2), 43.6 (CH_2), 34.0 (CH_2), 30.4 (CH_2), 26.9 (CH_2), 25.5 (CH_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}IO_3$ $[M]^+$ 372.0115, found:372.0111. IR (ATR) v (cm^{-1}) 2940, 1737, 1703, 1456, 1222, 1002, 744.

Methyl 2,3-dihydro-2-(2-iodophenyl)-1-oxo-1H-indene-2-carboxy late



Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:9 (R_f = 0. 4). White solide, 225mg, yield: 57%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 2H), 4.67 (d, *J* = 14.4 Hz, 2H), 3.78 (s, 3H), 3.35 (d, *J* = 18.0 Hz, 2H).^{13}C NMR (91 MHz, $CDCl_3$) δ 200.8 (C=O), 170.1 (C=O), 153.3 (C), 143.2 (C), 141.6 (CH), 136.4 (CH), 135.0 (C), 130.0 (CH), 129.1 (CH), 128.4 (CH), 128.1 (CH), 126.7 (CH), 125.3 (CH), 100.0 (C-I), 70.0 (C), 53.9 (CH_3), 42.1 (CH_2).HRMS (ESI) m/z calcd for $C_{17}H_{13}IO_3$ $[M]^+$ 391.9800, found:391.9802. IR (ATR) v (cm^{-1}) 2942, 2369, 1733, 1709, 1460, 1244, 1209, 1003, 761.

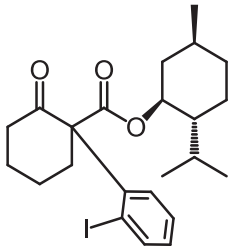
Methyl 1,2,3,4-tetrahydro-2-(2-iodophenyl)-1-oxonaphthalene-2- carboxylate



Following the general procedure A. Flash column chromatography: silica gel, AcOEt: Hexane 1:9 (R_f = 0. 4). White solide, 112mg, yield: 30%.^{1}H NMR (360 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.2 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz,

1H), 6.82 (d, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.42 (dt, *J* = 14.4, 3.6 Hz, 1H), 2.89 – 2.80 (m, 2H), 2.49 – 2.41 (m, 1H).^{13}C NMR (91 MHz, $CDCl_3$) δ 194.9 (C=O), 171.4 (C=O), 143.7 (C), 142.6 (CH), 139.3 (C), 134.1 (CH), 132.6 (C), 129.9 (CH), 129.2 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 97.6 (C-I), 67.2 (C), 53.2 (CH_3), 31.2 (CH_2), 25.7 (CH_2).HRMS (ESI) m/z calcd for $C_{18}H_{15}IO_3$ $[M]^+$ 405.9958, found:405.9960. IR (ATR) v (cm^{-1}) 2924, 1724, 1668, 1595, 1463, 1223, 1007, 776.

2-isopropyl-5-methylcyclohexyl1-(2-iodophenyl)-2-oxocyclohexane carboxy l –ate

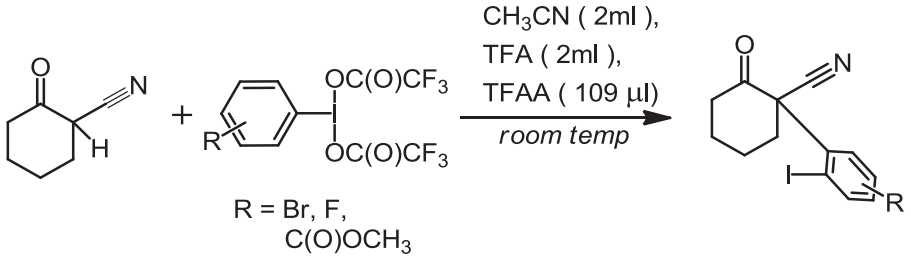


Following the general procedure A. Flash column chromatography : silica gel, AcOEt: Hexane 1:4 (R_f = 0. 5). White solide, 116mg, yield: 25%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.30 (dd, *J* = 16.0, 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.93 (t, *J* = 8.0 Hz, 2H), 4.74 (dtd, *J* = 18.0, 14.0, 4.0 Hz, 2H), 2.84 – 2.56 (m, 8H), 2.21 – 1.94 (m, 6H), 1.90 – 1.58 (m, 12H), 1.55 – 1.40 (m, 2H), 1.37 – 1.26 (m, 2H), 0.88 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 10H), 0.78 – 0.68 (m, 14H).^{13}C NMR (101 MHz, $CDCl_3$) δ 205.1 (C=O), 205.1 (C=O), 169.8 (C=O), 169.6 (C=O), 142.6 (CH), 142.4 (CH), 141.6 (CH), 141.3 (CH), 129.6 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.1 (CH), 128.0 (CH), 99.44 (C-I), 76.67, 76.56, 70.45, 70.20, 46.73, 46.71, 42.01, 41.88, 40.40, 40.20, 40.15, 36.58, 36.54, 34.18, 31.50, 31.47, 29.78, 26.32, 26.25, 25.54, 25.52, 22.95, 22.83, 22.55, 22.51, 22.12, 22.10, 20.89, 20.84, 15.98, 15.83.

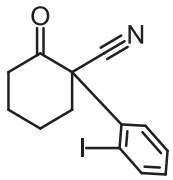
Arylation of 2-oxocyclohexanecarbonitrile

General procedure B



A 10 mL Schlenk tube was charged with appropriate $ArI(O_2CCF_3)_2$ (1.3 mmol) and a stirbar. The contents were briefly flushed with N_2, and CH_3CN (2.0 mL) and F_3CCOOH (2.0 mL) were added. The trifluoroacetic anhydride was injected *via* syringe, and the solution was allowed to stir for 15 min, before adding the 2-oxocyclohexanecarbonitrile (1.0 mmol). After stirring for an indicated time at room temperature, the solvent was removed and the crude product was purified by column chromatography (silica gel, cyclohexane: EtAc).

1-(2-iodophenyl)-2-oxocyclohexanecarbonitrile

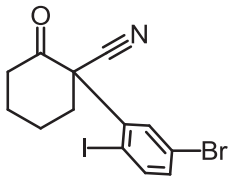


Following the general procedure B. The reaction was finished in 5 hours Flash column chromatography : silica gel, AcOEt: Hexane 1:9 (R_f = 0. 4). White oil, 260mg, yield: 80%.

Large-scale synthesis. A 400 mL Schlenk flask equipped with a a magnetic stirbar was charged with PIFA (44.72 g, 104 mmol) and then flushed with nitrogen with three evacuate/refill cycles. CH_3CN (anhydrous, 100 mL), trifluoroacetic acid (120 mL) and trifluoroacetic anhydride (25.2 g, 16.7 mL, 104 mmol) were added; the solution was left stirring for 30 min, and the solution of the cyanoketone (9.84 g, 80 mmol) in CH_3CN (20 min) was injected. The red solution was allowed to stir for 8 h, at which point the solvent was removed under vacuum. Column chromatography (silica gel, cyclohexane: EtAc) afforded the product as a viscous yellow oil. Yield: 19.2 g, 74%.

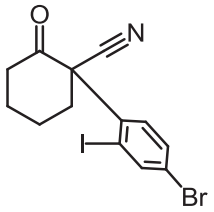
^{1}H NMR (360 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 3.10 – 3.00 (td, *J* = 14.4 Hz, 7.2Hz, 1H), 2.70 – 2.58 (m, 3H), 2.38 – 2.20 (m, 2H), 2.14 – 1.95 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 200.7 (C=O), 142.0 (CH), 137.1 (C), 130.1 (CH), 129.0 (CH), 128.6 (CH), 118.6 (CN), 98.76 (C-I), 59.4 (CH_2), 39.8 (CH_2), 38.6 (CH_2), 27.0 (CH_2), 22.4 (CH_2). HRMS (ESI) m/z calcd for $C_{13}H_{12}INO$ $[M]^+$ 324.9852, found: 324.9856. IR (ATR) v (cm^{-1}) 2918, 2864, 2230, 1723, 1461, 1114, 1072, 1013, 753.

1-(5-bromo-2-iodophenyl)-2-oxocyclohexanecarbonitrile



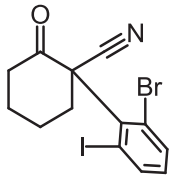
Following the General Procedure B, 2-cyanocyclohexanone (123 mg, 1.00 mmol) was allowed to react with 4-[bis(trifluoroacetoxy)iodo]-1-bromobenzene (610 mg, 1.2 mmol) for 6 h (partial precipitation of the product observed). Column chromatography: 10:1 cyclohexane:EtAc, R_f = 0.20. White solid, yield: 307 mg, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.08 (td, *J* = 13.6, 6.1 Hz, 1H), 2.75 – 2.60 (m, 2H), 2.57 (td, *J* = 12.8, 3.7 Hz, 1H), 2.35 (dtt, *J* = 14.4, 12.6, 4.1 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.19 – 2.10 (m, 1H), 2.00 (qt, *J* = 13.2, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4 (C=O), 143. 3 (CH), 139.3 (C), 133.4 (CH), 132.3 (CH), 123.2, 118.3 (CN), 97.2(C-I), 59.2 (CH_2), 40.0 (CH_2), 38.9 (CH_2), 27.4 (CH_2), 22.6 (CH_2).

1-(4-bromo-2-iodophenyl)-2-oxocyclohexanecarbonitrile



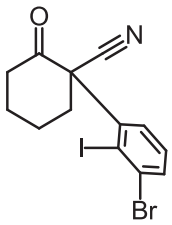
Following the General Procedure B, 2-cyanocyclohexanone (123 mg, 1.00 mmol) was allowed to react with 3-[bis(trifluoroacetoxy)iodo]-1-bromobenzene (611 mg, 1.2 mmol) for 6 h. TLC and GC analysis showed the formation of two products. *Major product*. Column chromatography: 10:1 cyclohexane:EtAc, R_f = 0.15. Pale-yellow oil, yield: 178 mg, 44%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 3.05 (ddd, *J* = 14.0, 13.2, 6.0 Hz, 1H), 2.66 (dddd, *J* = 14.0, 4.4, 2.9, 1.5 Hz, 1H), 2.62 – 2.54 (m, 2H), 2.40 – 2.17 (m, 2H), 2.15 – 2.05 (m, 1H), 1.98 (*appears as* qt, *J* = 13.1, 4.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4 (C=O), 144.2, 136.4, 131.8, 130.2, 123.6, 118.4 (CN), 99.5 (C-I), 59.2, 39.9, 38.8, 27.2, 22.6.

1-(2-bromo-6-iodophenyl)-2-oxocyclohexanecarbonitrile



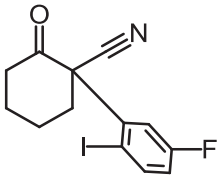
From the same reaction, a minor product was isolated with R_f = 0.19 (10:1 cyclohexane:EtAc). Yield: 70 mg, 17%. *Broad ^{1}H NMR peaks at room temp. due to fluxional behavior.* ^{1}H NMR **at 55 °C** (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 6.80 (t, *J* = 7.9 Hz, 1H), 2.96 (ddd, *J* = 17.0, 12.1, 6.3 Hz, 1H), 2.88 – 2.73 (m, 2H), 2.64 – 2.54 (m, 1H), 2.35 – 1.97 (m, 4H). ^{13}C NMR **at 55 °C** (126 MHz, $CDCl_3$) δ 199.5 (C=O), 142.5 (CH_{arom}), 136.8, 135.6 (CH_{arom}), 130.7 (CH_{arom}), 123.4, 117.8 (CN), 97.4 (C-I), 77.4, 77.2, 76.9, 61.5, 38.8 (CH_2), 35.9 (CH_2), 24.0 (CH_2), 21.4 (CH_2).

1-(3-bromo-2-iodophenyl)-2-oxocyclohexanecarbonitrile



Following the General Procedure B, 2-cyanocyclohexanone (123 mg, 1.00 mmol) was allowed to react with 2-[bis(trifluoroacetoxy)iodo]-1-bromobenzene (610 mg, 1.2 mmol) for 6 h. Column chromatography: 10:1 cyclohexane:EtAc, R_f = 0.19. Pale-yellow oil, yield: 258 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.39 – 7.27 (m, 2H), 3.11 (td, *J* = 13.5, 6.1 Hz, 1H), 2.76 – 2.52 (m, 3H), 2.51 – 2.20 (m, 2H), 2.20 – 2.09 (m, 1H), 2.09 – 1.95 (m, 1H).

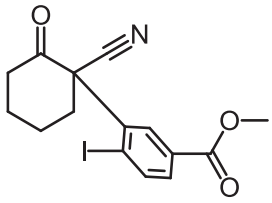
1-(5-fluoro-2-iodophenyl)-2-oxocyclohexanecarbonitrile



Following the General Procedure B, 2-cyanocyclohexanone (123 mg, 1.00 mmol) was allowed to react with 4-[bis(trifluoroacetoxy)iodo]-1-fluorobenzene (582 mg, 1.3 mmol) for 5 h. Column chromatography: 10:1 cyclohexane:EtAc, R_f = 0.19. White solid, yield: 179 mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J_{HH} = 8.7, J_{HF}= 5.8 Hz, 1H,

H-1), 7.18 (dd, J_{HF} = 10.0, J_{HH} = 2.9 Hz, 1H, H-3), 6.84 (ddd, J_{HH} = 8.7, J_{HF} = 7.5, J_{HH} = 2.9 Hz, 1H, H-3), 3.07 (td, *J* = 13.6, 6.1 Hz, 1H), 2.67 (dddd, *J* = 13.9, 4.3, 2.9, 1.6 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.40 – 2.20 (m, 2H), 2.19 – 2.07 (m, 1H), 1.99 (qt, *J* = 13.2, 4.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3 (C=O), 163.0 (d, *J* = 249.1 Hz, CF), 143.3 (d, *J* = 7.6 Hz, C-1), 139.4 (d, *J* = 7.1 Hz, **C**$_{Ar}$-Cy), 118.3 (CN) , 117.5 (d, *J* = 21.3 Hz), 117.2 (d, *J* = 24.8 Hz), 91.9 (d, *J* = 3.7 Hz, C-I), 59.2 (d, *J* = 1.4 Hz, **C**-CN), 39.9 , 38.8 , 27.4 , 22.5. ^{19}F NMR (376 MHz, H-coupled, $CDCl_3$) δ -111.83 (ddd, *J* = 10.0, 7.5, 5.8 Hz).

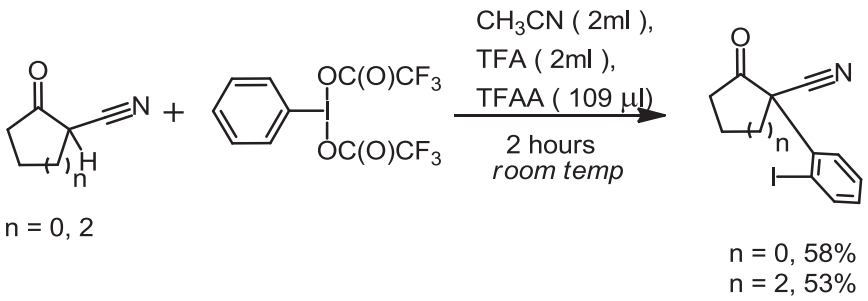
(S)-2-(2-iodophenyl)-2-methyl-3-oxo-3-phenylpropanenitrile



Following the General Procedure B, 2-cyanocyclohexanone (123 mg, 1.00 mmol) was allowed to react with methyl 4-[bis(trifluoroacetoxy)iodo]-benzoate (620 mg, 1.27 mmol) for 7 h, during which time the reaction mixture went from a white suspension to a light-yellow solution. Column chromatography: gradient 10:1 –> 5:1 cyclohexane:EtAc, R_f = 0.13 (10:1 cyclohexane : EtAc). Colorless oil, yield: 292 mg, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.92 (s, 3H), 3.14 (td, *J* = 13.4, 6.1 Hz, 1H), 2.75 (dq, *J* = 13.1, 3.2 Hz, 1H), 2.66 (dddd, *J* = 13.5, 4.5, 2.9, 1.4 Hz, 1H), 2.59 (td, *J* = 13.0, 3.7 Hz, 1H), 2.39 (dtt, *J* = 14.5, 12.9, 3.8 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.16 (dtd, *J* = 14.4, 4.6, 2.3 Hz, 1H), 1.97 (qt, *J* = 13.2, 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.71 (CO), 165.98 (COO), 142.35, 137.65, 130.77, 130.59, 129.48, 118.32 (CN), 105.77 (C-I), 77.30, 77.05, 76.79, 59.25, 52.53, 39.84, 39.04, 27.94, 22.46.

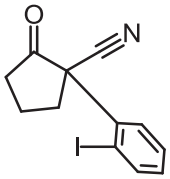
Arylation of other α-cyano cycloalkanones

General procedure C



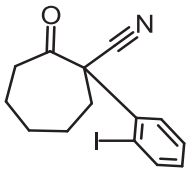
A 10 mL Schlenk tube was charged with $ArI(O_2CCF_3)_2$ (1.3 mmol) and a stirbar. The contents were briefly flushed with N_2, and CH_3CN (2.0 mL) and F_3CCOOH (2.0 mL) were added. The trifluoroacetic anhydride was injected *via* syringe, and the solution was allowed to stir for 15 min, before adding the α-cyanoketone (1.0 mmol). After stirring for an indicated time at room temperature, the solvent was removed and the crude product was purified by column chromatography (silica gel, hexane: EtAc).

1-(2-iodophenyl)-2-oxocyclopentanecarbonitrile



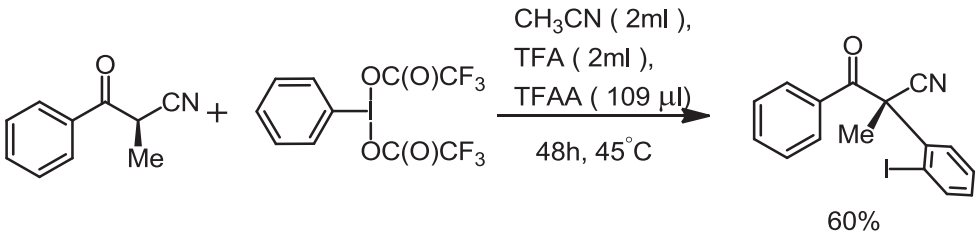
Following the general procedure C. The reaction was finished in 2 hours. Flash column chromatography : silica gel, AcOEt: Hexane 1:4 (R_f = 0. 3). chloroless oil, 178mg, yield: 58%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 3.02 (ddd, *J* = 14.4 Hz, 10.8 Hz, 7.2 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.76 – 2.62 (m, 2H), 2.41 – 2.21 (m, 2H). ^{13}C NMR (91 MHz, $CDCl_3$) δ 207.2 (C=O), 142.7 (CH), 135.8 (CH), 131.0 (CH), 130.5 (CH), 128.8 (CH), 117.5 (CN), 95.2 (C-I), 58.8 (CH_2), 37.9 (CH_2), 36.7(CH_2), 19.8 (CH_2). HRMS (ESI) m/z calcd for $C_{13}H_{12}INO$ $[M]^+$ 310.9699, found: 310.9693. IR (ATR) v (cm^{-1}) 2916, 2232, 1752, 1463, 1427, 1400, 1101, 1009, 762.

1-(2-iodophenyl)-2-oxocycloheptanecarbonitrile



Following the general procedure C. The reaction was finished in 2 hours. Flash column chromatography : silica gel, AcOEt: Hexane 3:7 (R_f = 0. 6). White oil, 178mg, yield: 53%.^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 3.62 (ddd, *J* = 12.6 Hz, 9.0 Hz, 3.6 Hz, 1H), 2.81 (dt, *J* = 14.4 Hz, 7.2 Hz, 1H), 2.55 (dt, *J* = 14.4 Hz, 3.6 Hz, 1H), 2.26 – 1.99 (m, 6H), 1.40 – 1.24 (m, 1H).^{13}C NMR (91 MHz, $CDCl_3$) δ 203.8 (C=O), 142.0, 139.8, 130.3, 128.8, 128.5, 119.0 (CN), 99.5 (C-I), 60.7 (CH_2), 43.5, 36.4, 26.6, 26.5, 21.7.HRMS (ESI) m/z calcd for $C_{14}H_{14}INO[M]^+$ 339.0012, found: 339.0016. IR (ATR) v (cm^{-1}) 2934, 2869, 2233, 1709, 1462, 1445, 1236, 1011, 756.

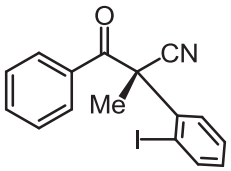
Arylation of (R)-2-methyl-3-oxo-3-phenylpropanenitrile



60%

2-benzoylpripionitrile (159 mg, 1.00 mmol) was allowed to react with PIFA (559 mg, 1.3 mmol) at 45 °C for 48 h. Column chromatography: 10:1 cyclohexane:EtAc, R_f = 0.43. Pale-yellow oil, yield: 216 mg, 60%.

(S)-2-(2-iodophenyl)-2-methyl-3-oxo-3-phenylpropanenitrile

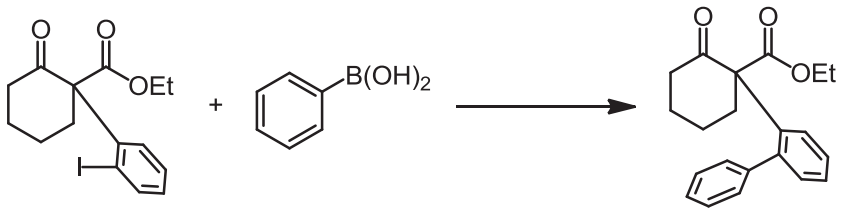


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.82 (m, 4H), 7.56 – 7.46 (m, 2H), 7.40 – 7.30 (m, 2H), 7.05 (ddd, *J* = 7.9, 7.4, 1.6 Hz, 1H), 2.17 (s, 3H, Me).

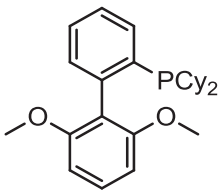
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (C=O), 142.8, 139.4, 134.3, 133.5, 130.2, 130.0, 129.2, 128.8, 128.4, 119.7 (CN), 96.1 (C-I), 55.0 (C), 24.8 (CH_3).

4.3.5. *Derivatives of Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate*

Ethyl 1-([1,1'-biphenyl]-2-yl)-2-oxocyclohexanecarboxylate

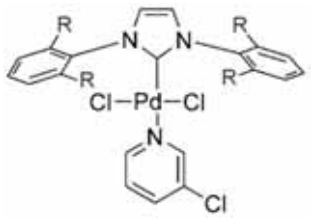


Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate(0.54mmol, 200mg), benzene boronic acid(0.81mmol, 98.76mg), $Pd(OAc)_2$(0.02mmol, 5mg), PPh3(0.06mmol, 17mg), Cs_2CO_3(0.8mmol, 260mg) were in the 10mLschlenk tube under an inert atmosphere, A DMF-water mixture(95:5, 102mL) was add as solvent, the tube was sealed and heated to 100°C**.** After an indicated period of time, the mixture was allowed to cool to room temp., The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.5).Yellow oil, 90mg, yield:52%.



SPhos Suzuki cross-coupling ligand

An oven-dried resealable schlenk tube containing a magnetic stir bar was charged with $Pd(OAc)_2$(0.006mmol, 1.4mg), SPhos (0.001mmol, 5mg), and boronic acid (0.92mmol, 112mg), K_3PO_4(1.22mmol, 259mg) and ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate(0.61mmol, 228mg). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with N_2 (3 times). Dry toluene (2.0mL) was added through the septum via syringe and the resulting mixture was stirred. The reaction was heated at 100 °C. It doesn't work.[28]



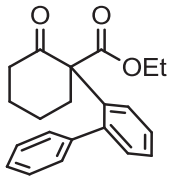
Suzuki cross-coupling catalyst

PEPPSI

An oven-dried resealable schlenk tube containing a magnetic stir bar was charged with PEPPSI(0.036mmol, 25mg), boronic acid (1.37mmol, 167mg), Cs_2CO_3(1.82mmol,

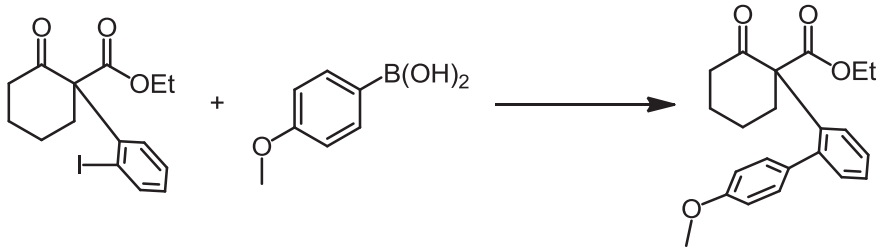
593mg) and ethyl 1-(2-iodophenyl)-2- oxocyclohexanecarboxylate(0.91mmol, 339mg).[29] The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with N_2 (3 times). Dry dioxane (2.0mL) was added through the septum via syringe and the resulting mixture was stirred. The reaction was heated at 80 °C overnight. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.5).Yellow lipid, 174mg, yield: 60%.

An oven-dried resealable schlenk tube containing a magnetic stir bar was charged with PEPPSI(0.03mmol, 22mg), phenylboronic acid (1.24mmol, 151mg), Cs_2CO_3(1.24mmol, 404mg) and ethyl 1-(2-iodophenyl)-2- oxocyclohexanecarboxy - late(0.62mmol, 230mg). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with N_2 (3 times). Dry dioxane (3.0mL) was added through the septum via syringe and the resulting mixture was stirred. The reaction was heated at 80 °C for 14h. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.5).Yellow oil, 122mg, yield:61%.

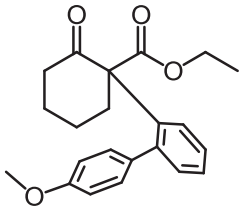


^{1}H NMR (360 MHz, $CDCl_3$, 55 ˚C) δ 7.37 – 7.30 (m, 5H), 7.24 – 7.13 (m, 4H), 4.24 – 4.02 (m, 2H), 2.61 – 2.46 (m, 2H), 2.23 – 2.15 (m, 1H), 2.09 – 2.03 (m, 1H), 1.79 – 1.63 (m, 2H), 1.53 – 1.38 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$, 55 ˚C) δ 208.0 (C=O), 171.9 (C=O), 142.7 (C), 142.6 (C), 135.6 (C), 132.7, 130.3, 129.5, 127.9, 127.5, 127.3, 127.2, 68.7, 61.5, 40.7, 35.3, 27.7, 21.6 (CH_3), 14.1.HRMS (ESI) m/z calcd for $C_{21}H_{22}O_3$ $[M]^+$ 322.1461, found: 322.1468.IR (ATR) ν (cm^{-1}) 3055, 2937, 2864, 1729, 1706, 1477, 1464, 1230, 1043, 772, 752.

Ethyl 1-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2-oxocyclohexane carboxylate

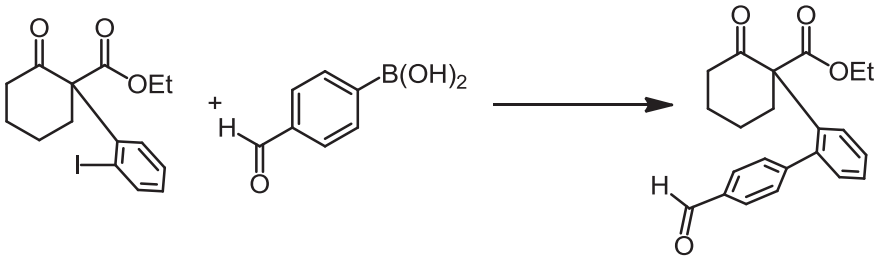


A mixture of Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.51 mmol, 189 mg), (4-methoxyphenyl)boronic acid (1.02 mmol, 155 mg), PEPPSI (35 mg, 10mol%), Cs_2CO_3(1.02 mmol, 331 mg) in dioxane (4 mL) were refluxed at 90 ºC for 12h. Reaction was monitored by GC and stopped. The reaction mixture was cooled to room temperature and the solvent evaporated. Flash column chromatography : silica gel, AcOEt: Hexane 1:4 (R_f = 0. 5). White solid, 120mg, yield: 67%

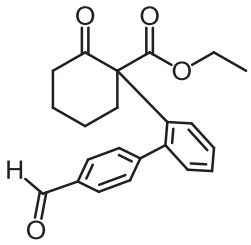


^{1}H NMR (360 MHz, $CDCl_3$, 50˚C) δ 7.35 – 7.27 (m, 2H), 7.17 – 7.14 (m, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 7.2 Hz, 2H), 4.20 – 4.03 (m, 2H), 3.83 (s, 3H), 2.60 – 2.45 (m, 2H), 2.23 – 2.09 (m, 2H), 1.77 – 1.64 (m, 2H), 1.53 – 1.36 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$, 50˚C) δ 208.2 (C=O), 171.9 (C=O), 159.2 (C), 142.3 (C), 135.8 (C), 134.9 (C), 133.0, 130.6, 130.2, 127.3, 127.2, 113.4, 68.7, 61.5, 55.4, 40.7, 35.3, 27.8, 21.5, 14.1 (CH_3).HRMS (ESI) m/z calcd for $C_{22}H_{24}O_4$ $[M]^+$ 352.1570, found: 352.1567. IR (ATR) v (cm^{-1}) 2936, 1729, 1704, 1462, 1230, 1034, 834, 767, 742.

Ethyl 1-(4'-formyl-[1,1'-biphenyl]-2-yl)-2-oxocyclohexane carboxylate



A mixture of Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.47 mmol, 173 mg), (4-formylphenyl)boronic acid (0.93 mmol, 139 mg), PEPPSI (32 mg, 10mol%), Cs2CO3(0.93 mmol, 303 mg) in dioxane (4 mL) were refluxed at 90 °C for 12h. Reaction was monitored by GC and stopped. The reaction mixture was cooled to room temperature and the solvent evaporated. Flash column chromatography : silica gel , AcOEt: Hexane 1:4 (R_f = 0.4). White solid, 54mg, yield: 33%.

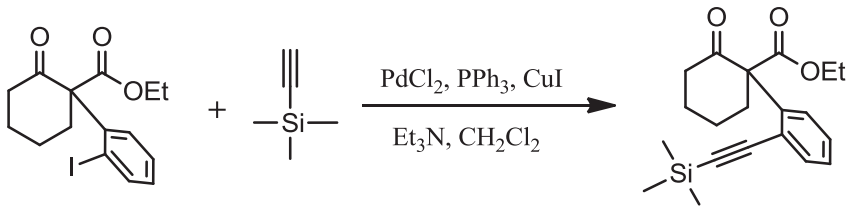


^{1}H NMR (360 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.40 – 7.33(m, 4H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.14 – 3.97 (m, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.31 – 2.24 (m, 1H), 2.16 – 2.05 (m, 1H), 1.83 – 1.64 (m, 2H), 1.57 – 1.41 (m, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (91 MHz, $CDCl_3$) δ 208.0 (C=O), 191.9 (C(O)H), 171.6 (C=O), 148.9 (C), 141.1 (C), 135.3 (C), 135.1 (C), 131.9, 130.2, 129.8, 129.1, 128.1, 127.3, 68.1 (C), 61.6, 40.6, 35.7, 27.6, 21.4, 13.9.

HRMS (ESI) m/z calcd for $C_{22}H_{22}O_4$ $[M]^+$ 350.1410, found:350.1410. IR (ATR) v (cm^{-1}) 2924, 2852, 1730, 1705, 1605, 1234, 1210, 837, 762.

Ethyl 2-oxo-1-(2-((trimethylsilyl)ethynyl)phenyl)cyclohexane carboxylate

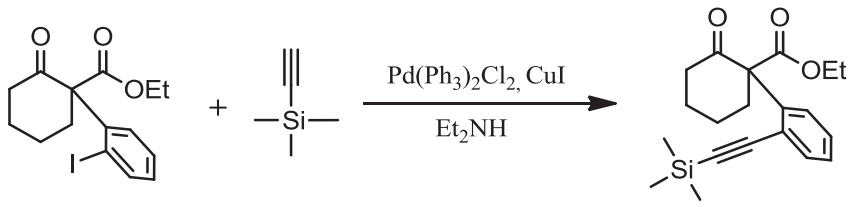


A mixture of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.56mmol, 207mg), TMS-acetylene(0.67mmol, 65.81mg, 95*μ*L), $PdCl_2$(0.0112mmol, 2mg, 2mol%), PPh_3(0.0112mmol, 3mg, 2mol%), CuI(0.0056mmol, 1mg, 1mol%), Et_3N(2.5mL) in CH_2Cl_2(2ml) was stirred under an inert atmosphere for 1h at room temperature. The

mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 80mg, yield:42%.

A mixture of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (1.67mmol, 621mg), TMS-acetylene (2.5mmol, 245.9mg, 354μL), $PdCl_2$ (0.0668mmol, 12mg, 4mol%), PPh_3 (0.0668mmol, 18mg, 4mol%), CuI(0.0334mmol, 6mg, 2mol%), Et_3N (6.0mL) in CH_2Cl_2 (1ml) was stirred under an inert atmosphere for 1h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 348mg, yield:61%.

A mixture of ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.26 mmol, 95mg), TMS-acetylene(0.52mmol, 51.1mg, 74μL), $PdCl_2$(0.02mmol, 2mg, 8mol%), PPh_3(0.02mmol, 5.5mg, 8mol%), CuI(0.01mmol, 2mg, 4mol%), Et_3N(1.0mL) in CH_2Cl_2(1ml) was stirred under an inert atmosphere for 1h at 40 °C. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 53mg, yield:60%.

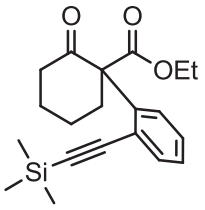


Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.65mmol, 242mg) was dissolved in Et_2NH (2mL) under an inert atmosphere, TMS-acetylene (1.04mmol, 102 mg, 147μL), $Pd(Ph_3)_2Cl_2$ (0.03mmol, 18mg, 4mol%), CuI (0.013mmol, 3mg, 2mol%) were added successively and the mixture was left under an inert atmosphere stirring for 36h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 155mg, yield:70%.

Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.61mmol, 230mg) was dissolved in Et_2NH (2mL) under an inert atmosphere, TMS-acetylene (1.10mmol, 108 mg, 155μL), $Pd(Ph_3)_2Cl_2$ (0.05mmol, 34mg, 8mol%), CuI (0.024mmol, 5mg, 4mol%) were added successively and the mixture was left under vigorous stirring for 16h at 45 °C. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and

dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 166mg, yield:80%.

Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.69mmol, 255mg) was dissolved in Et_2NH (5mL) under an inert atmosphere, TMS-acetylene (1.38mmol, 136 mg, 195μL), $Pd(Ph_3)_2Cl_2$ (0.06mmol, 39mg, 8mol%), CuI (0.028mmol, 5mg, 4mol%) were added successively and the mixture was left under an inert atmosphere stirring for 16h at 45 °C. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5).Yellow oil, 211mg, yield:90%.

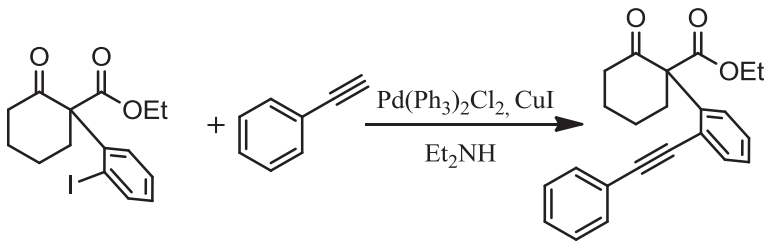


^{1}H NMR (360 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 4.39 – 4.08 (m, 2H), 2.90 (ddd, *J* = 18.0, 10.8, 7.2 Hz, 1H), 2.70 (ddd, *J* = 14.4, 10.8, 7.2 Hz, 1H), 2.54 (ddt, *J* = 18.0, 10.8, 7.2 Hz, 2H), 1.96 (ddd, *J* = 16.2, 12.6, 3.6 Hz, 2H), 1.80 – 1.66 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.21 (s, 8H).

^{13}C NMR (91 MHz, $CDCl_3$) δ 205.0 (C=O), 170.8 (C=O), 140.7 (C), 135.0 (CH_2), 128.7 (CH_2), 127.4 (CH_2), 127.1 (CH_2), 123.4 (C≡C), 104.6 (C≡C), 101.4 (Ar-C≡C), 68.1, 61.9, 41.4, 36.0, 26.6, 22.4, 14.1, -0.1 ($3CH_3$).

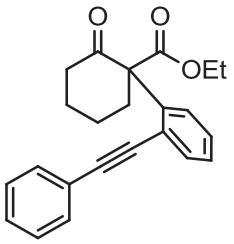
HRMS (ESI) m/z calcd for $C_{20}H_{26}O_3Si$ $[M]^+$ 342.1543, found: 342.1547. IR (ATR) v (cm^{-1}) 2937, 2864, 2154, 1716, 1463, 1444, 1236, 1206, 862, 841, 754.

Ethyl 2-oxo-1-(2-(phenylethynyl)phenyl)cyclohexanecarboxylate



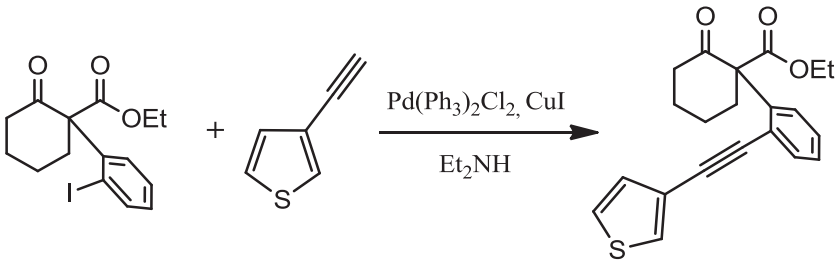
Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.53mmol, 199mg) was dissolved in Et_2NH (4mL) under an inert atmosphere, ethynylbenzene (0.95 mmol, 97

mg, 105 μL), $Pd(Ph_3)_2Cl_2$ (0.04 mmol, 30 mg, 8 mol%), CuI (0.02 mmol, 4 mg, 4 mol%) were added successively and the mixture was left under an inert atmosphere stirring for 6h at 55 °C. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.5). yellow oil, 171mg, yield:93%.

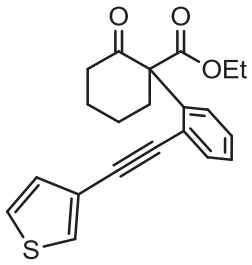


^{1}H NMR (360 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 1H), 7.52 – 7.49 (m, 2H), 7.36 – 7.27 (m, 5H), 7.14 – 7.11 (m, 1H), 4.35 – 4.16 (m, 2H), 2.93 – 2.85 (m, 1H), 2.72 – 2.61 (m, 3H), 1.99 – 1.80 (m, 2H), 1.78 – 1.63 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$) δ 205.5 (C=O), 170.8 (C=O), 140.3, 134.2, 131.2, 128.4, 128.3, 128.3, 127.3, 127.1, 123.4, 123.1 (C), 95.4 (C≡C), 89.2 (C≡C), 67.9, 61.7, 41.2, 36.2, 26.7, 22.0, 13.9. HRMS (ESI) m/z calcd for $C_{23}H_{22}O_3$ $[M]^+$ 346.1466, found: 346.1461. IR (ATR) v (cm^{-1}) 3060, 2931, 2864, 1714, 1492, 1442, 1235, 1207, 1130, 745, 690.

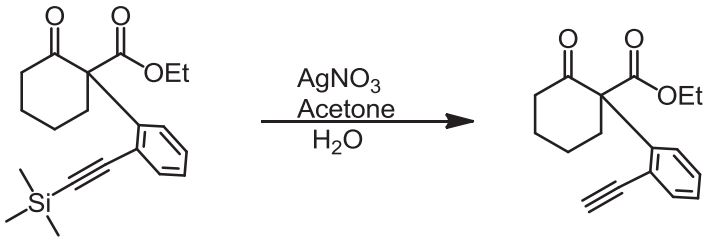
Ethyl 2-oxo-1-(2-(thiophen-3-ylethynyl)phenyl)cyclohexane carboxylate



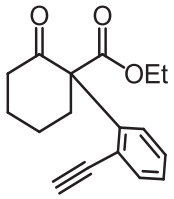
Ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate (0.64mmol, 241mg) was dissolved in Et_2NH (5mL) under an inert atmosphere, 3-ethynylthiophene (1.17 mmol, 127 mg, 116μL), $Pd(Ph_3)_2Cl_2$ (0.05mmol, 36mg, 8mol%), CuI (0.03mmol, 5mg, 4mol%) were added successively and the mixture was left under an inert atmosphere stirring for 24h at 55 °C. The mixture was washed with saturated aqueous $NaHCO_3$, brine, successively and dried, Flash column chromatography: Silica gel, AcOEt: Hexane 1:9 (R_f=0.3).Yellow lipid. Yield: 86%.



^{1}H NMR (360 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 1H), 7.52 (dd, *J* = 3.6, 1.44 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.18 (dd, *J* = 7.2, 1.08 Hz, 1H), 7.13 – 7.11 (m, 1H), 4.38 – 4.09 (m, 2H), 2.89 – 2.82 (m, 1H), 2.71 – 2.58 (m, 3H), 1.99 – 1.80 (m, 2H), 1.80 – 1.67 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (90 MHz, CDCl3) δ 205.6 (C=O), 170.9 (C=O), 140.4, 134.0, 129.4, 128.6, 128.3, 127.3, 127.2, 125.4, 123.5, 122.2, 90.9 (C≡C), 88.7 (C≡C), 67.9, 61.8, 41.3, 36.2, 26.8, 22.1, 14.0. HRMS (ESI) m/z calcd for $C_{21}H_{20}SO_3$ $[M]^+$ 352.1025, found: 352.1028. IR (ATR) v (cm^{-1}) 3060, 2931, 2864, 1714, 1492, 1235, 1207, 1071, 754, 690.2.4.9.7. ethyl 1-(2-ethynylphenyl)-2-oxocyclohexanecarboxylate.

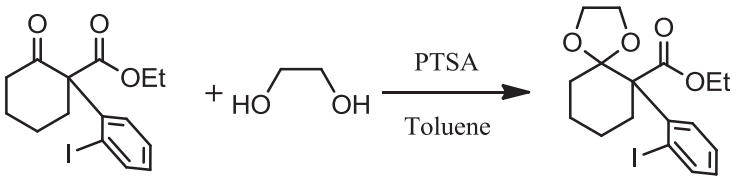


Water (0.5mL, 0.03mmol) and $AgNO_3$ (4mg, 0.03mmol) were added to a solution of ethyl 2-oxo-1-(2-((trimethylsilyl)ethynyl)phenyl) cyclo hexanecarboxylate (88mg, 0.26mmol) in acetone (1.95mL) and the resulting mixture was stirred in the dark at the room temperature for 40 hours. [30]It was then poured into a saturated aqueous NaCl solution (10mL) and extracted with Et_2O (6 X 10 mL). The organic extract was washed with brine (3 X 10 mL), dried and concentrated under reduced pressure. The residue was purified by silica gel. Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.4).Yellow solid. Yield:87%.



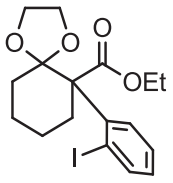
^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 4.39 – 4.22 (m, 2H), 3.34 (s, 1H), 2.88 – 2.80 (m, 1H), 2.74 – 2.59 (m, 3H), 2.04 – 1.85 (m, 2H), 1.84 – 1.68 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 204.7 (C=O), 170.5 (C=O), 141.0, 135.0, 128.9, 127.3, 127.1, 122.0, 84.2 (C≡C), 83.3 (C≡C), 67.9, 61.9, 41.3, 35.9, 25.9, 22.5, 13.9. HRMS (ESI) m/z calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1148, found: 270.1153. IR (ATR) v (cm^{-1}) 3267, 2920, 1712, 1438, 1237, 1206, 1120, 1020, 756, 687.

ethyl 6-(2-iodophenyl)spiro[4.5]decane-6-carboxylate



A round-bottom flask was charged with ethyl 1-(2-iodophenyl)-2-oxocyclohexane carboxylate (1.11mmol, 414mg), ethylene glycol (8.88mmol, 551.1mg), PTSA (0.04mmol, 8mg, 4mol%) and toluene (30mL). The flask was equipped with a Dean-Stark trap and the well-stirred mixture was heated at 110 °C overnight. The mixture was pured on to 10% aqueous $NaHCO_3$ solution (30mL) and extracted with ether (3×40mL). The organic layer was then wash with H_2O (4×30mL) and saturated NaCl (30mL). Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.5).Yellow oil, 120mg, yield:40%.

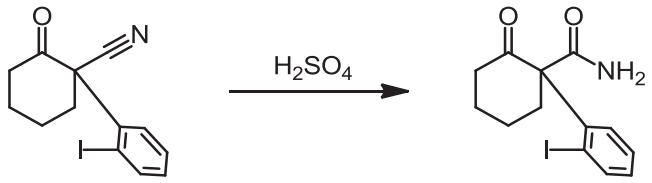
A round-bottom flask was charged with ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxyl ate (3.54 mmol, 1.32g), ethylene glycol (28.3mmol, 1.76g), PTSA (35.4mmol, 6.7g, 10mol%) and toluene (30mL). The flask was equipped with a Dean-Stark trap and the well-stirred mixture was heated at 140 °C for 14h. The mixture was pured on to 10% aqueous $NaHCO_3$ solution(30mL) and extracted with ether (3×40mL). The organic layer was then wash with H_2O (4×30mL) and saturated NaCl(30mL). Flash column chromatography: Silica gel, AcOEt: Hexane 1:4 (R_f=0.5).Yellow oil, 902mg, yield:62%.



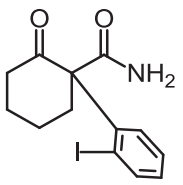
^{1}H NMR (360 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 4.38 – 4.14 (m, 2H), 3.80 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.64 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.55 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.67 (dd, *J* =28.8, 10.8 Hz, 3H), 2.14 (d, *J* = 14.4 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.64 – 1.47 (m, 2H), 1.42 – 1.28 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (91 MHz, $CDCl_3$) δ 172.7 (C=O), 143.0, 142.1, 131.7, 128.3, 127.2, 111.4, 99.4 (C-I), 65.11, 64.53, 62.08, 61.50, 35.47, 34.20, 23.89, 21.79, 14.07.^{13}C NMR (91 MHz, $CDCl_3$) δ 172.5, 142.9, 141.9, 131.5, 128.2, 127.0, 111.3, 99.3, 65.0, 64.4, 61.9, 61.4, 35.3, 34.1, 23.7, 21.6, 13.9. HRMS (ESI) m/z calcd for $C_{17}H_{21}IO_4$ $[M]^+$ 416.0377, found: 416.0389.

4.3.6. *Derivatives of Arylated of α-cyano cycloalkanones*

1-(2-iodophenyl)-2-oxocyclohexanecarboxamide

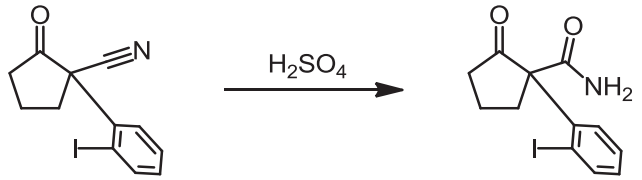


1-(2-iodophenyl)-2-oxocyclohexanecarbonitrile (114mg, 0.35mmol) was stirred with concentrated sulfuric acid (3ml) at 35°C for 17h. The reaction mixture was poured onto ice. The mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography. AcOEt: Hexane 3:7 (R_f = 0.3). White solid, 75mg, yield: 63%.

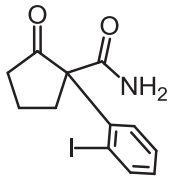


^{1}H NMR (360 MHz, $CDCl_3$) δ 7.92 (d, *J* = 10.8 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.44 (s, 1H), 5.70 (s, 1H), 2.77 (d, *J* = 18.0 Hz, 1H), 2.66 (d, *J* = 10.8 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.26 – 2.17 (m, 1H), 1.97 – 1.78 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8 (C=O), 169.8 (C=O), 143.7, 142.2, 130.7, 129.1, 128.5, 99.0 (C-I), 71.0, 42.5, 35.7, 25.0, 22.7.HRMS (ESI) m/z calcd for $C_{13}H_{14}INO_2$ $[M]^+$ 342.9961, found: 342.9966. IR (ATR) v (cm^{-1}) 3438, 3168, 2935, 1681, 1607, 1462, 1323, 1127, 1010, 745.

1-(2-iodophenyl)-2-oxocyclopentanecarboxamide

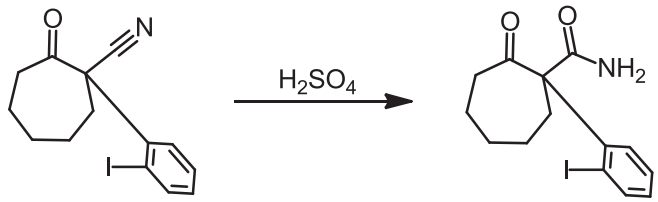


1-(2-iodophenyl)-2-oxocyclopentanecarbonitrile (1.44g, 4.63mmol) was stirred with concentrated sulfuric acid (4ml) at 35°C for 12h. The reaction mixture was poured onto ice. The mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography. AcOEt: Hexane 1:1(R_f = 0.5). White solid, yield: 62%.



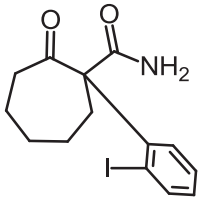
^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 5.66 (two overlapping br s, 2H), 3.34 (dt, *J* = 13.8, 7.1 Hz, 1H), 2.71 – 2.29 (m, 3H), 2.09 (tt, *J* = 12.1, 6.1 Hz, 1H), 1.85 (tt, *J* = 14.4, 7.2 Hz, 1H).^{13}C NMR (91 MHz, $CDCl_3$) δ 216.5 (C=O), 170.0 (C=O), 142.9, 141.7, 130.0, 129.5, 128.5, 98.6 (C-I), 77.5, 77.2, 76.8, 70.9, 40.1, 34.9, 19.9.HRMS (ESI) m/z calcd for $C_{12}H_{12}INO_2$ $[M]^+$ 328.9986, found: 328.9985.IR (ATR) ν (cm^{-1}) 3446, 3276, 3199, 2921, 1729, 1668, 1597, 1367, 1136, 1009, 760.

1-(2-iodophenyl)-2-oxocycloheptanecarboxamide



1-(2-iodophenyl)-2-oxocycloheptanecarbonitrile (662mg, 1.95mmol) was stirred with concentrated sulfuric acid (4ml) at 35°C for 21h. The reaction mixture was poured onto ice. The mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL).

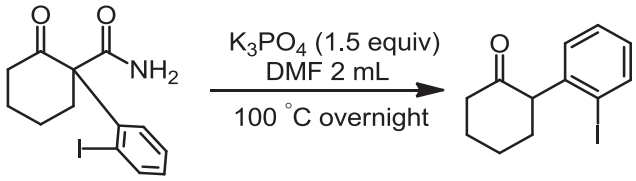
The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography. AcOEt: Hexane 1:1(R_f = 0.4). Yellow solid, yield: 32%.



^{1}H NMR (360 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.06 (br, s, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.04 (br, s, 1H), 2.75 (dd, *J* = 10.8, 7.2 Hz, 1H), 2.66 – 2.56 (m, 2H), 2.53 – 2.33 (m, 1H), 1.92 – 1.55 (m, 4H), 1.41 (dt, *J* = 14.4, 7.2 Hz, 2H).^{13}C NMR (91 MHz, $CDCl_3$) δ 211.4 (C=O), 173.17 (C=O), 142.4, 142.1, 130.8, 129.3, 128.2, 99.9 (C-I), 72.0, 41.8, 35.8, 28.1, 24.8, 23.8.HRMS (ESI) m/z calcd for$C_{14}H_{16}INO_2$ $[M]^+$ 357.0300, found: 357.0298 .

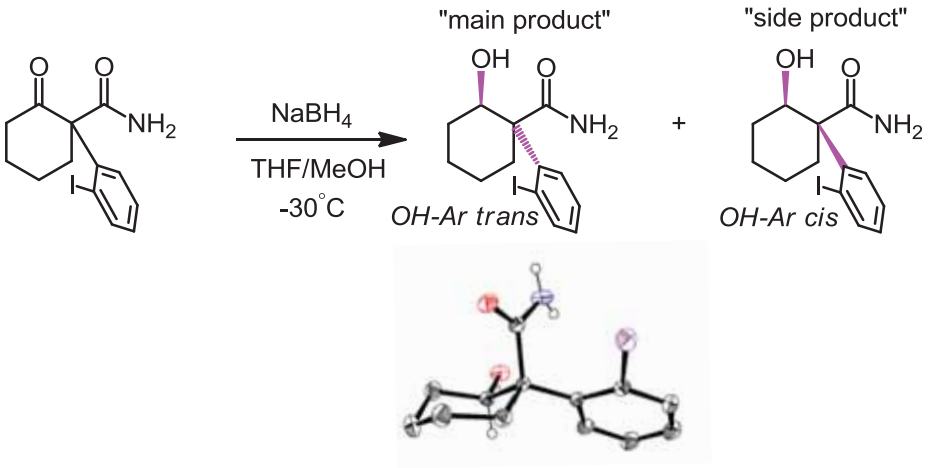
4.3.7. *Use of new product as a building block*

2-(2-iodophenyl)cyclohexanone

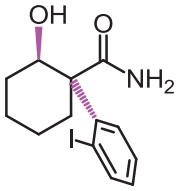


^{1}H NMR (360 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 4.00 (dd, *J* = 10.8, 3.6 Hz, 1H), 2.56 (dd, *J* = 7.2, 3.6 Hz, 2H), 2.37 – 2.13 (m, 2H), 2.10 – 1.69 (m, 4H).^{13}C NMR (91 MHz, $CDCl_3$) δ 209.1 (C=O), 141.8, 139.5, 129.1, 128.8, 128.4, 102.5 (C-I), 61.8 (CH), 42.6 (CH_2), 34.9 (CH_2), 27.9 (CH_2), 25.8 (CH_2).

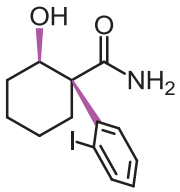
Reduction of 1-(2-iodophenyl)-2-oxocyclohexanecarboxamide



1-(2-iodophenyl)-2-oxocyclohexanecarboxamide (100mg, 0.29 mmol) was stirred in 14 mL mixture solvent (MeOH/THF = 5/2) at -30°C. Sodium borohydride (11mg, 0.29mmol) was added to the solution. The reaction was complete in 20 hours. Evaporating out the mixture solvent. Adding dichloromethane to the reaction mixture. The mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography. AcOEt: Hexane 1:1, main product (R_f = 0.4), white solid, 63mg, melting point: 185-195°C, yield: 63%; side product (R_f = 0.3), white solid, 30mg, yield: 30%.

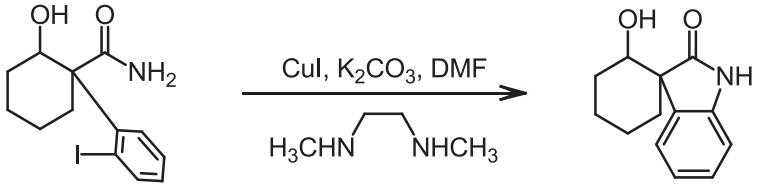


^{1}H NMR (500 MHz, DMSO, r.t.) δ 7.95 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 3.6 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 1H), 6.93 (t, *J* = 3.6 Hz, 1H), 6.86 (s, 1H), 5.67 (s, 1H), 4.76 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.41 – 2.37 (m, 1H), 1.93 (t, *J* = 7.2 Hz, 1H), 1.86 – 1.52 (m, 4H), 1.52 – 1.40 (m, 1H), 1.41 – 1.28 (m, 1H).^{13}C NMR (90 MHz, $CDCl_3$) δ 178.98, 143.79, 142.24, 130.74, 128.98, 128.34, 97.25, 70.27, 56.55, 56.48, 31.45, 29.64, 22.17, 20.94. HRMS (ESI) m/z calcd for $C_{13}H_{16}INO_2$ $[M]^+$ 345.0116, found: 345.0188. IR (ATR) v (cm^{-1}) 3477, 3344, 2931, 1662, 1600, 1462, 1339, 1052, 1005, 766.

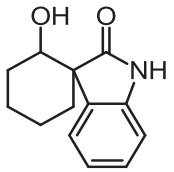


^{1}H NMR (500 MHz, DMSO, 398K) δ 7.96 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 3.6 Hz, 1H), 6.92 (d, *J* = 3.6 Hz, 1H), 6.00 (s, 2H), 4.63 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 1H), 2.57 (ddd, *J* = 14.8, 11.8, 3.5 Hz, 1H), 2.47 – 2.33 (m, 1H), 2.07 – 2.01 (m, 1H), 1.84 – 1.74 (m, 1H), 1.71 – 1.57 (m, 1H), 1.52 – 1.33 (m, 3H).

C-N cross coupling



2-hydroxy-1-(2-iodophenyl)cyclohexanecarboxamide (62mg, 0.18 mmol), CuI (1.7mg, 9 x 10^{-3}mmol, 5 mol%), K_2CO_3 (32mg, 0.23mmol) and N,N'-Dimethylethylene - diamine (1.6mg, 0.018mmol, 10 mol%) were stirred in 2mL DMF at room temperature for 2 hours. The mixture was transferred to a separatory funnel. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic fraction was dried over Na_2SO_4 and the concentrated to dryness. The crude product was purified by flash chromatography. AcOEt: Hexane 1:1 (R_f = 0.3). White solid, yield: 40%.



^{1}H NMR (360 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.83 (d, *J* = 4.0 Hz, 1H), 2.49 – 2.19 (m, 1H), 2.20 – 2.06 (m, 1H), 1.94 – 1.80 (m, 1H), 1.80 – 1.64 (m, 3H), 1.63 – 1.42 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 179.7 (C=O), 142.3, 135.0, 127.0, 122.0, 120.9, 108.4, 73.3, 52.4, 33.4, 29.6, 24.1, 19.6.HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_2$ $[M]^+$ 217.0997, found: 217.0995.

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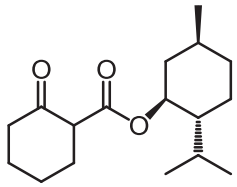
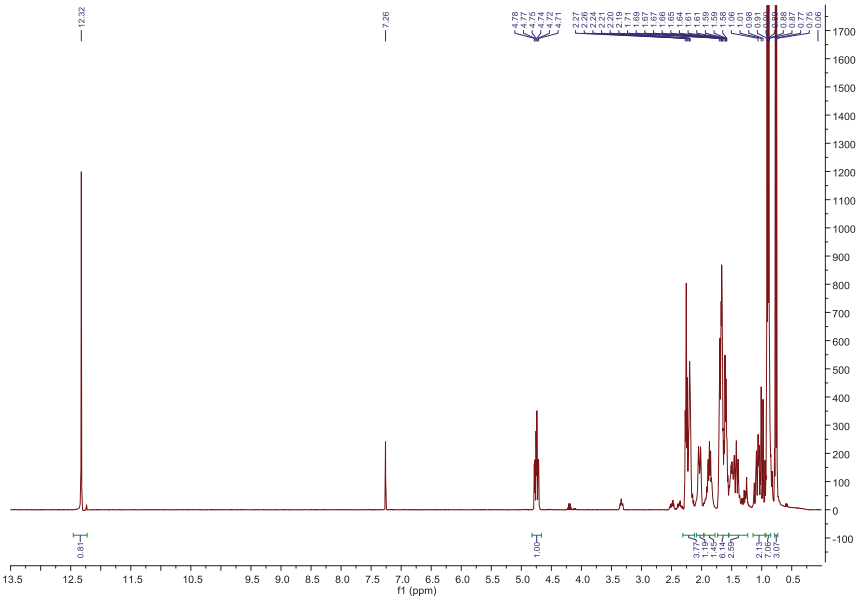
4.4. Spectral data

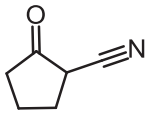
(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-oxocycloh exanecarboxylate



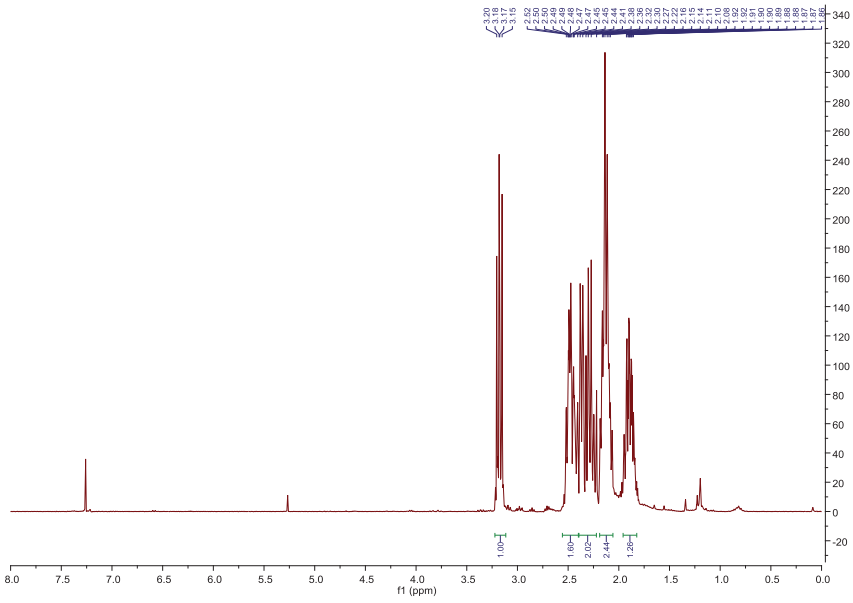
^{1}H NMR (360 MHz, $CDCl_3$)



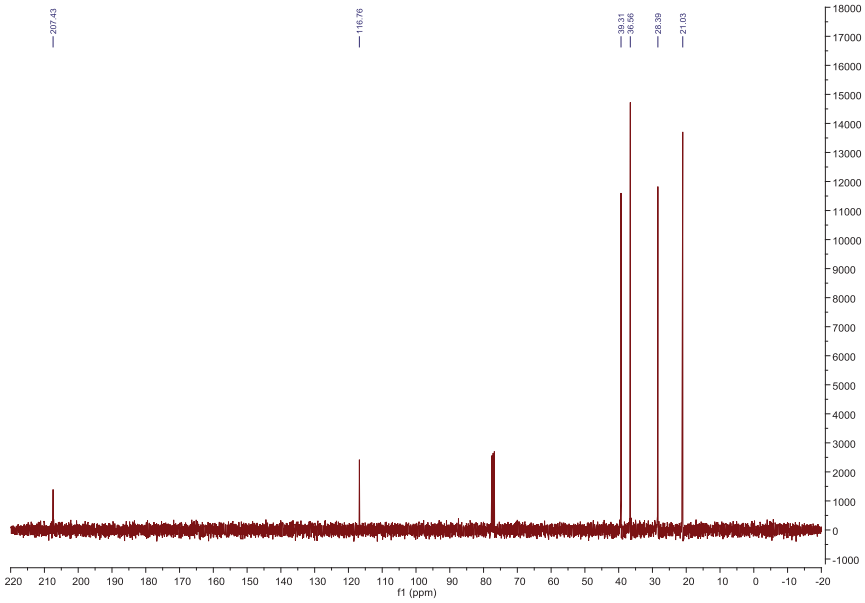
2-oxocyclopentanecarbonitrile



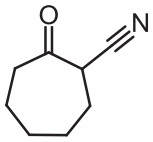
^{1}H NMR (360 MHz, $CDCl_3$)



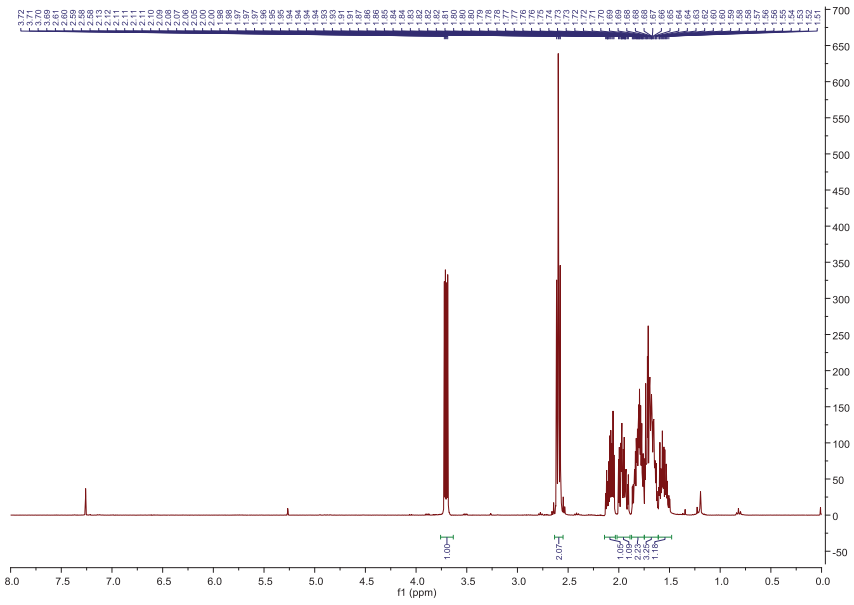
^{13}C NMR (91 MHz, $CDCl_3$)



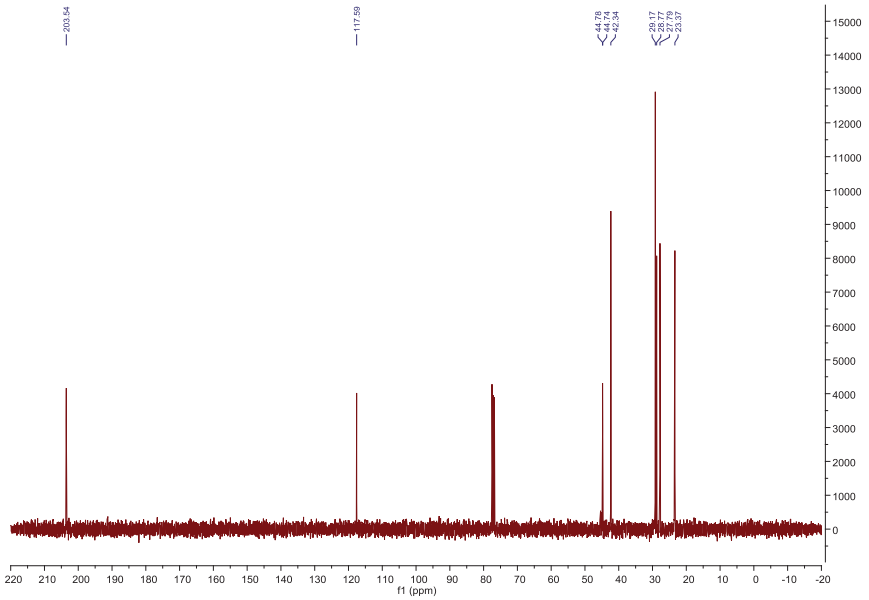
2-oxocycloheptanecarbonitrile



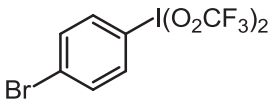
^{1}H NMR (360 MHz, $CDCl_3$)



^{13}C NMR (91 MHz, $CDCl_3$)



p-Br-PIFA



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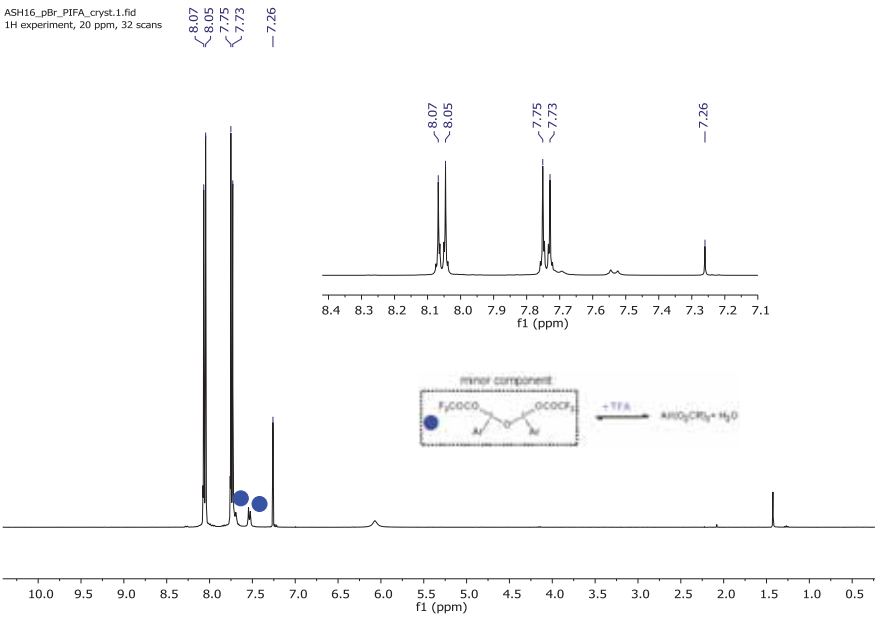
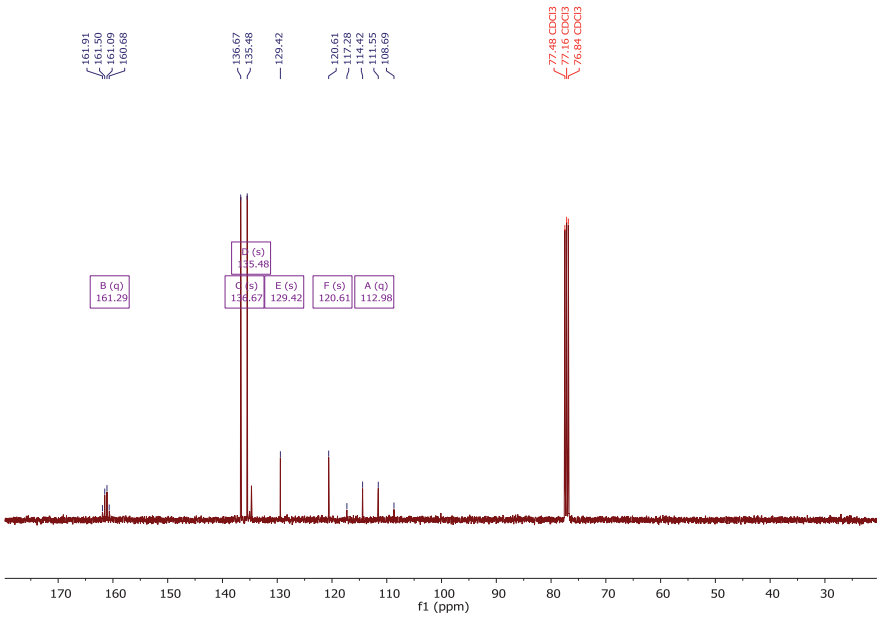
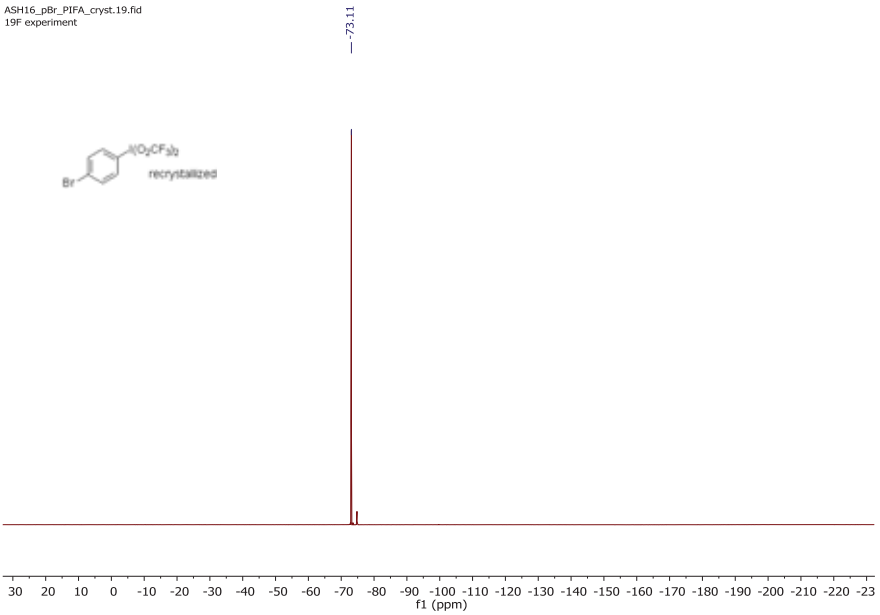


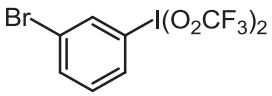
^{13}C NMR (101 MHz, $CDCl_3$)


161.91
161.50
161.09
160.68
136.67
135.48
129.42
120.61
117.28
114.42
111.55
108.69
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
D (s)
135.48
B (q)
161.29
C (s)
136.67
E (s)
129.42
F (s)
120.61
A (q)
112.98
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

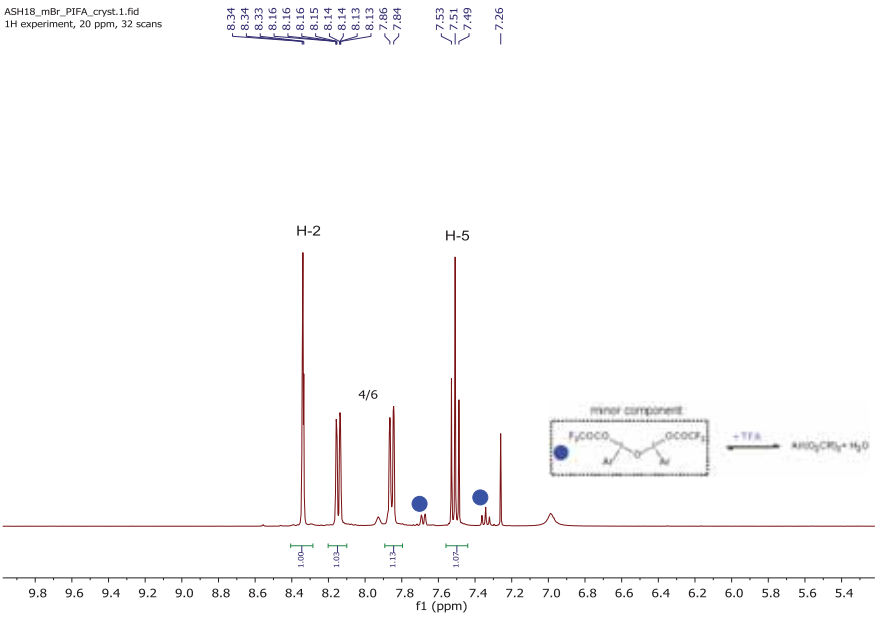
^{19}F NMR (376 MHz, $CDCl_3$)



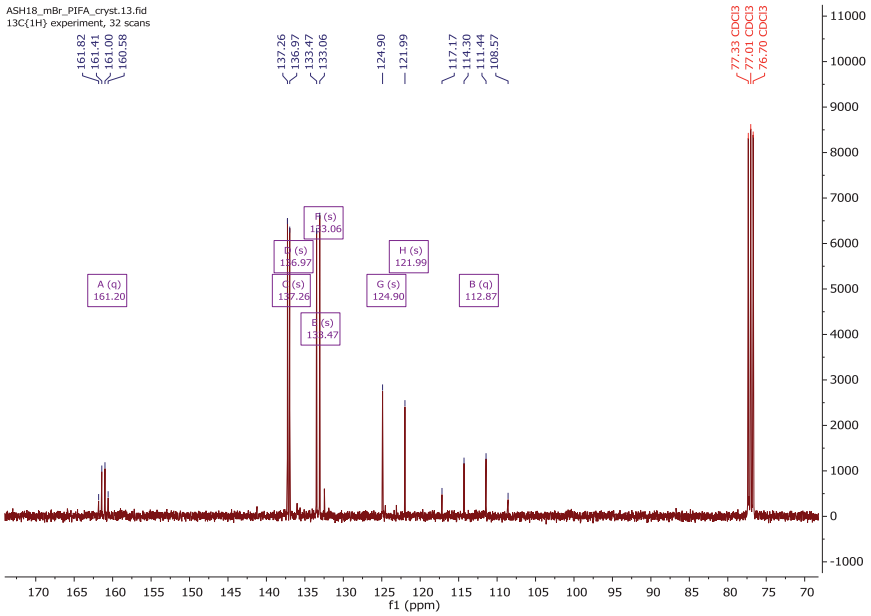
m-Br-PIFA



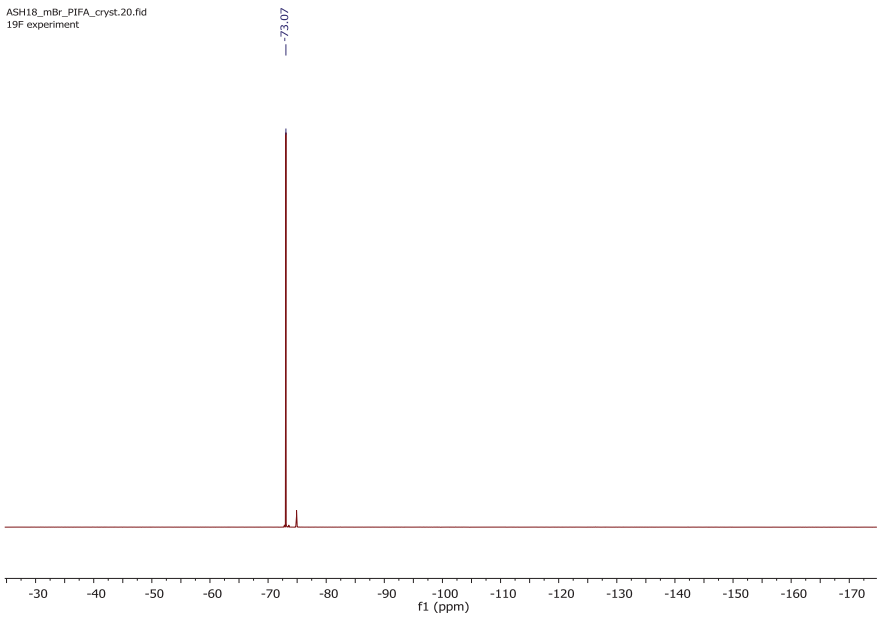
^{1}H NMR (400 MHz, $CDCl_3$)



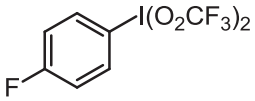
^{13}C NMR (101 MHz, $CDCl_3$)



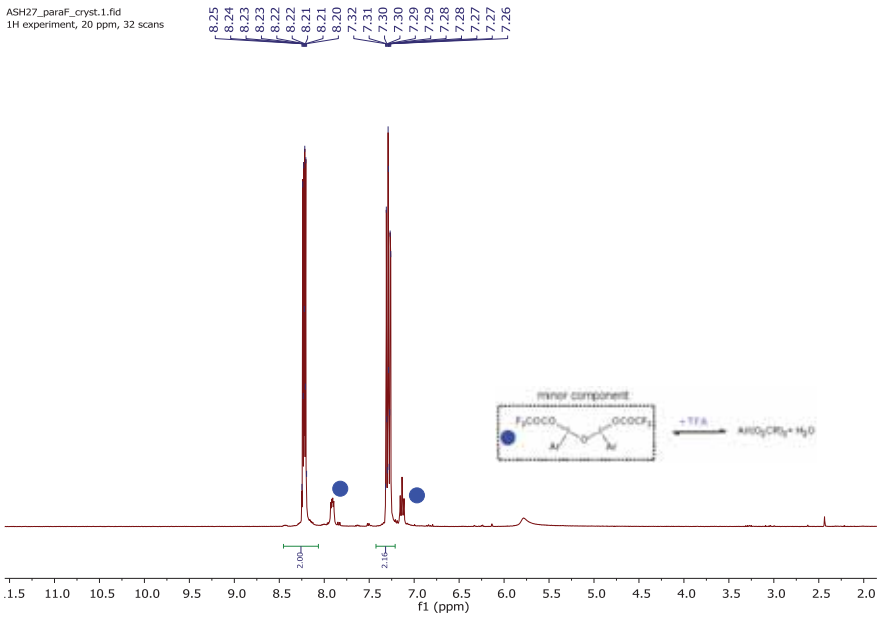
^{19}F NMR (376 MHz, $CDCl_3$)



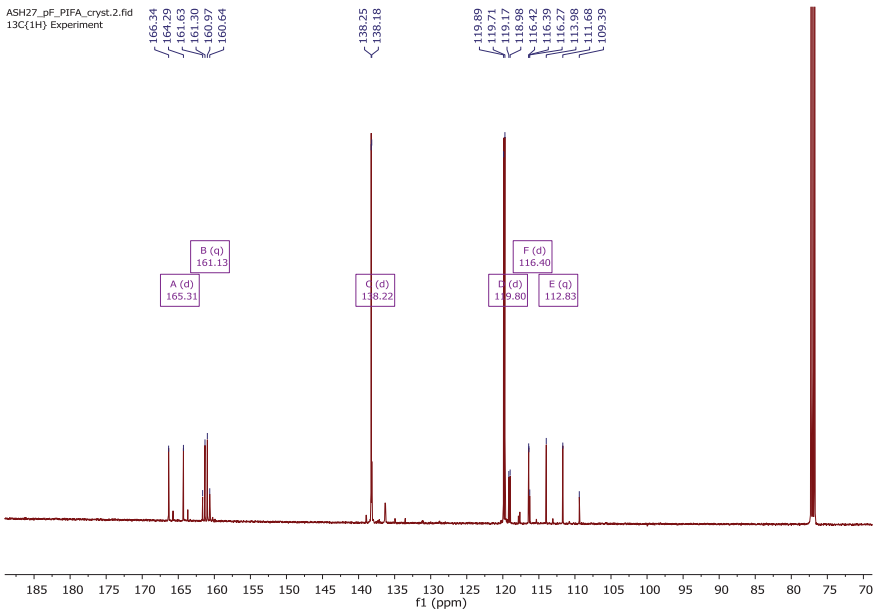
p-F-PIFA



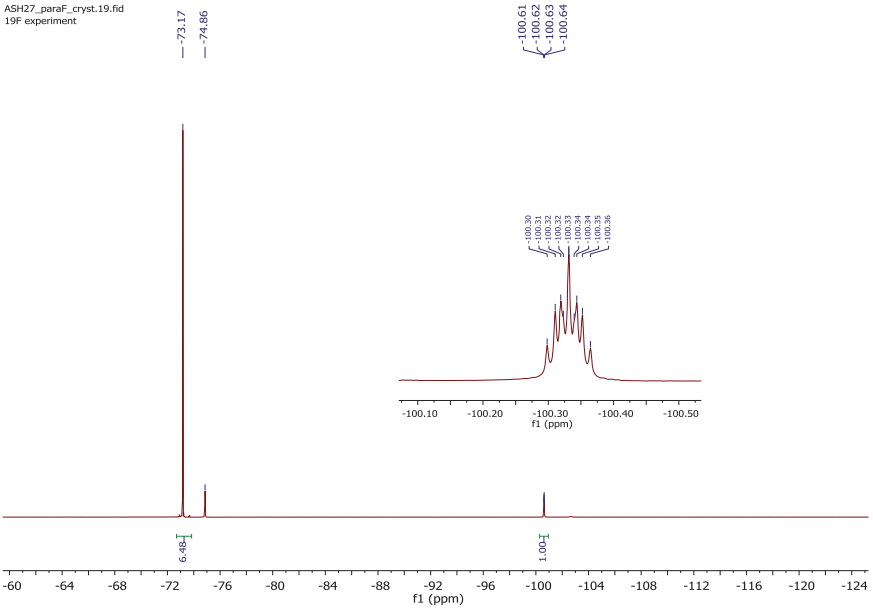
^{1}H NMR (400 MHz, $CDCl_3$)



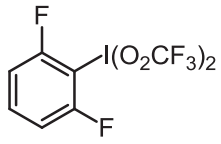
^{13}C NMR (101 MHz, $CDCl_3$)



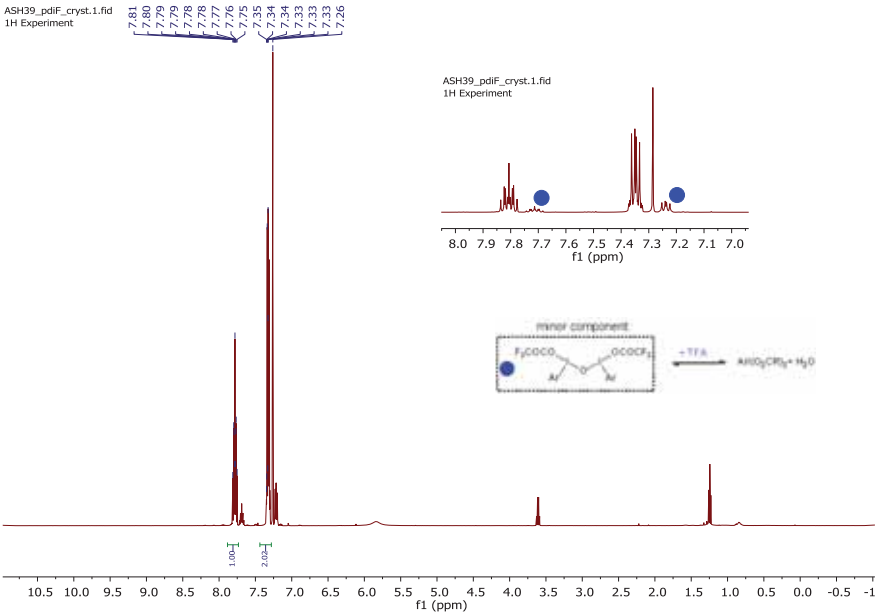
^{19}F NMR (376 MHz, $CDCl_3$)



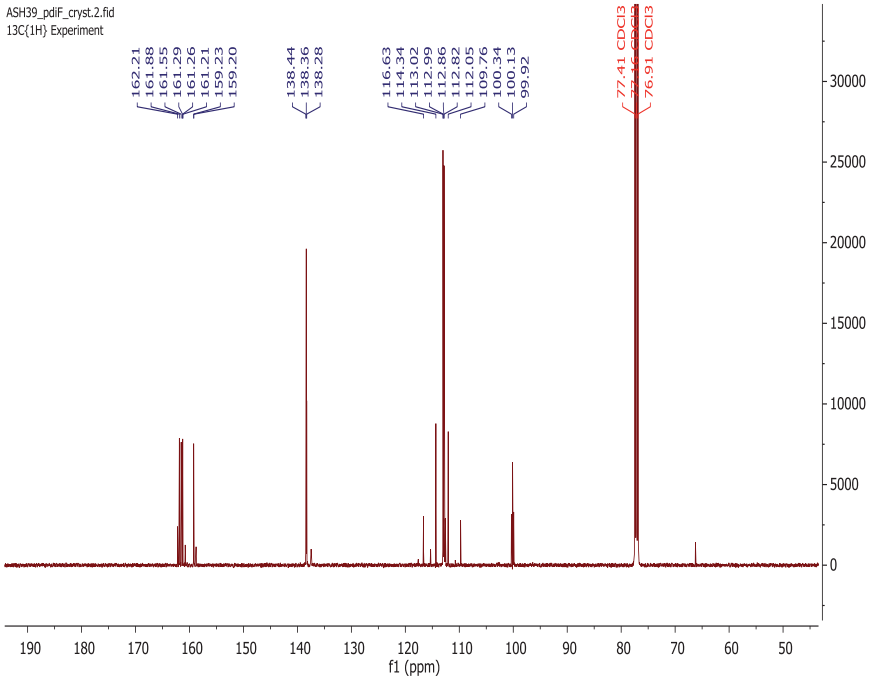
o-F-PIFA



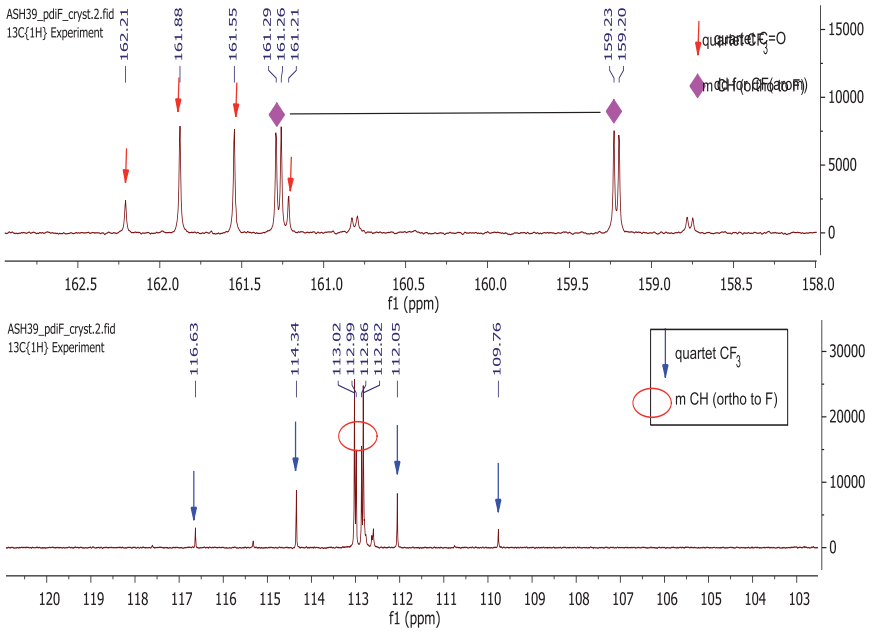
^{1}H NMR (400 MHz, $CDCl_3$)



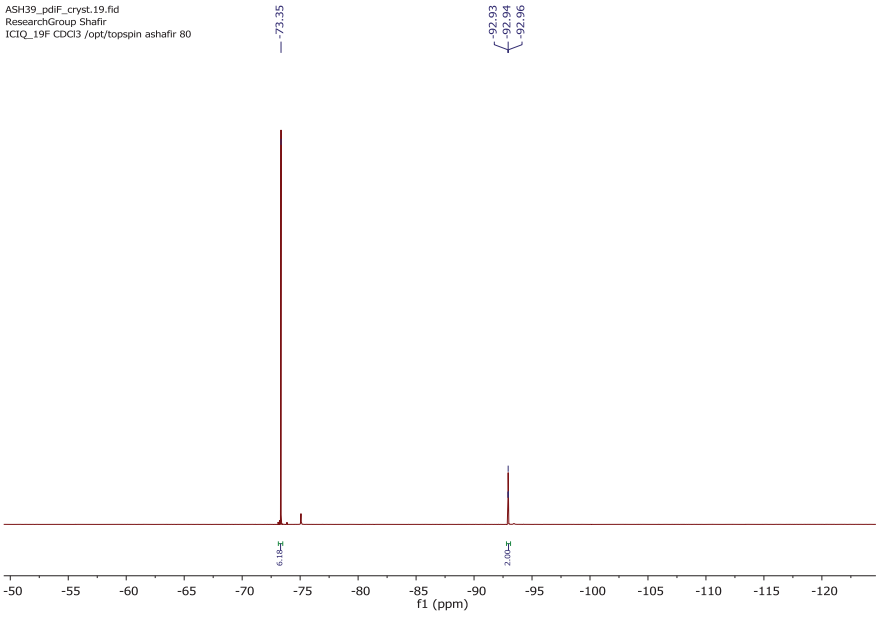
^{13}C NMR (101 MHz, $CDCl_3$)



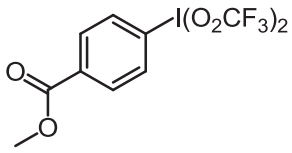
^{13}C NMR (101 MHz, $CDCl_3$) – selected regions



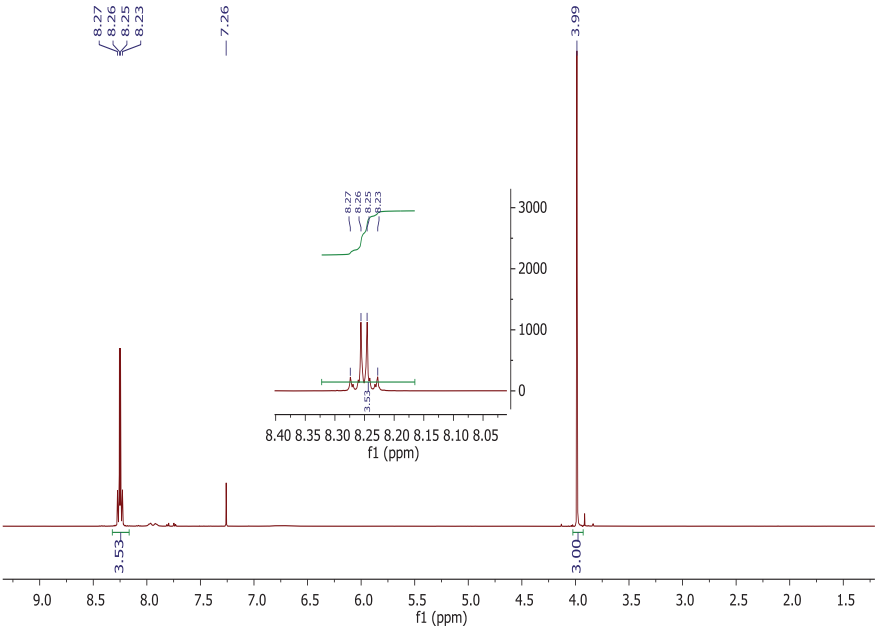
^{19}F NMR (376 MHz, $CDCl_3$)



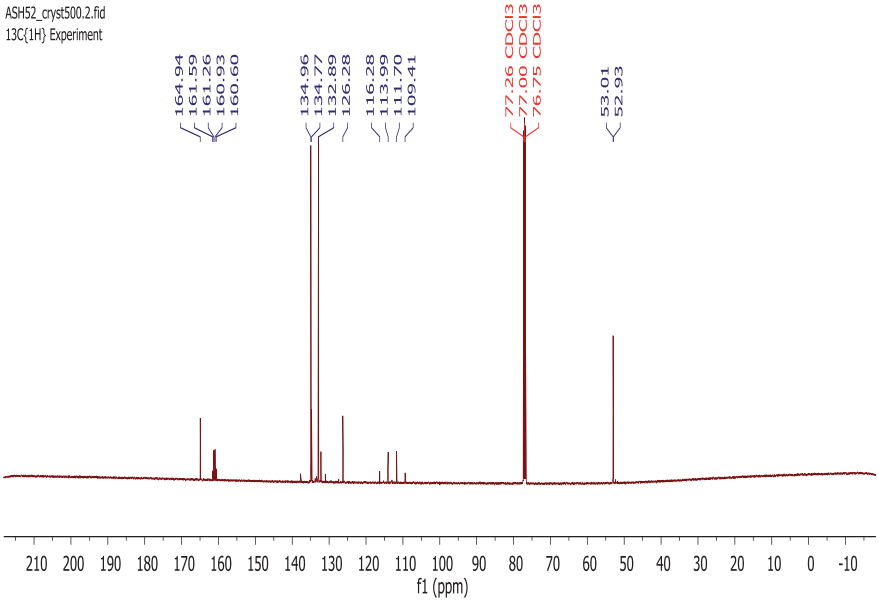
New PIFA



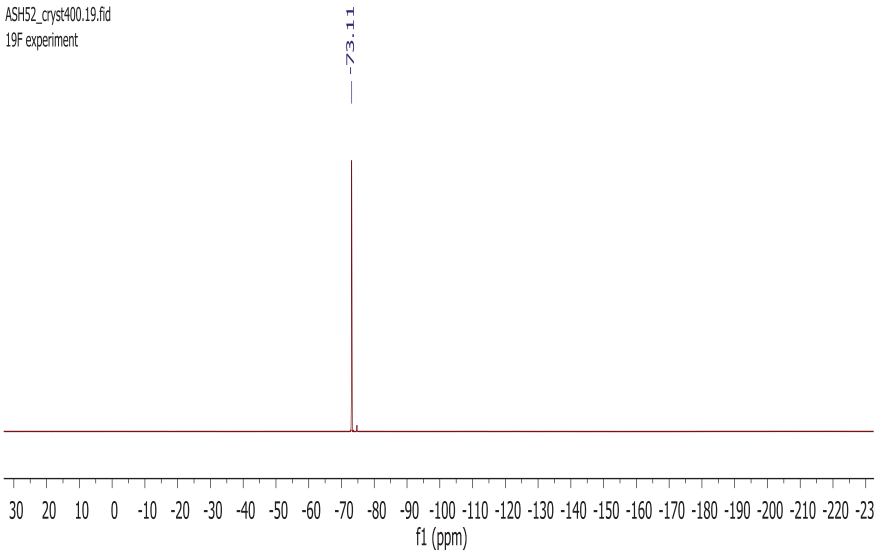
^{1}H NMR (500 MHz, $CDCl_3$)



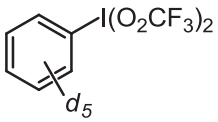
^{13}C NMR (126 MHz, $CDCl_3$)



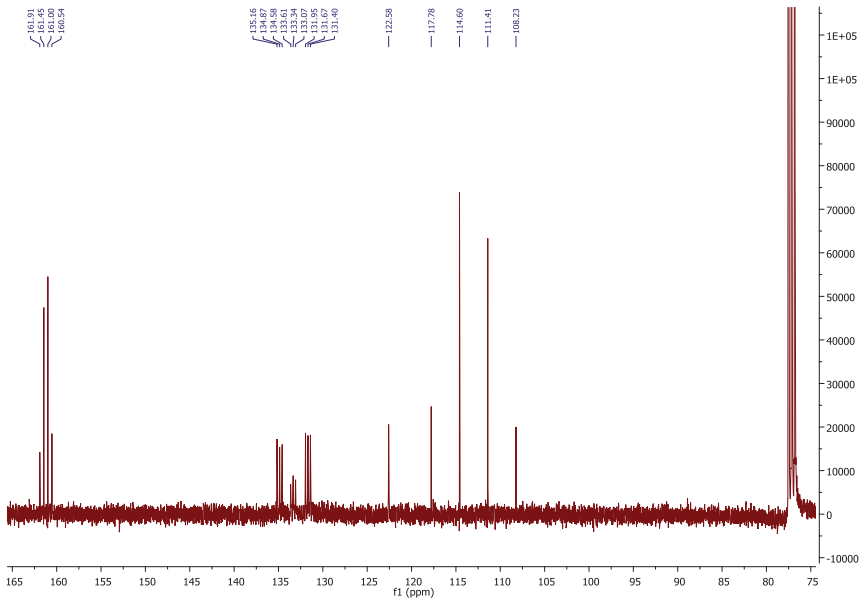
^{19}F NMR (376 MHz, $CDCl_3$)



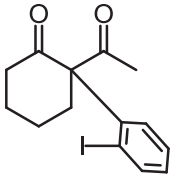
d_5-PIFA



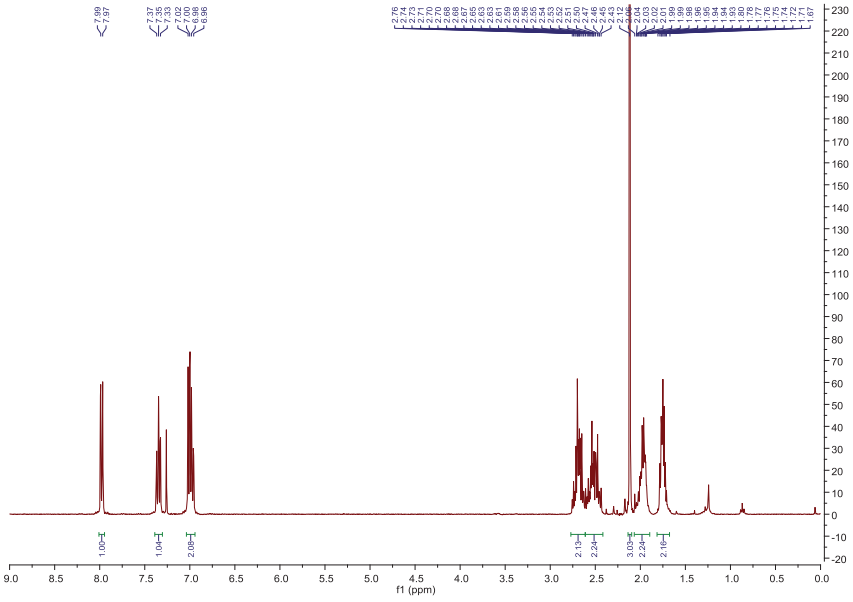
^{13}C NMR (91 MHz, $CDCl_3$)



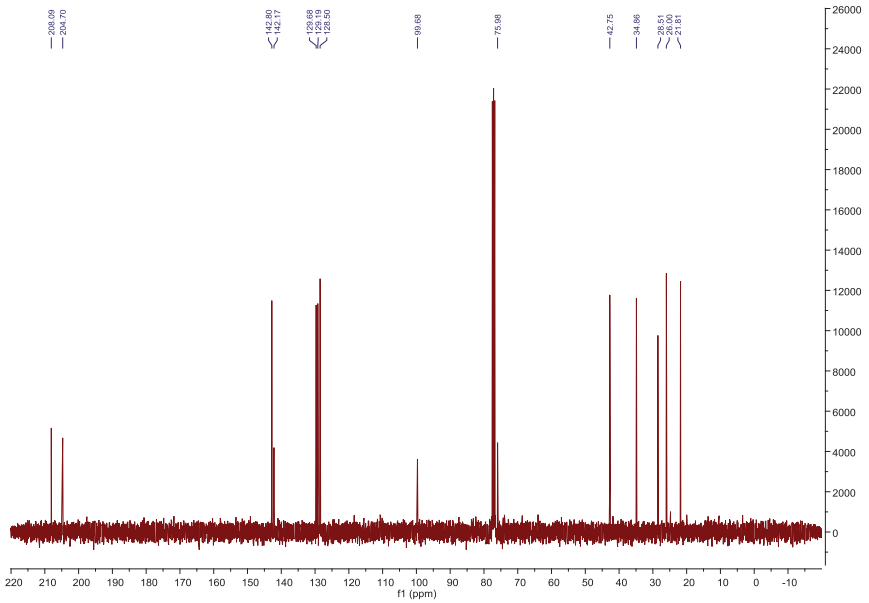
2-acetyl-2-(2-iodophenyl)cyclohexanone



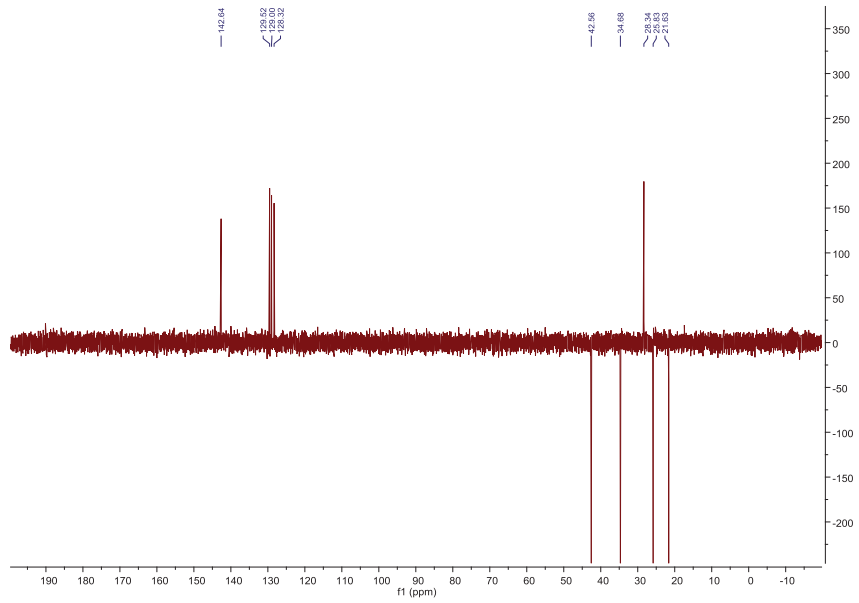
^{1}H NMR (360 MHz, $CDCl_3$)



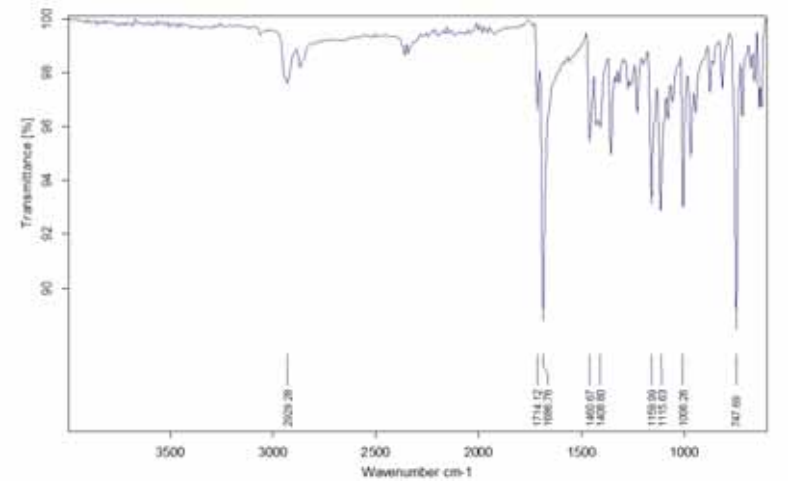
^{13}C NMR (91 MHz, $CDCl_3$)



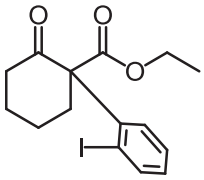
DEPT 135 (101 MHz, $CDCl_3$)



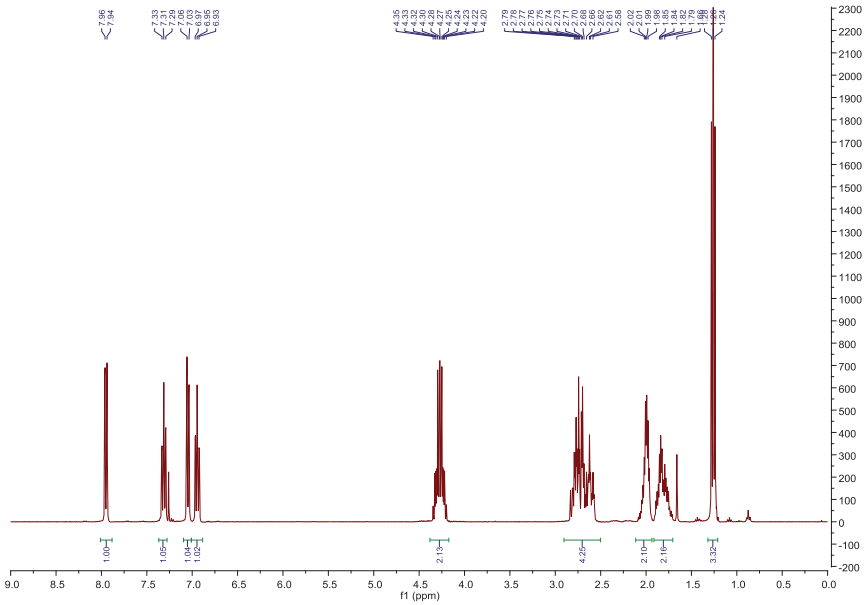
IR (ATR) ν (cm^{-1})



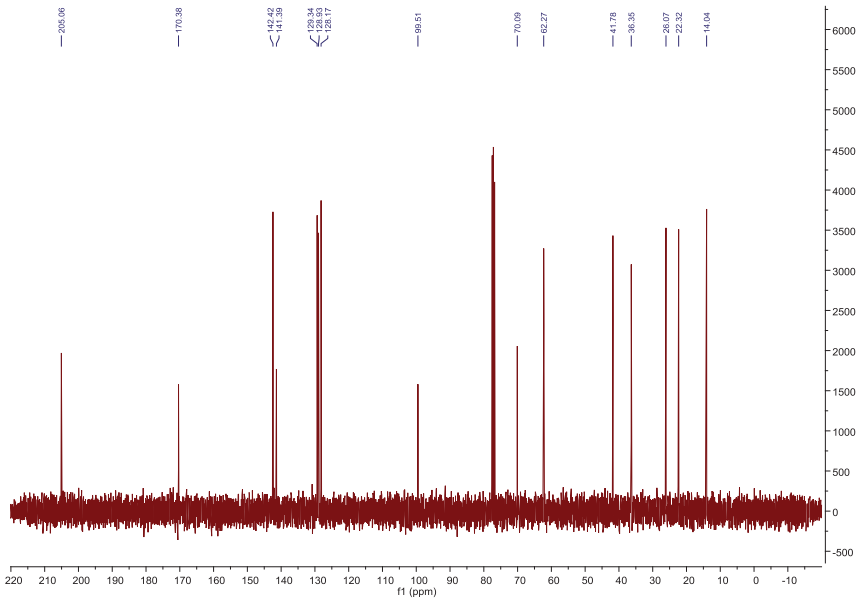
ethyl 1-(2-iodophenyl)-2-oxocyclohexanecarboxylate



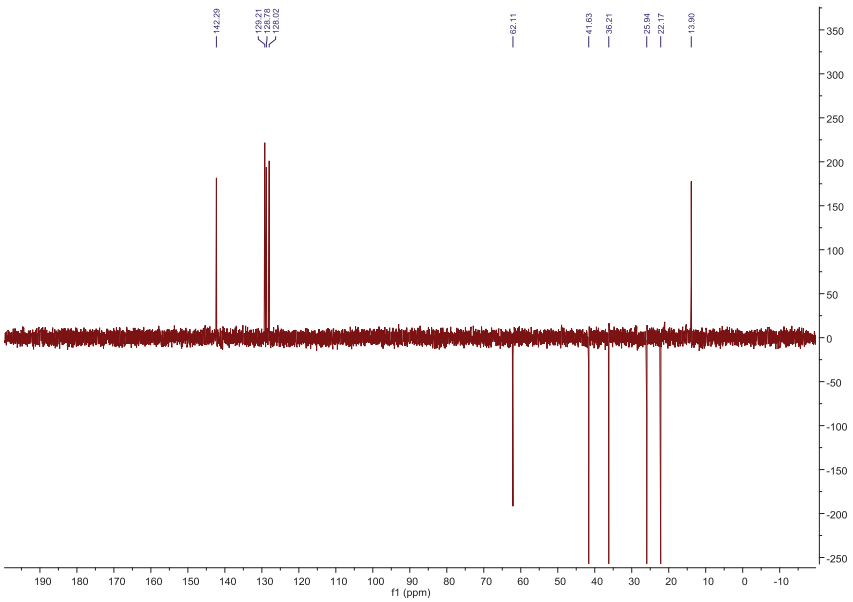
^1H NMR (360 MHz, $CDCl_3$)



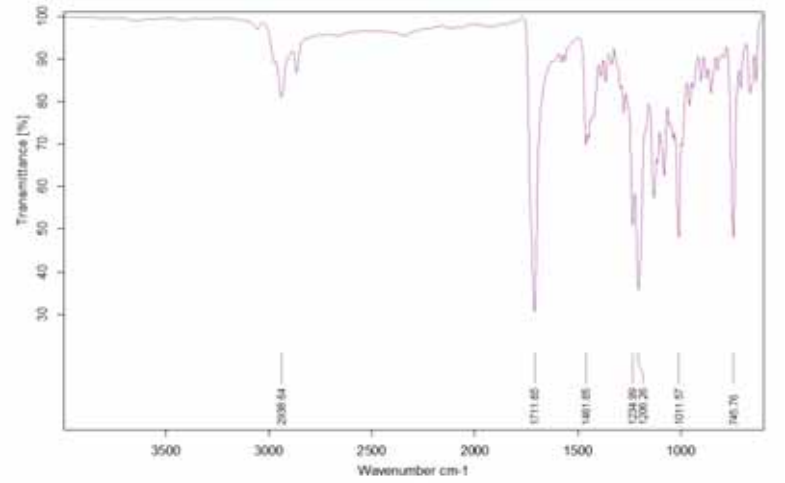
^{13}C NMR (91 MHz, $CDCl_3$)



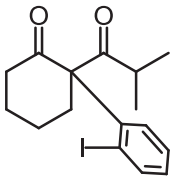
DEPT 135 (101 MHz, $CDCl_3$)



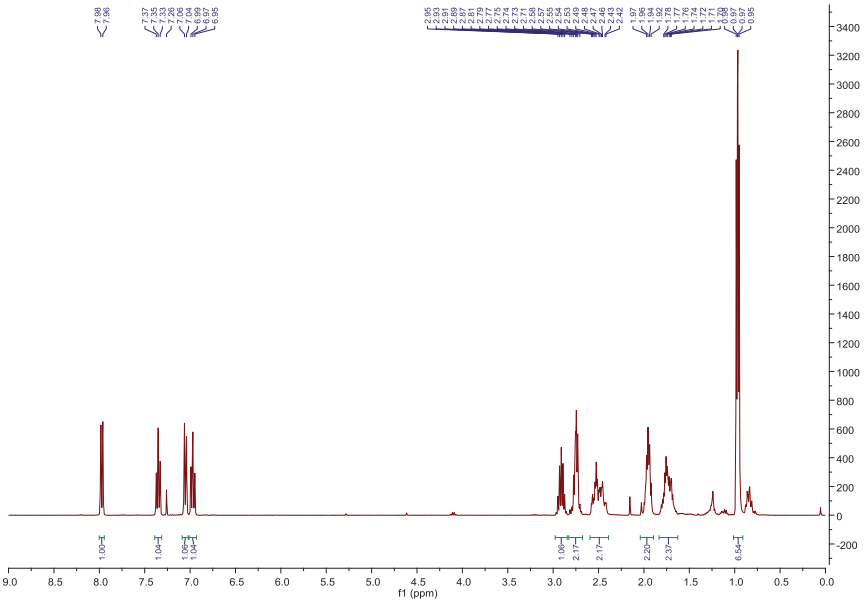
IR (ATR) v (cm^{-1})



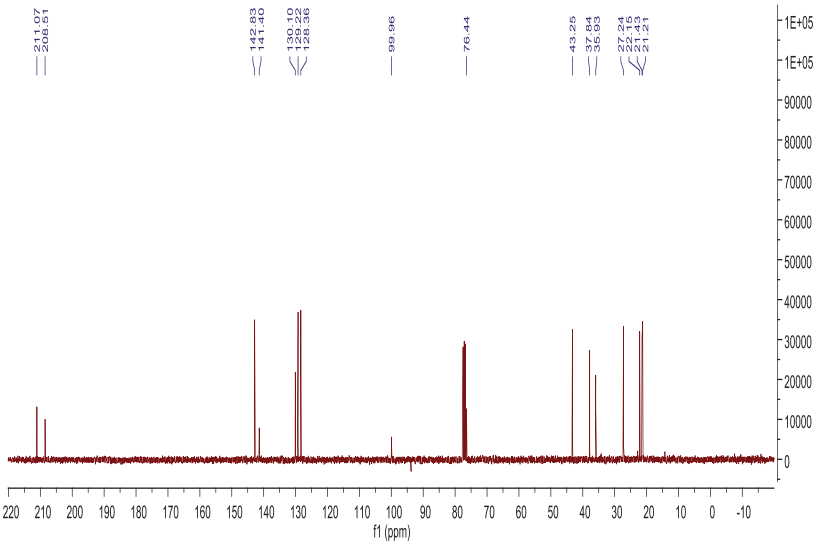
2-(2-iodophenyl)-2-isobutyrylcyclohexanone



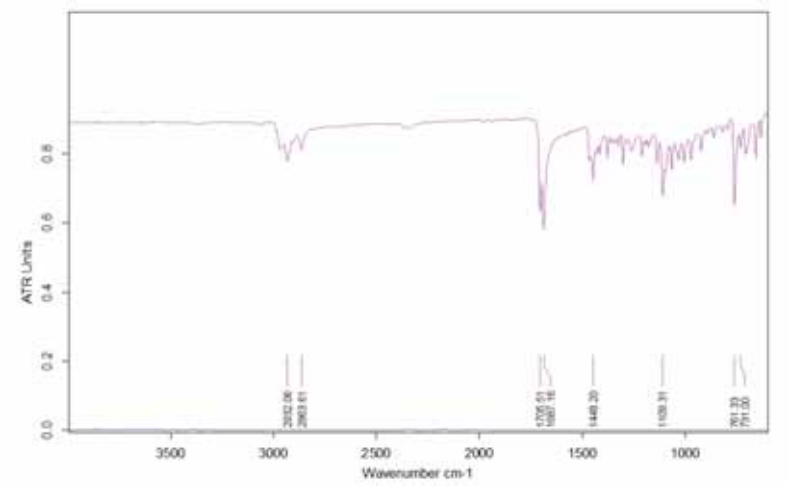
^{1}H NMR (360 MHz, $CDCl_3$)



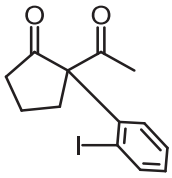
^{13}C NMR (91 MHz, $CDCl_3$)



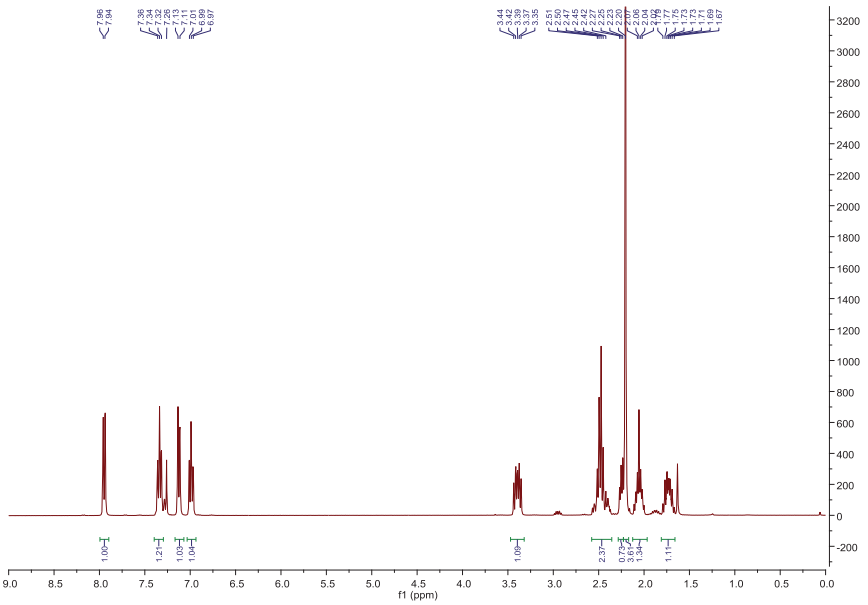
IR (ATR) v (cm^{-1})



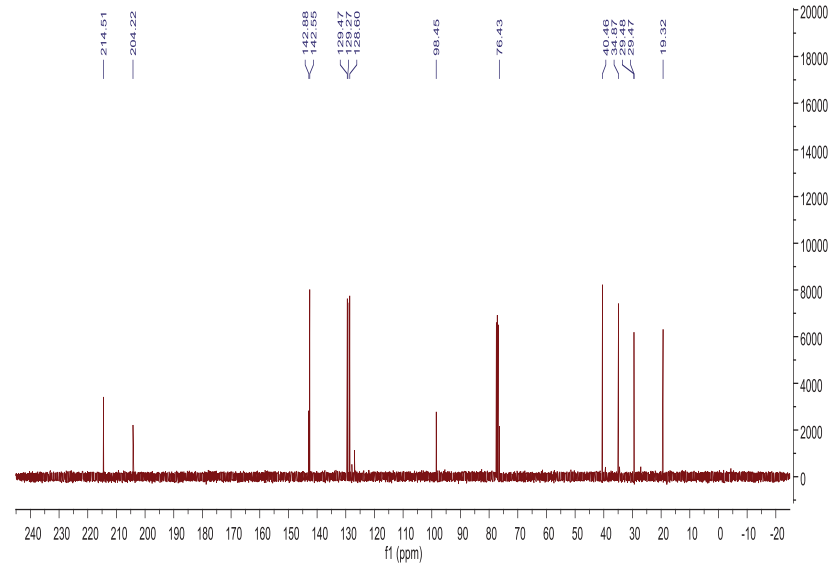
2-acetyl-2-(2-iodophenyl)cyclopentanone



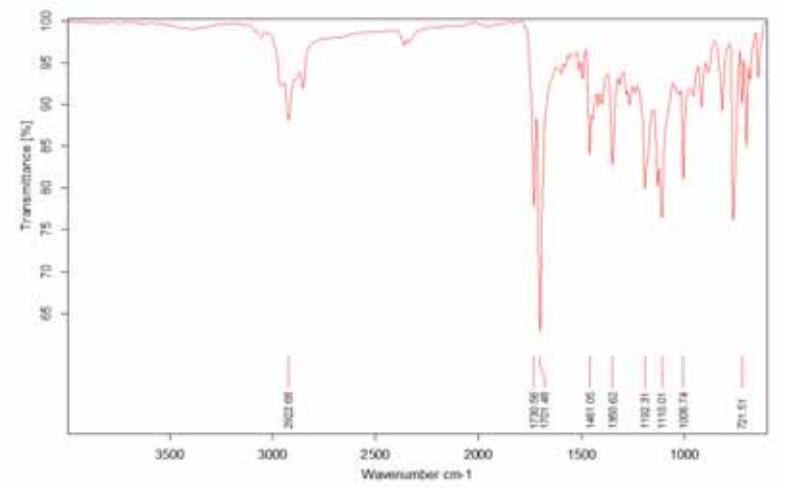
^{1}H NMR (360 MHz, $CDCl_3$)



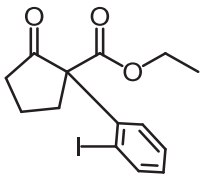
^{13}C NMR (91 MHz, $CDCl_3$)



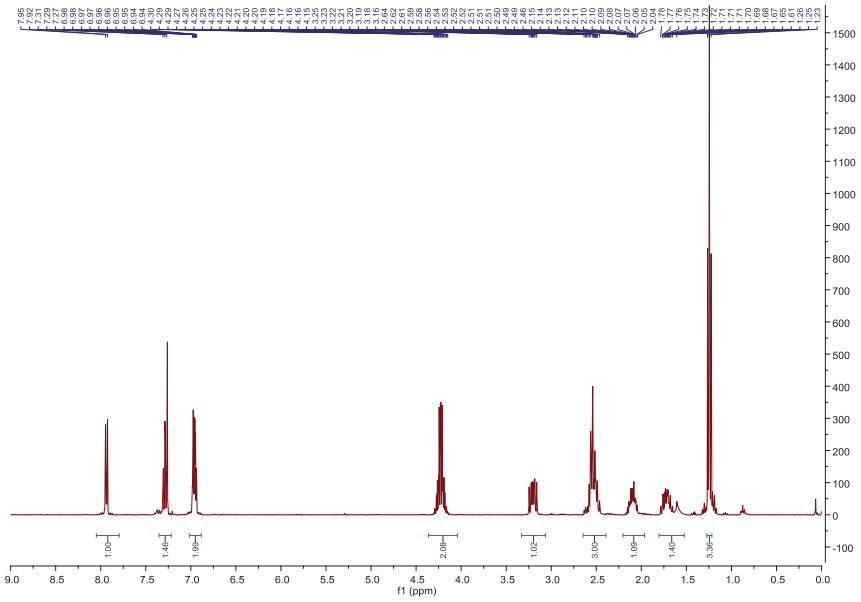
IR (ATR) ν (cm^{-1})



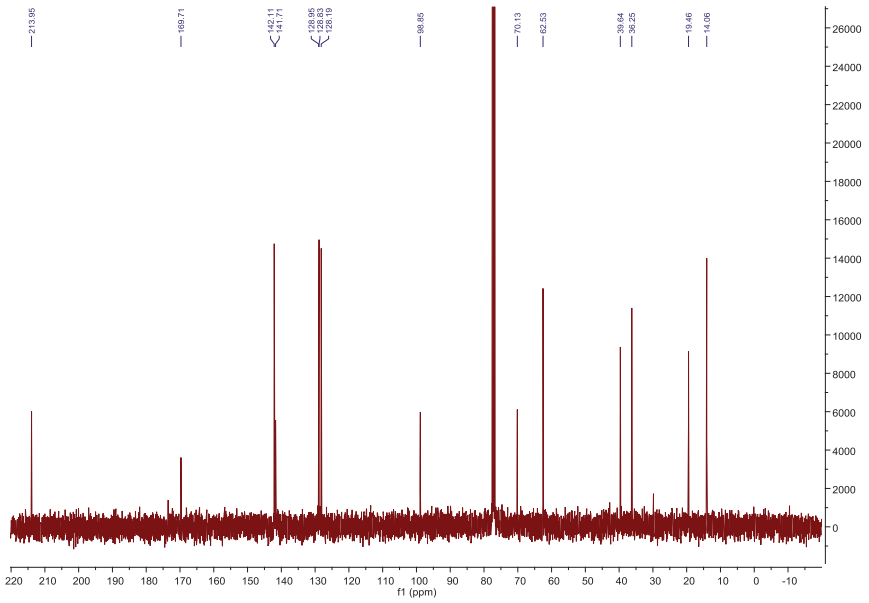
ethyl 1-(2-iodophenyl)-2-oxocyclopentanecarboxylate



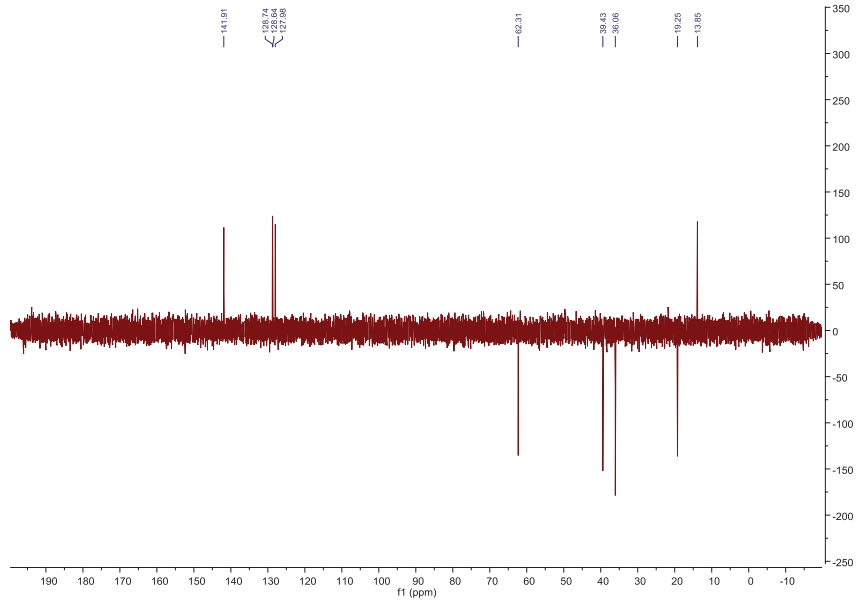
^{1}H NMR (360 MHz, $CDCl_3$)



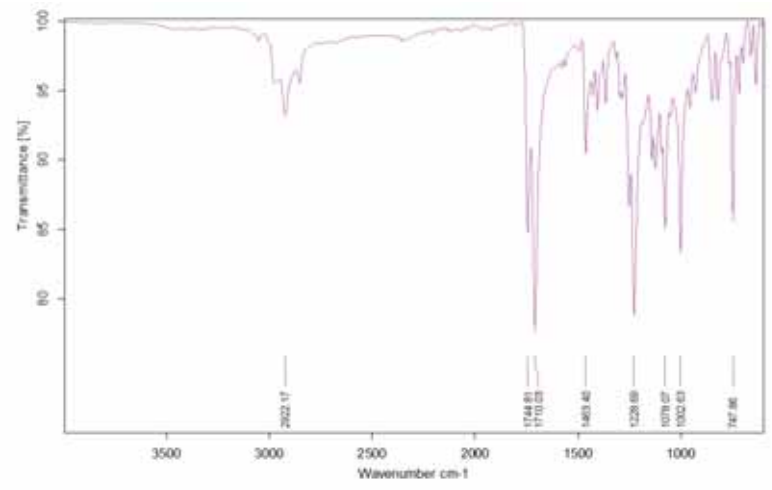
^{13}C NMR (91 MHz, $CDCl_3$)



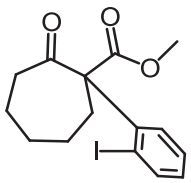
DEPT 135 (101 MHz, $CDCl_3$)



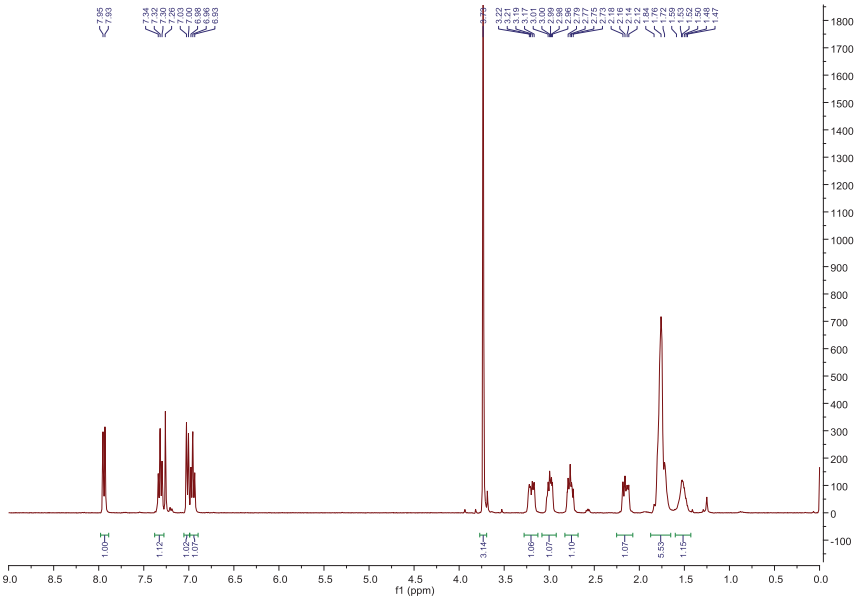
IR (ATR) ν (cm^{-1})



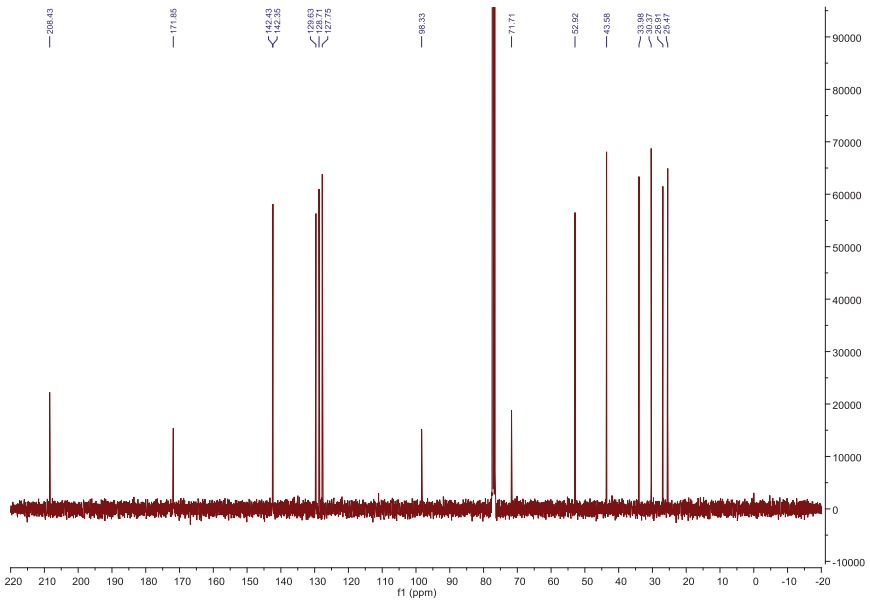
methyl 1-(2-iodophenyl)-2-oxocycloheptanecarboxylate



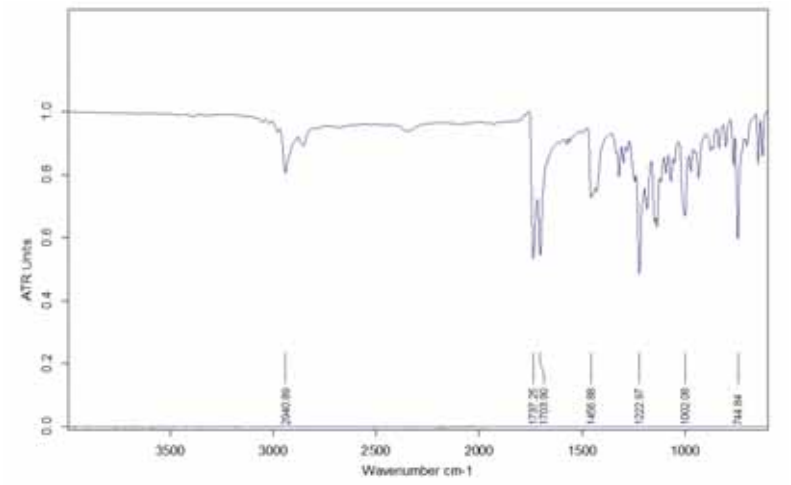
^{1}H NMR (360 MHz, $CDCl_3$)



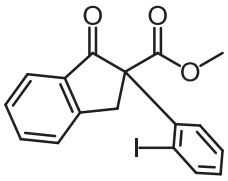
^{13}C NMR (91 MHz, $CDCl_3$)



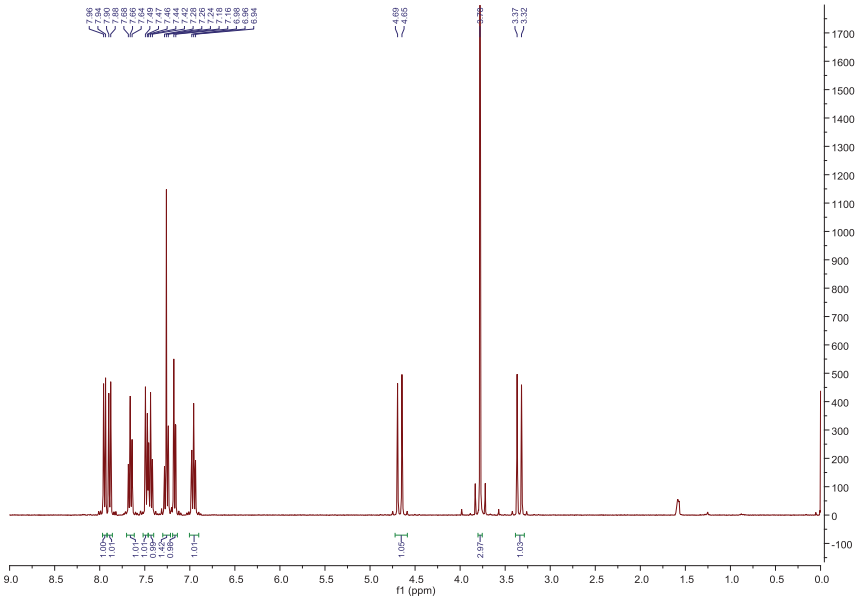
IR (ATR) v (cm^{-1})



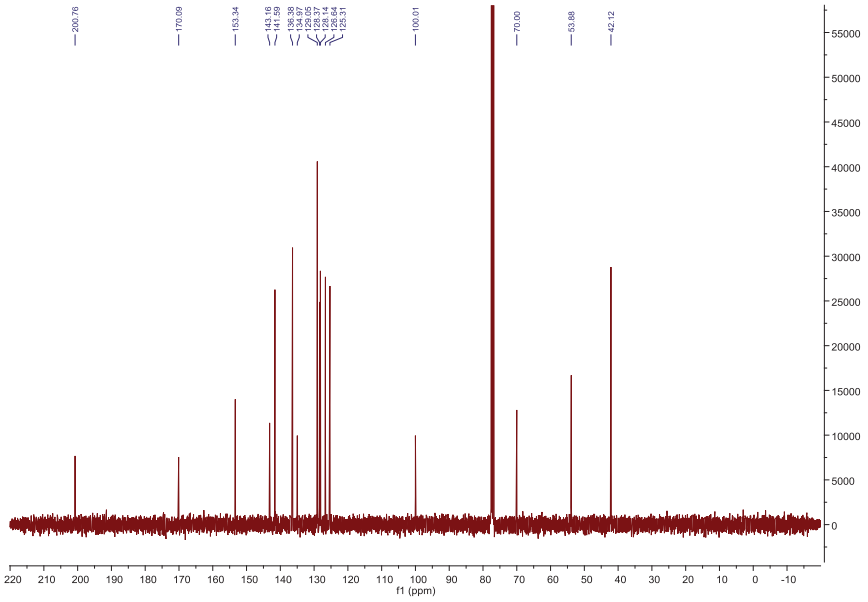
methyl 2-(2-iodophenyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate



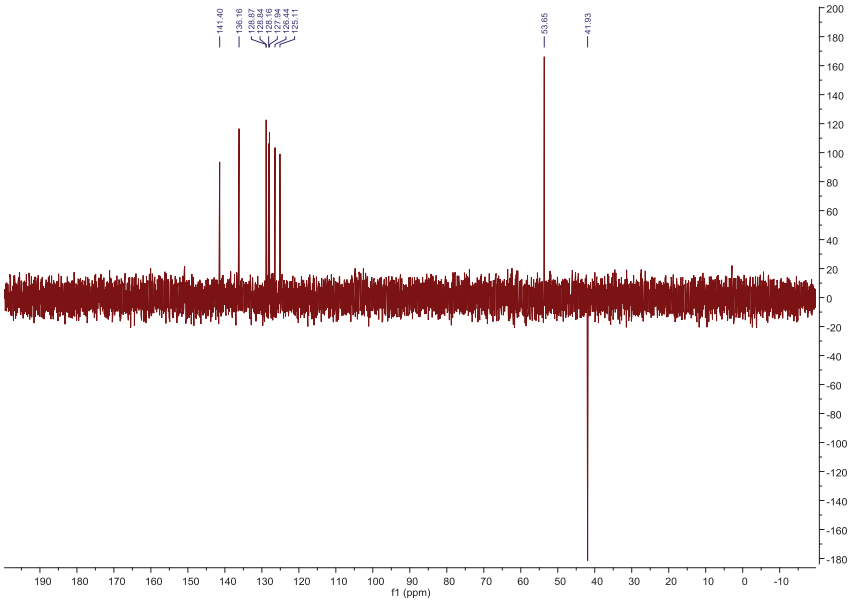
^{1}H NMR (360 MHz, $CDCl_3$)



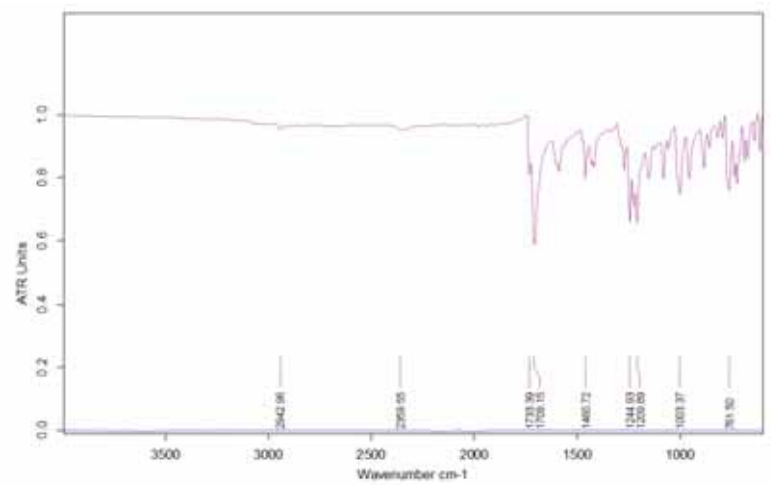
^{13}C NMR (91 MHz, $CDCl_3$)



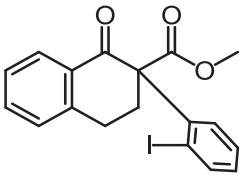
DEPT 135 (101 MHz, $CDCl_3$)



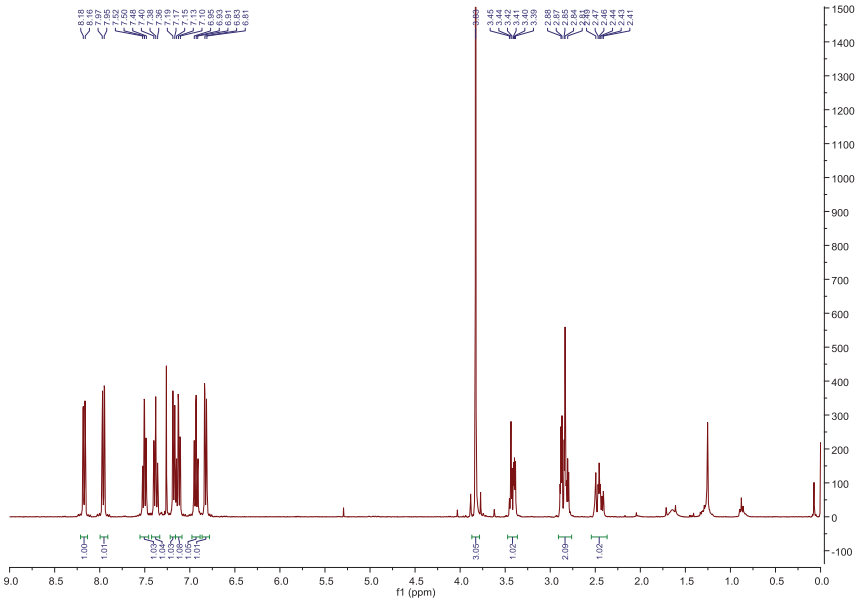
IR (ATR) v (cm^{-1})



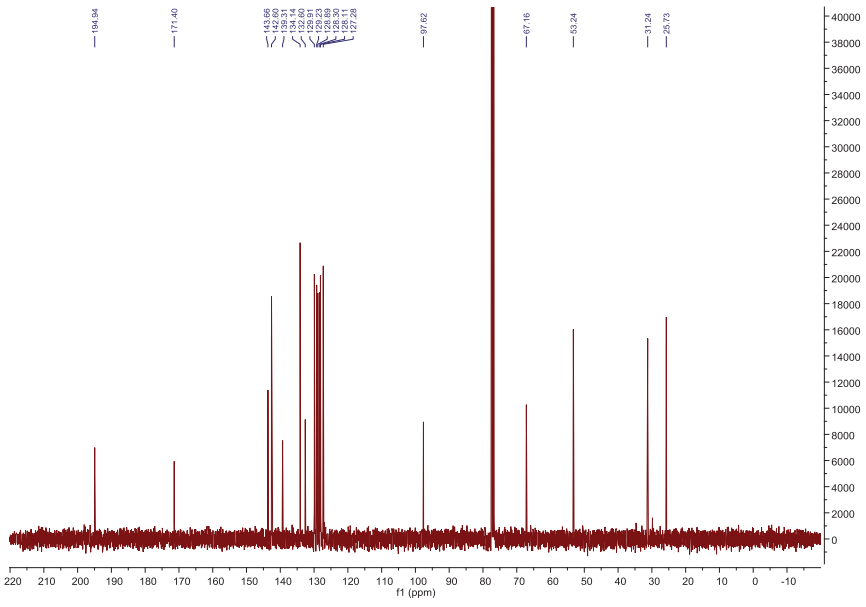
methyl 2-(2-iodophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxy late



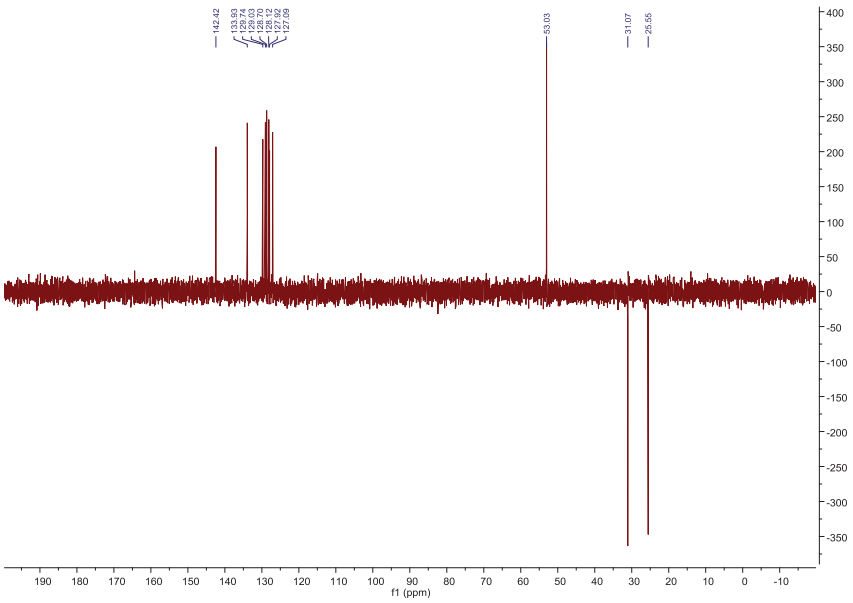
^{1}H NMR (360 MHz, $CDCl_3$)



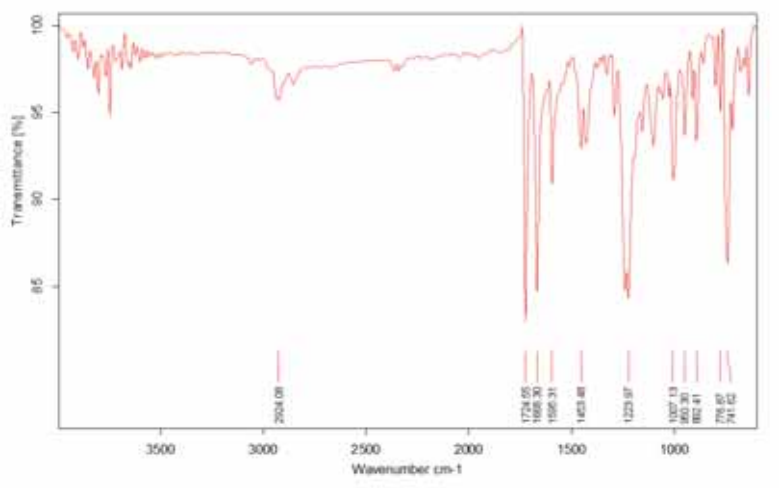
^{13}C NMR (91 MHz, $CDCl_3$)



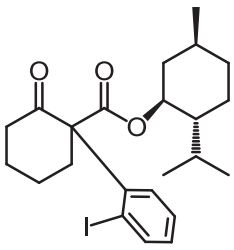
DEPT 135 (101 MHz, $CDCl_3$)



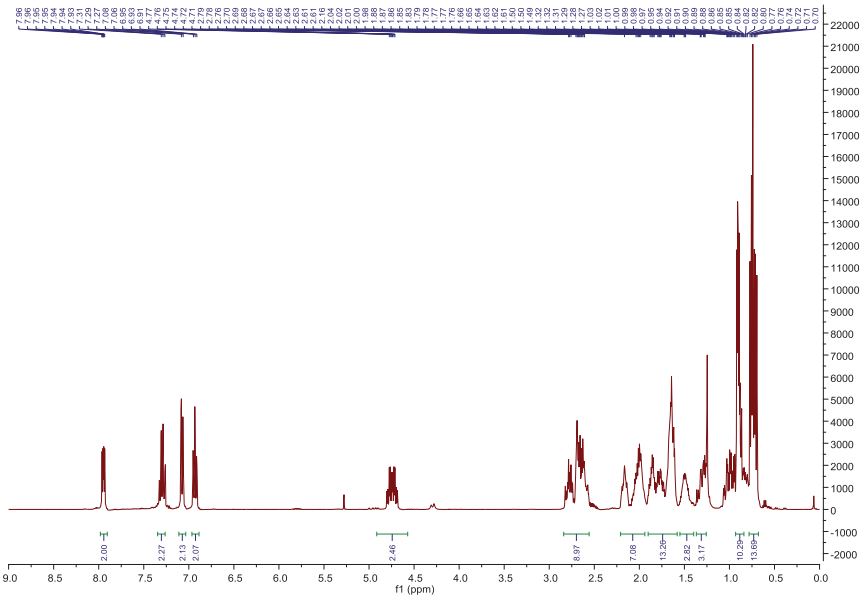
IR (ATR) v (cm^{-1})



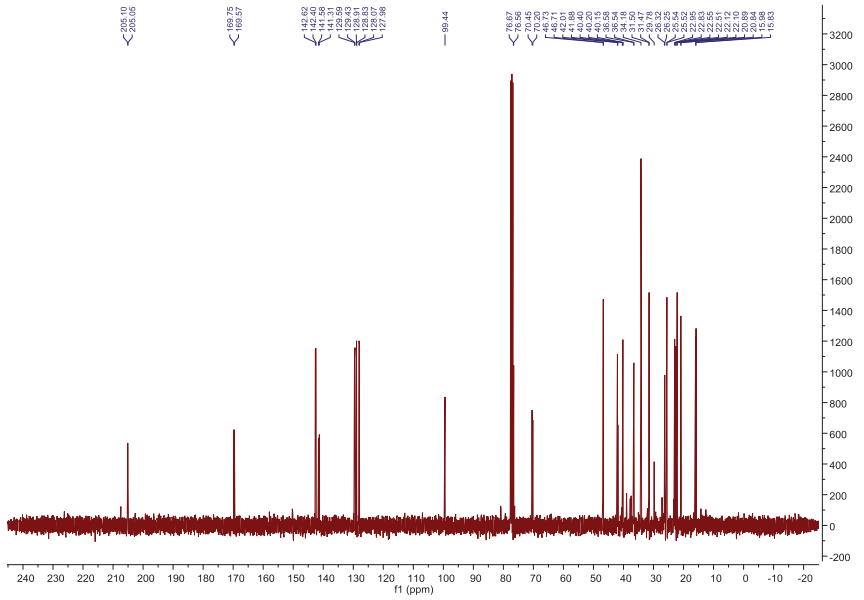
2-isopropyl-5-methylcyclohexyl1-(2-iodophenyl)-2-oxocyclohexane carboxy l –ate



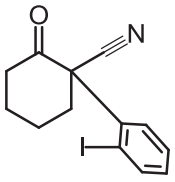
^{1}H NMR (400 MHz, $CDCl_3$)



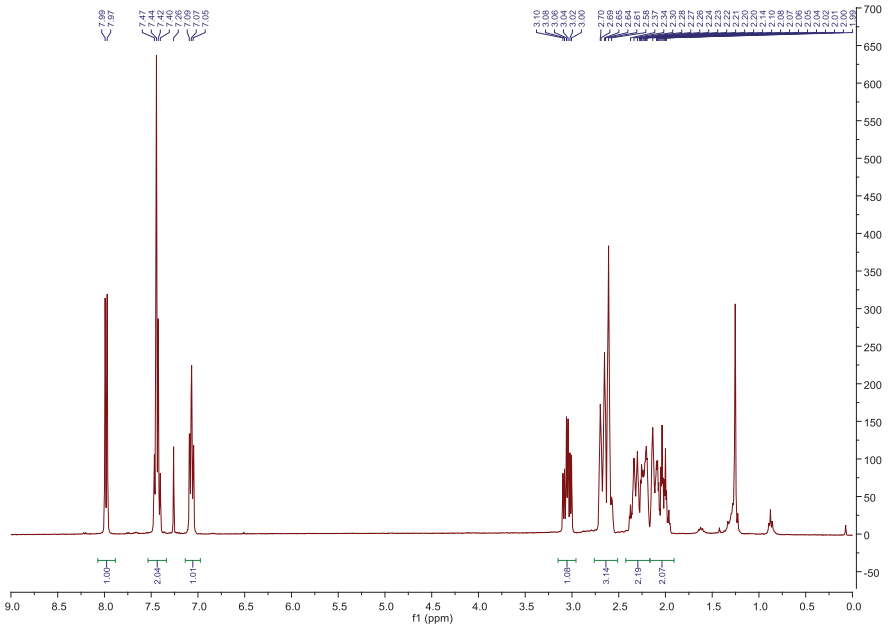
^{13}C NMR (101 MHz, $CDCl_3$)



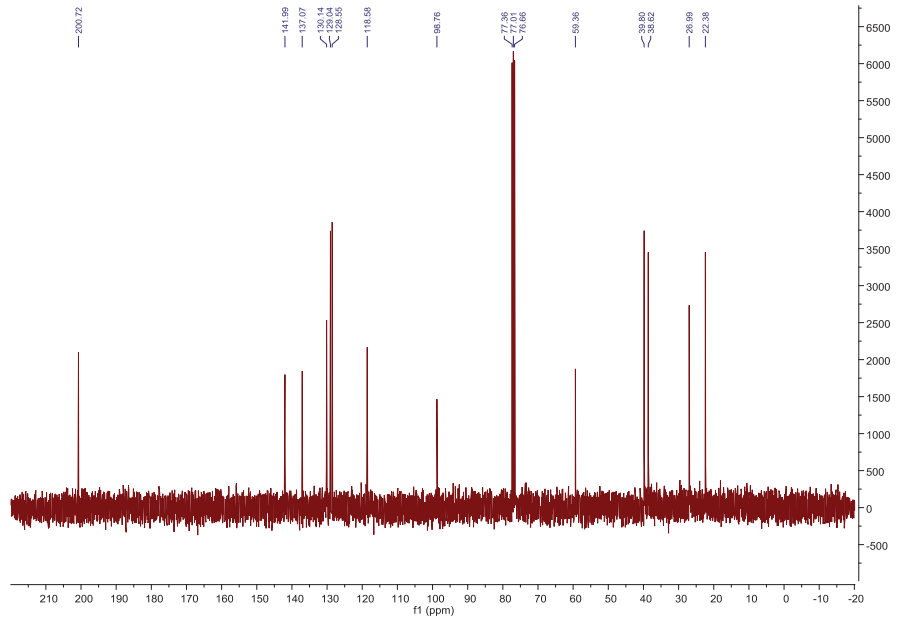
1-(2-iodophenyl)-2-oxocyclohexanecarbonitrile



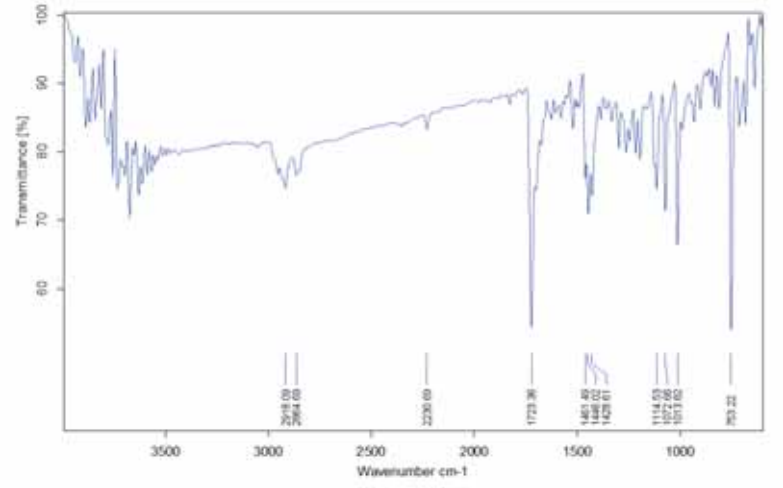
^{1}H NMR (360 MHz, $CDCl_3$)



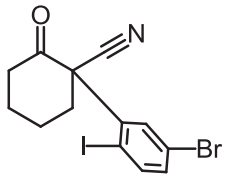
^{13}C NMR (91 MHz, $CDCl_3$)



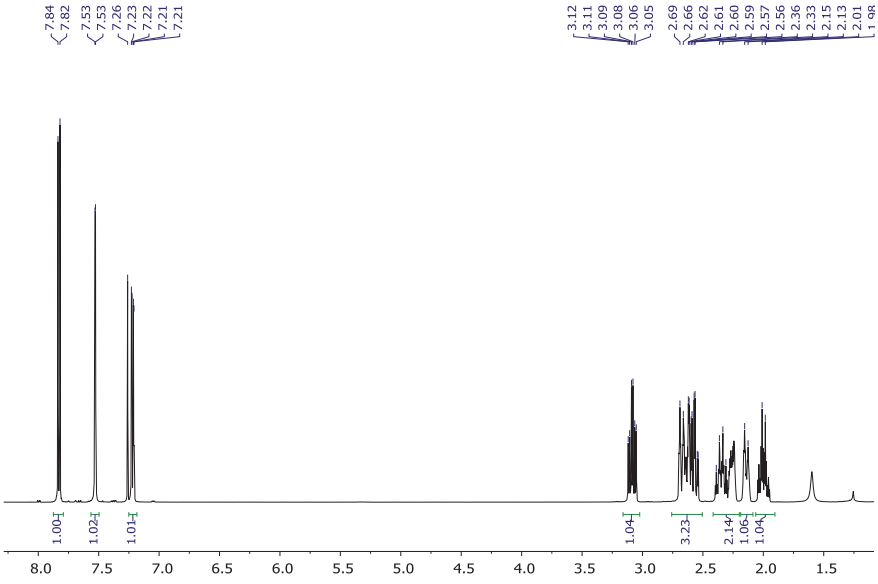
IR (ATR) v (cm^{-1})

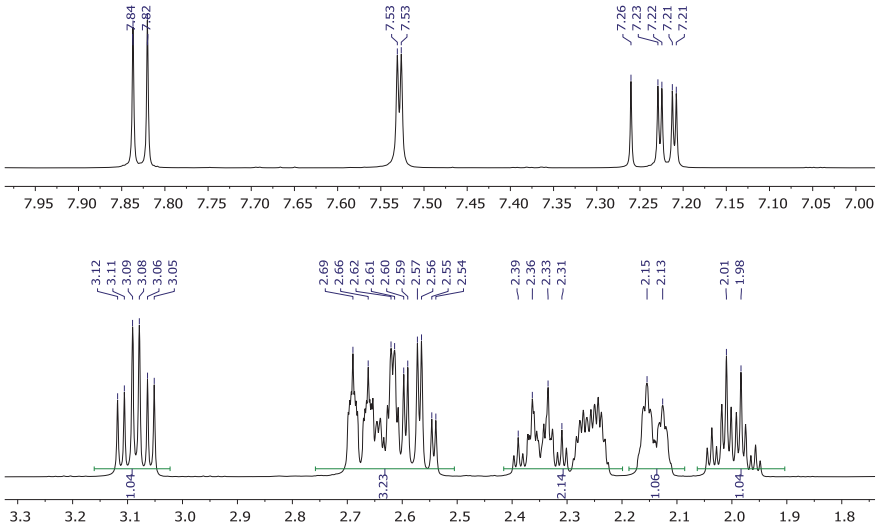


1-(5-bromo-2-iodophenyl)-2-oxocyclohexanecarbonitrile

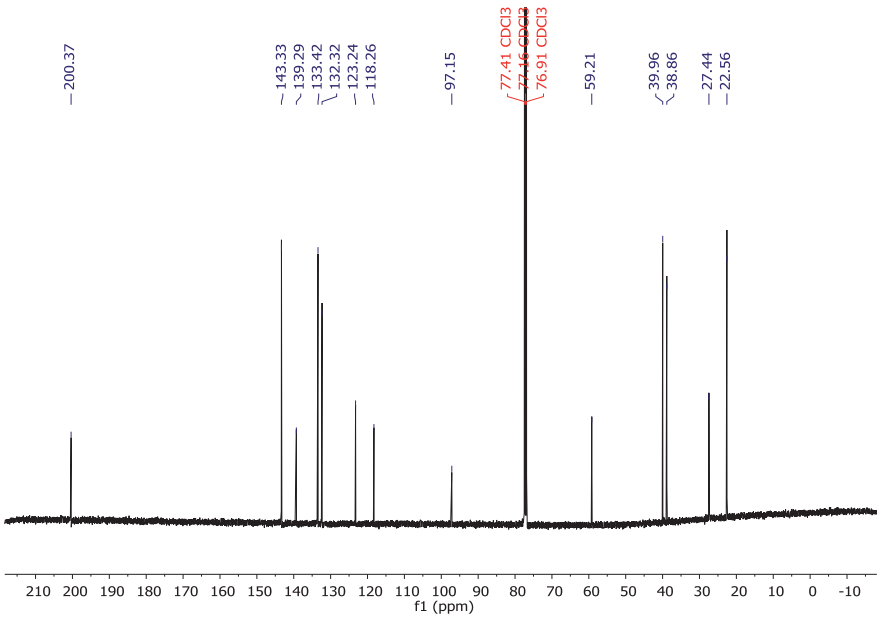


^{1}H NMR (500 MHz, $CDCl_3$)

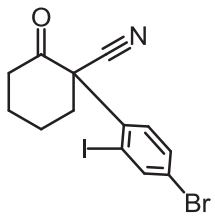




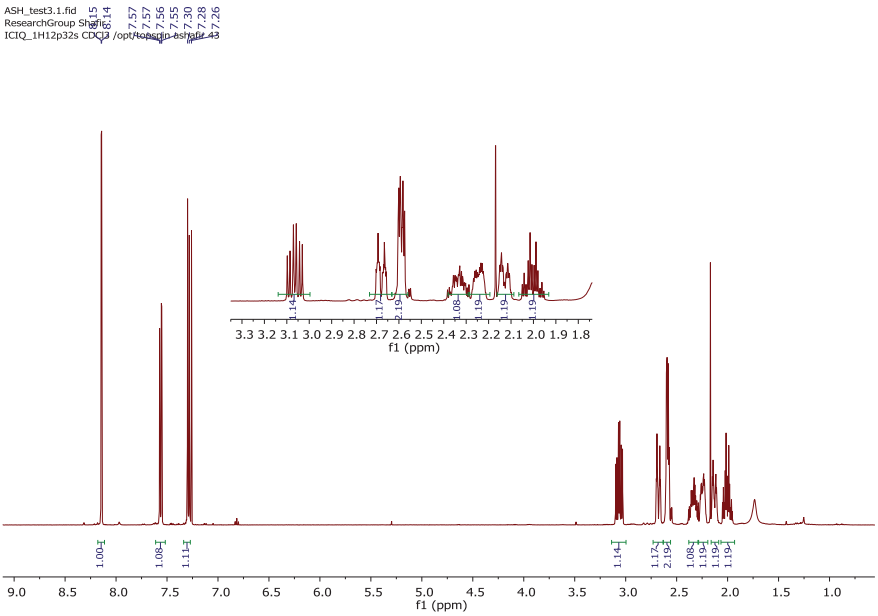
^{13}C NMR (126 MHz, $CDCl_3$)



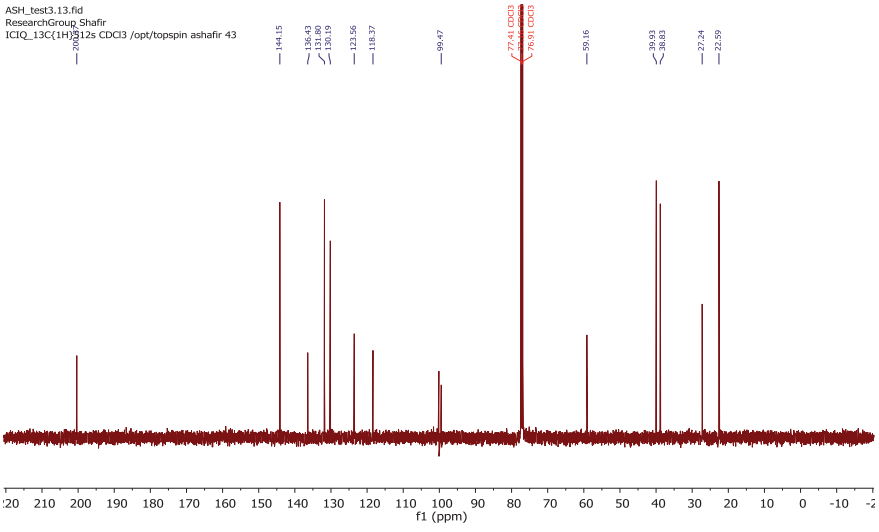
1-(4-bromo-2-iodophenyl)-2-oxocyclohexanecarbonitrile



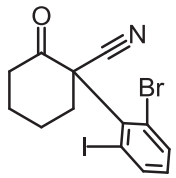
^{1}H NMR (500 MHz, $CDCl_3$)



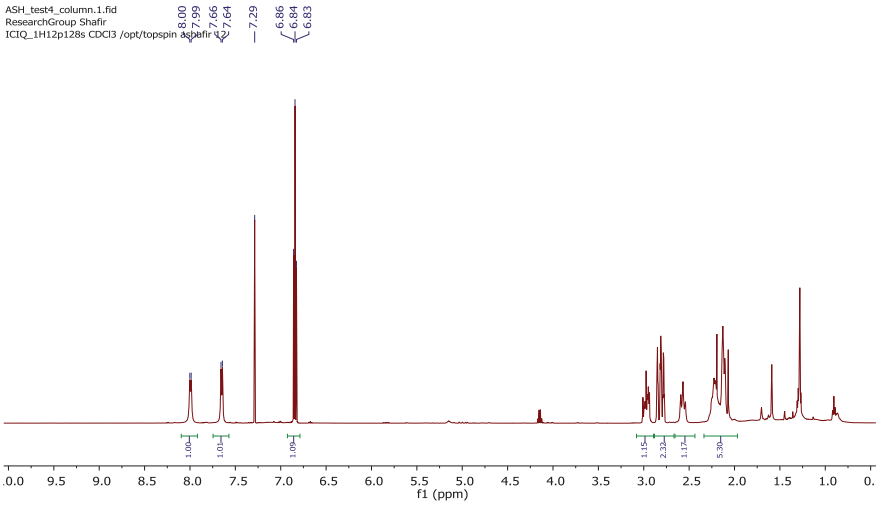
^{13}C NMR (126 MHz, $CDCl_3$)



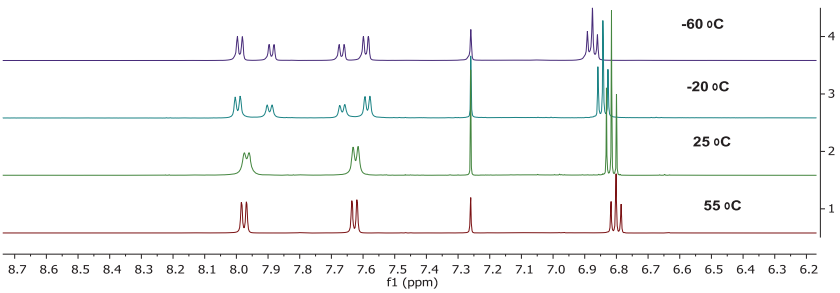
1-(2-bromo-6-iodophenyl)-2-oxocyclohexanecarbonitrile

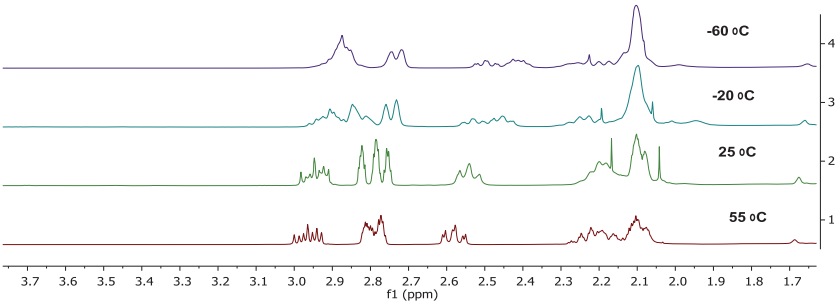


^{1}H NMR (500 MHz, $CDCl_3$): **Room Temperature**

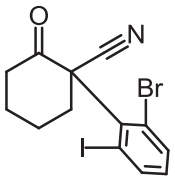


Variable Temperature ^{1}H NMR

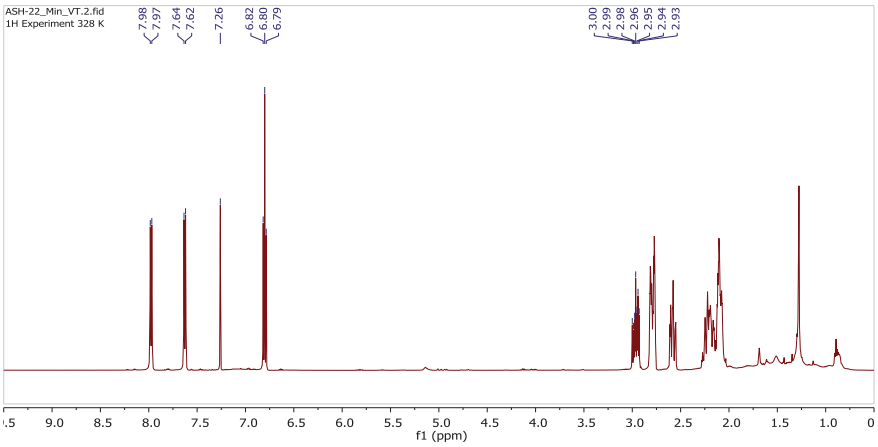




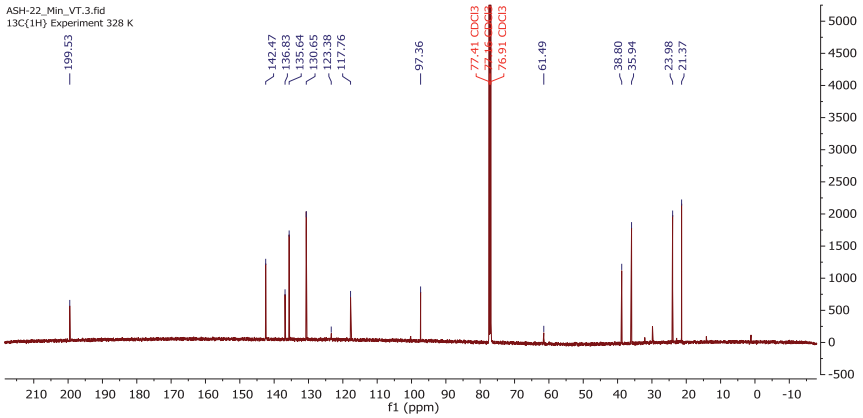
1-(2-bromo-6-iodophenyl)-2-oxocyclohexanecarbonitrile



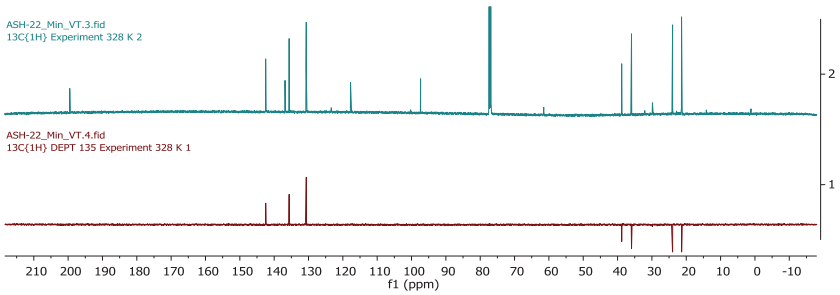
^{1}H NMR (500 MHz, $CDCl_3$): **High Temperature (55 ^{o}C)**



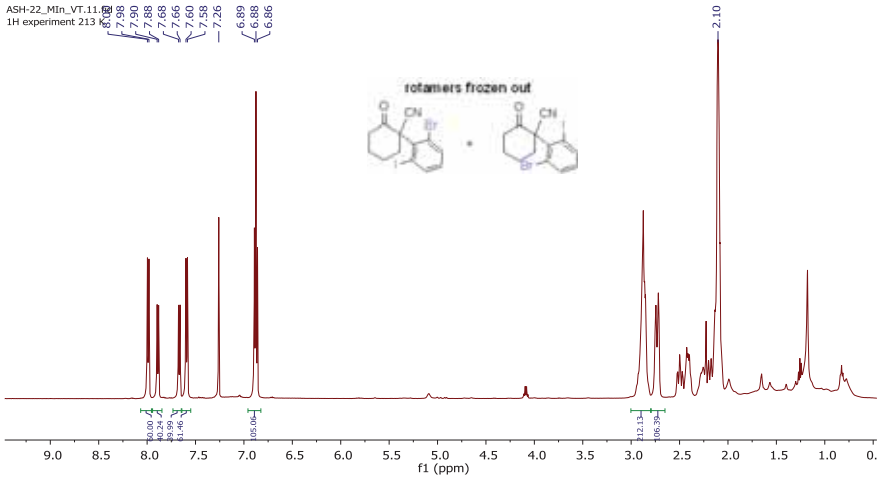
^{13}C NMR (126 MHz, $CDCl_3$) at 55 °C



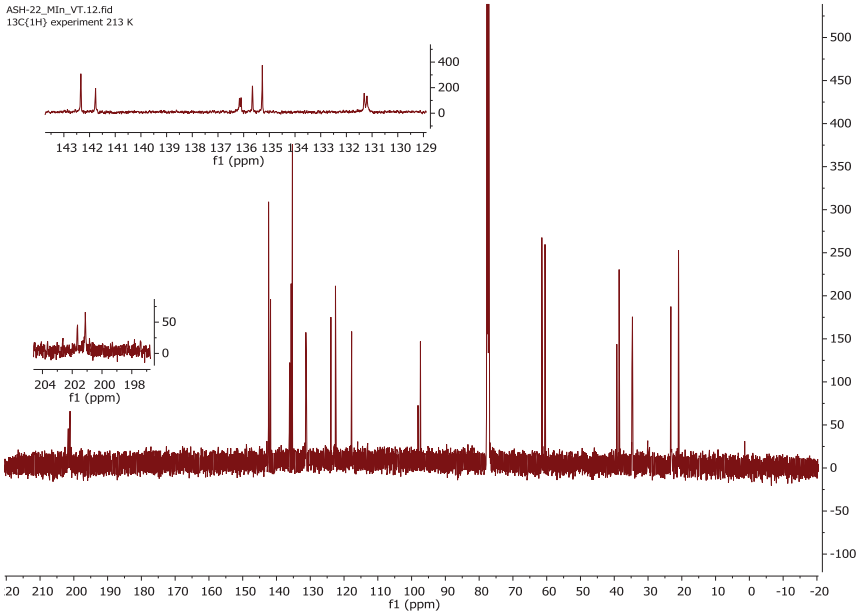
^{13}C and DEPT135 at 55 °C



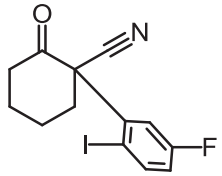
^{1}H NMR (500 MHz, $CDCl_3$): **Low Temperature (-60 °C)**



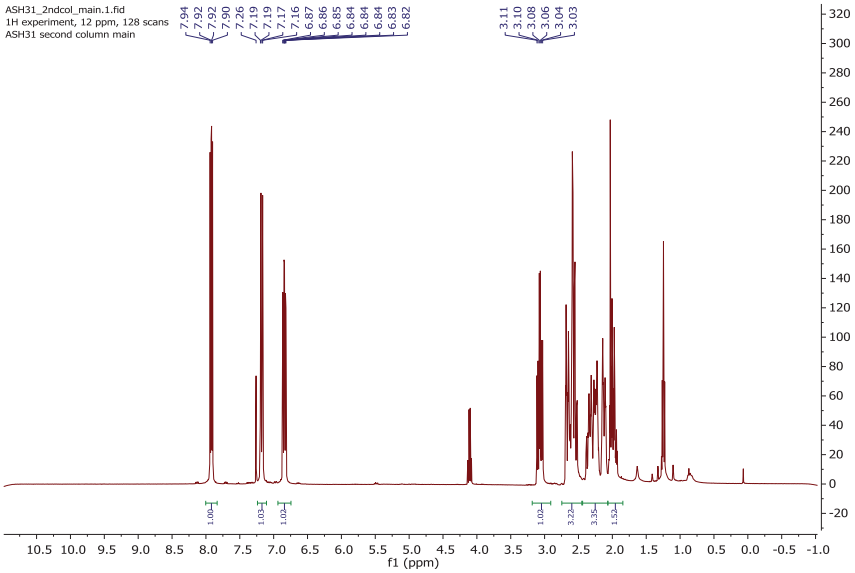
^{13}C NMR (126 MHz, $CDCl_3$) at -60 ^{o}C (doubling of all resonances)



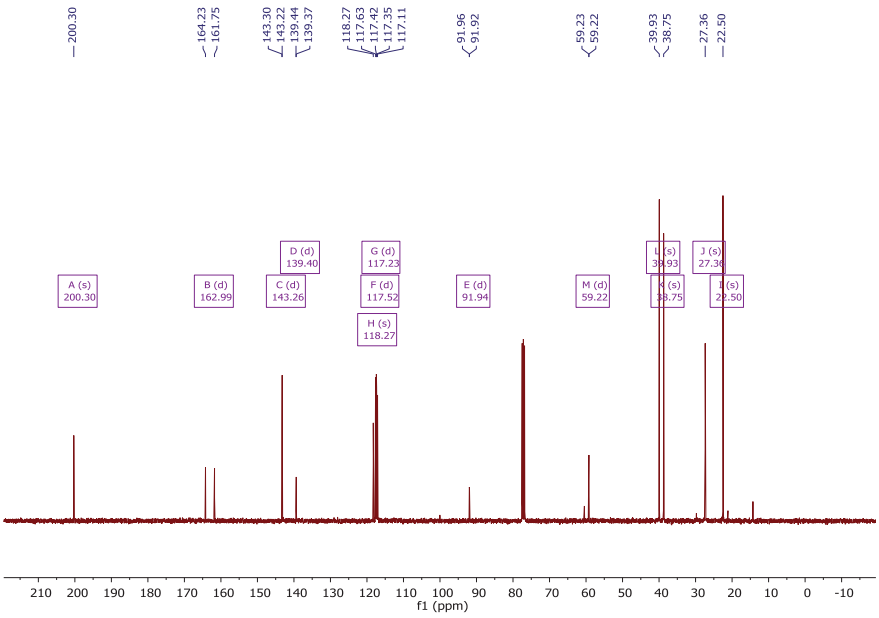
1-(5-fluoro-2-iodophenyl)-2-oxocyclohexanecarbonitrile



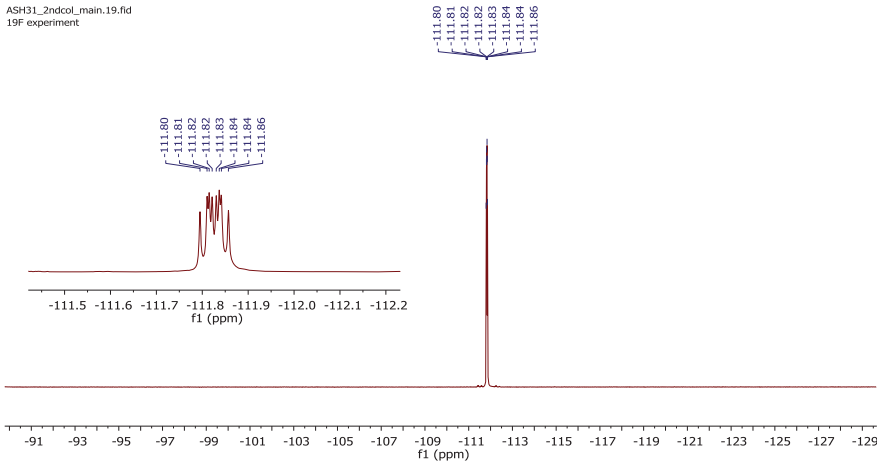
^{1}H NMR (400 MHz, $CDCl_3$)



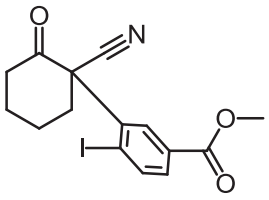
^{13}C NMR (101 MHz, $CDCl_3$)



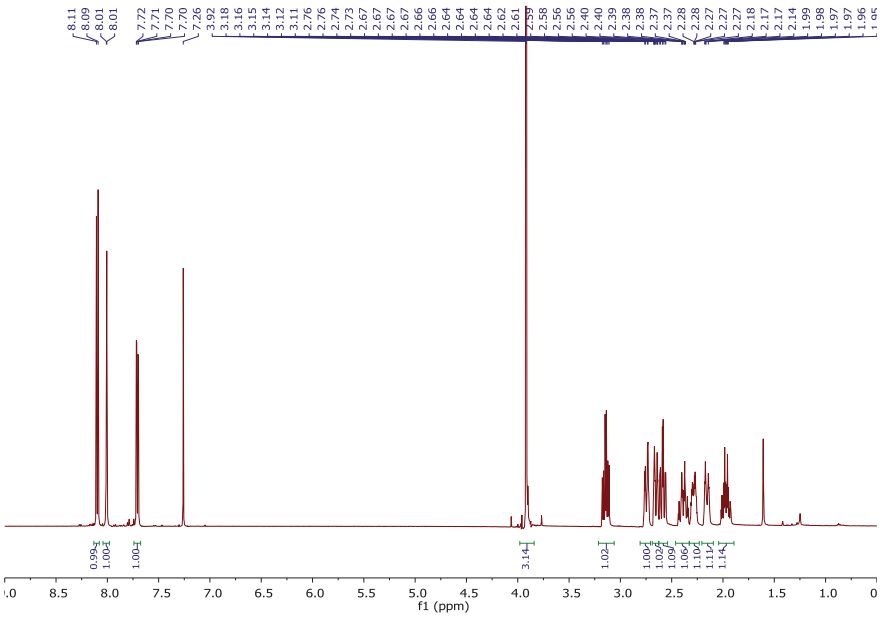
^{19}F NMR (376 MHz, $CDCl_3$)



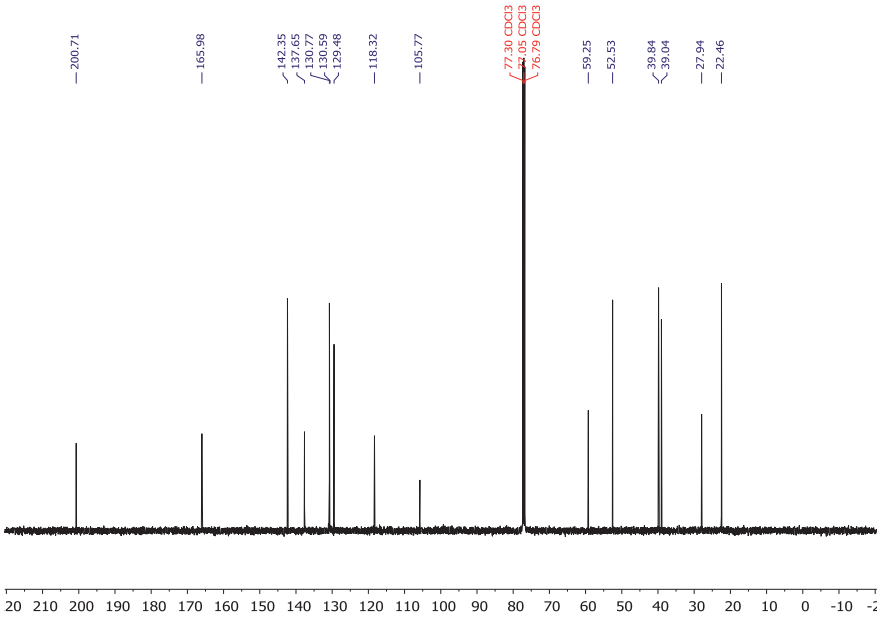
(S)-2-(2-iodophenyl)-2-methyl-3-oxo-3-phenylpropanenitrile



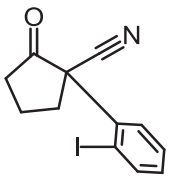
^{1}H NMR (500 MHz, $CDCl_3$)



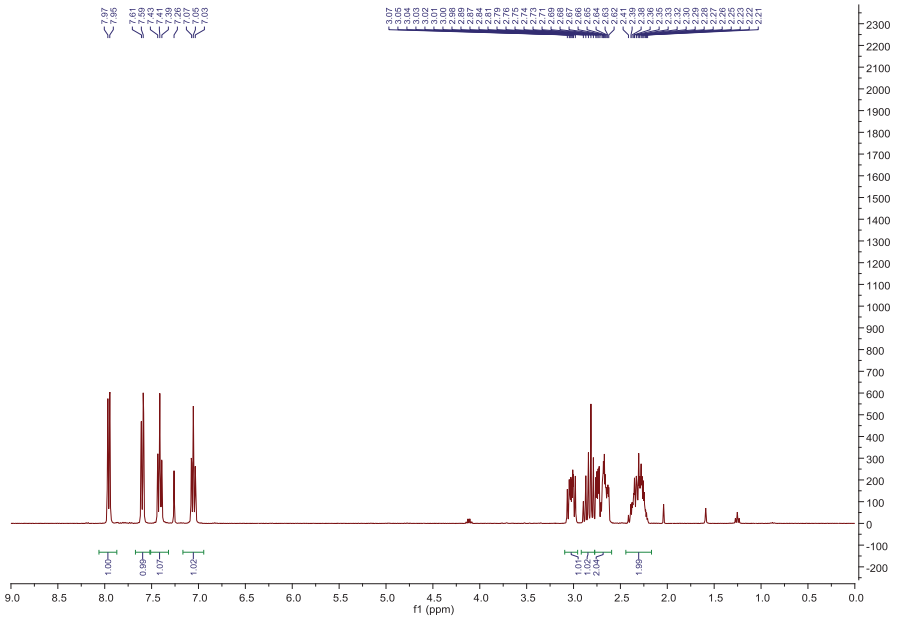
^{13}C NMR (500 MHz, $CDCl_3$)



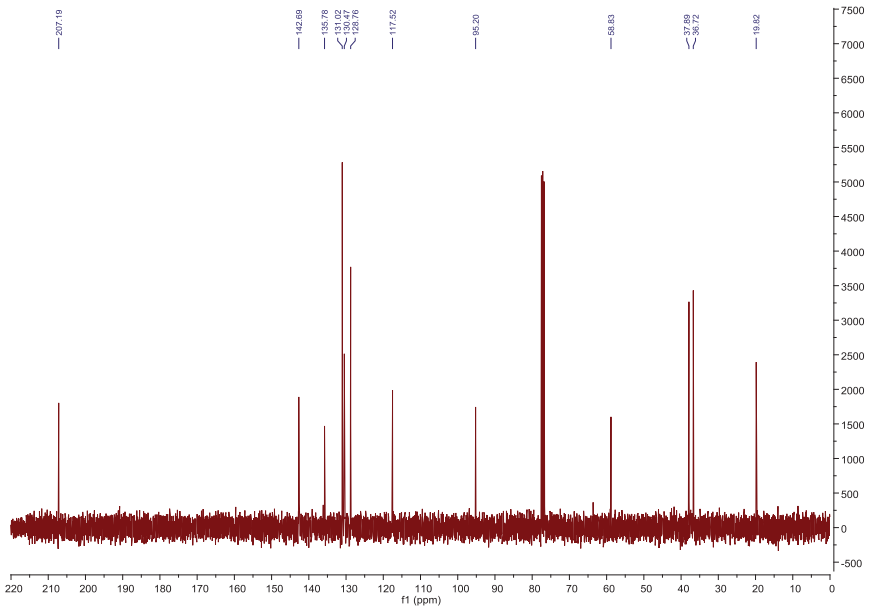
1-(2-iodophenyl)-2-oxocyclopentanecarbonitrile



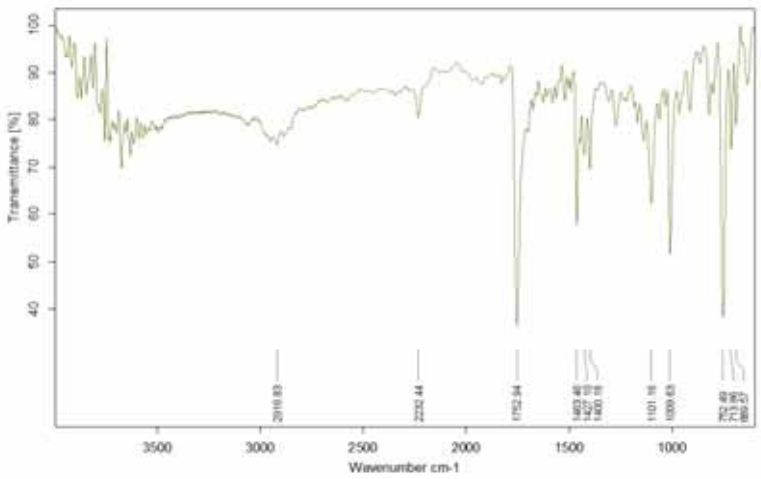
^{1}H NMR (360 MHz, $CDCl_3$)



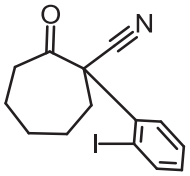
^{13}C NMR (91 MHz, $CDCl_3$)



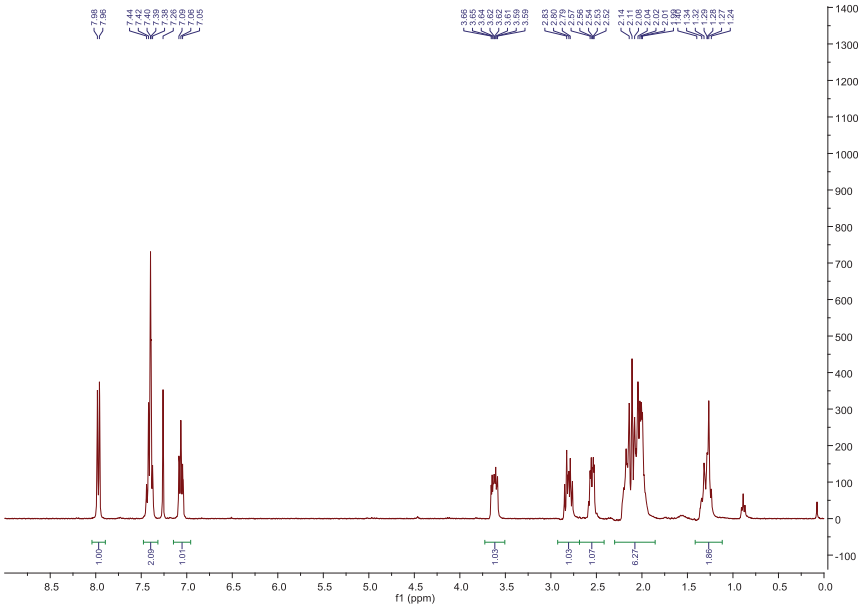
IR (ATR) v (cm^{-1})



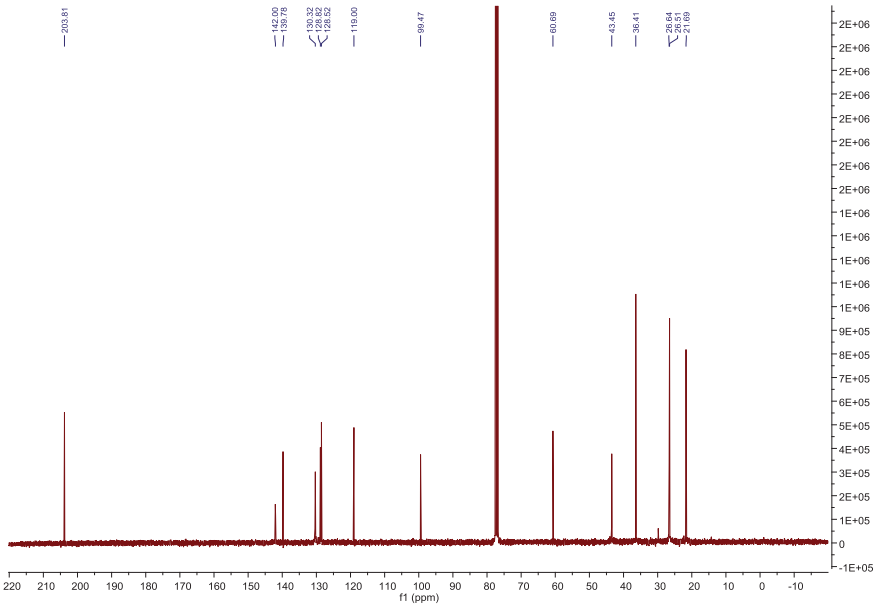
1-(2-iodophenyl)-2-oxocycloheptanecarbonitrile



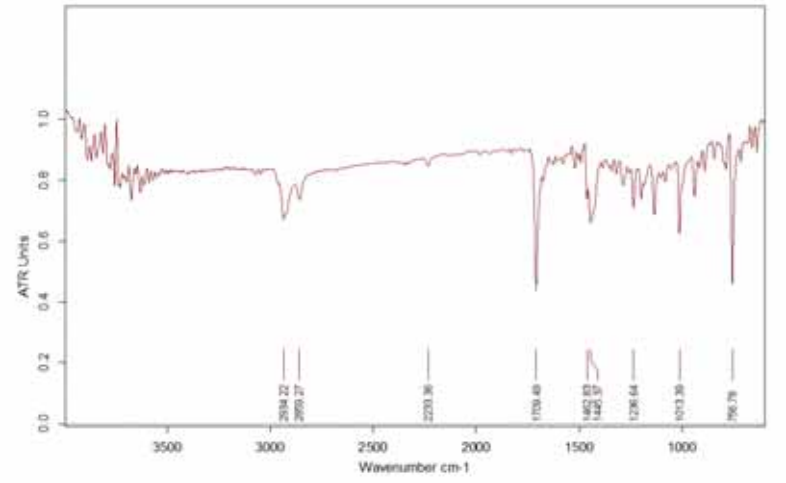
^{1}H NMR (360 MHz, $CDCl_3$)



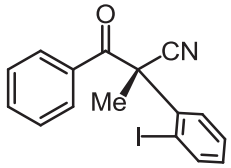
^{13}C NMR (91 MHz, $CDCl_3$)



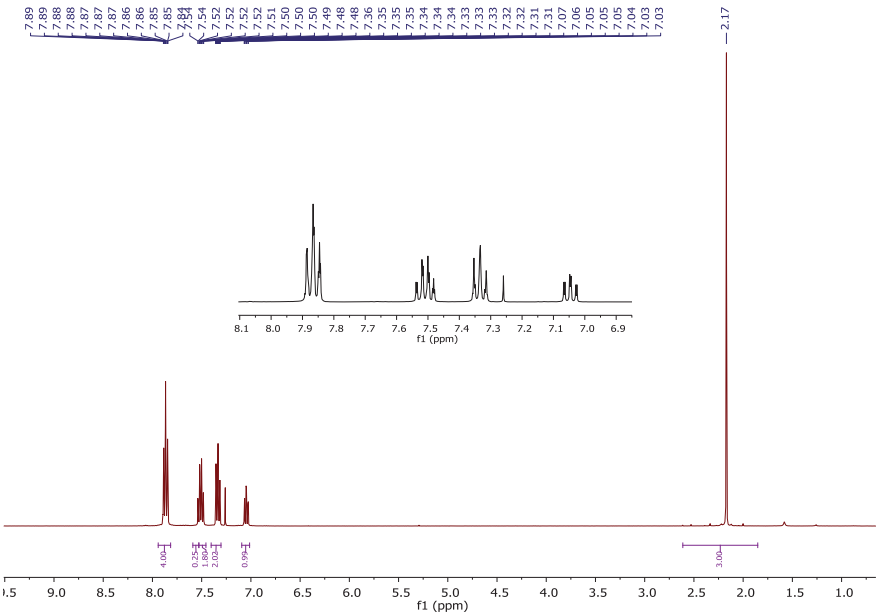
IR (ATR) v (cm^{-1})



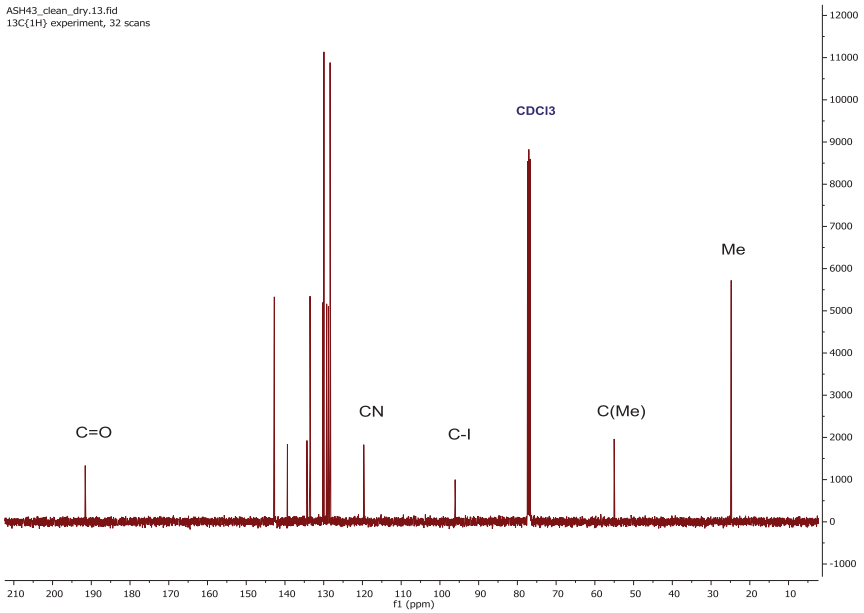
(S)-2-(2-iodophenyl)-2-methyl-3-oxo-3-phenylpropanenitrile



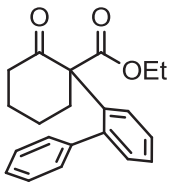
^{1}H NMR (400 MHz, $CDCl_3$)



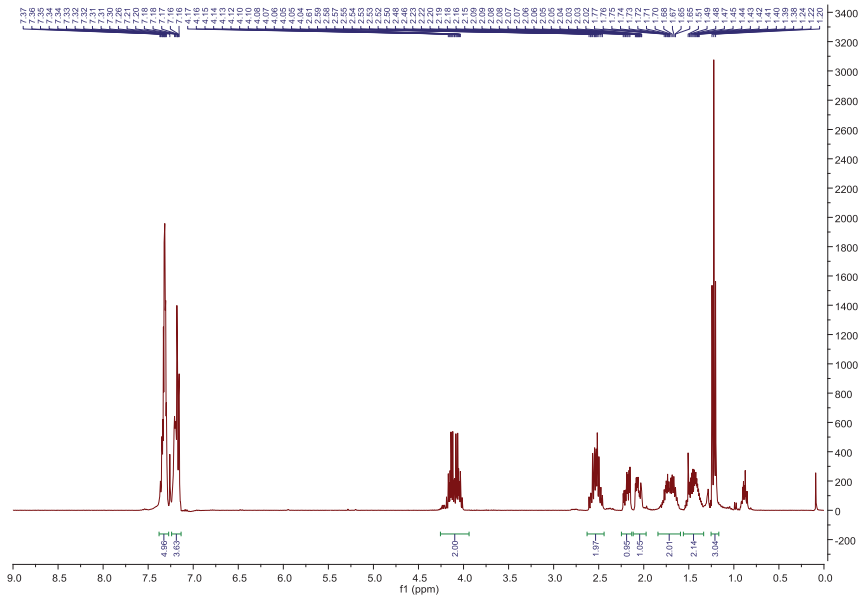
^{13}C NMR (101 MHz, $CDCl_3$)



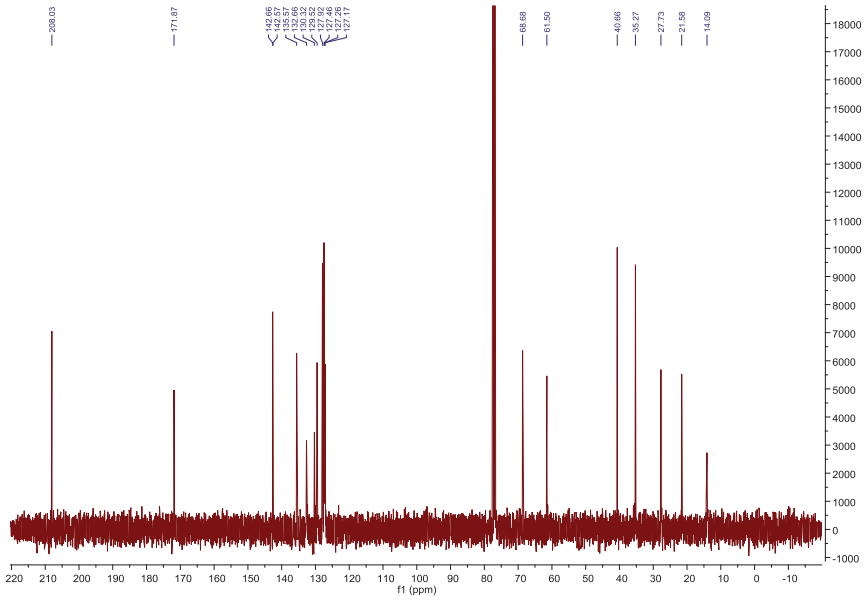
ethyl 1-([1,1'-biphenyl]-2-yl)-2-oxocyclohexanecarboxylate



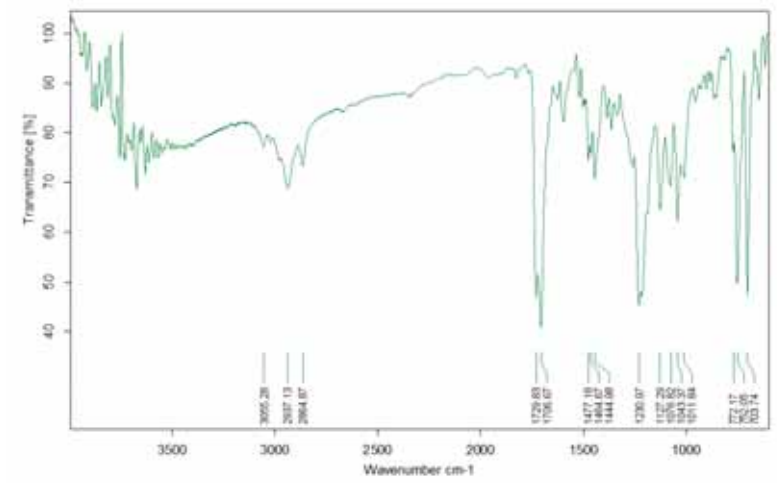
^{1}H NMR (360 MHz, $CDCl_3$, 55 °C)



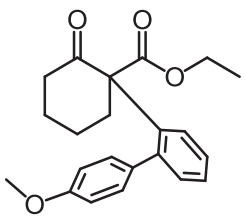
^{13}C NMR (91 MHz, $CDCl_3$, 55 °C)



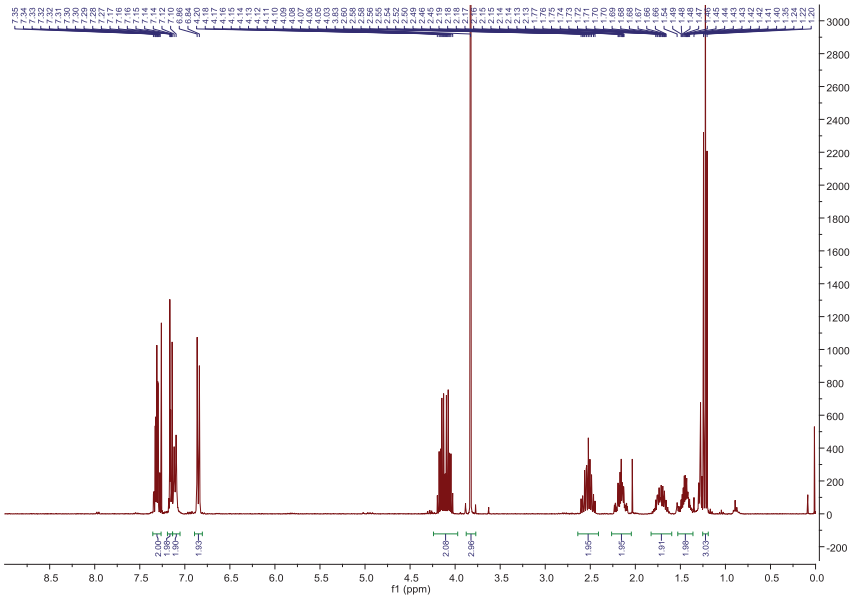
IR (ATR) ν (cm^{-1})



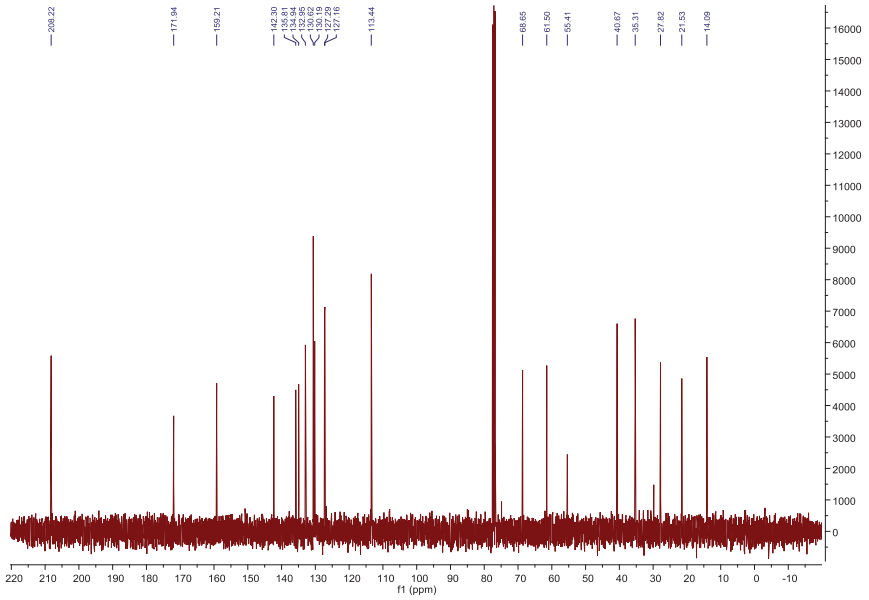
ethyl 1-(4'-methoxy-[1,1'-biphenyl]-2-yl)-2-oxocyclohexanecarboxylate



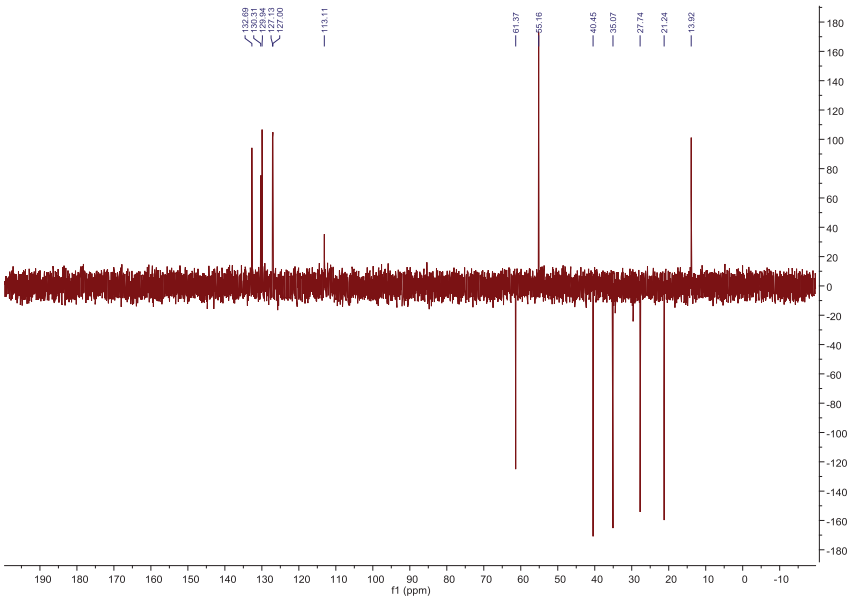
^{1}H NMR (360 MHz, $CDCl_3$, 50 °C)



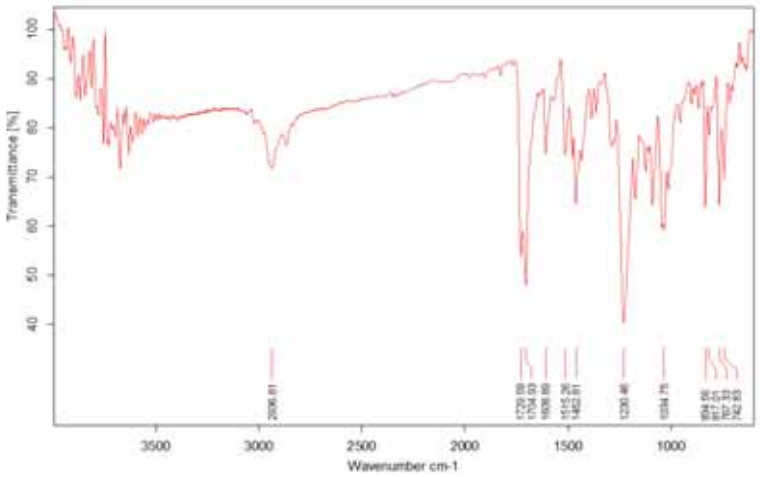
^{13}C NMR (91 MHz, $CDCl_3$, 50 °C)



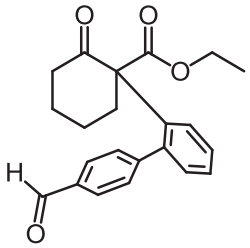
DEPT 135 (101 MHz, $CDCl_3$)



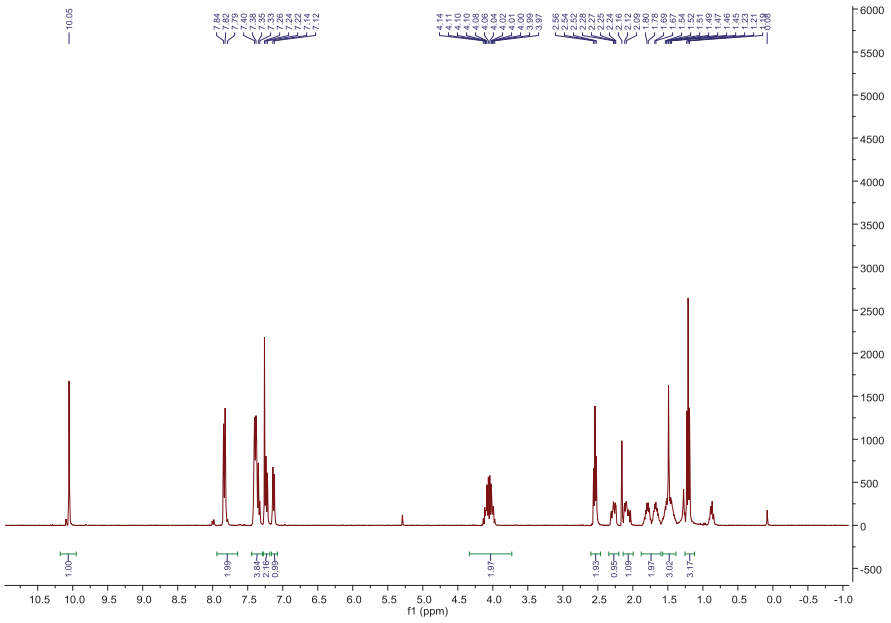
IR (ATR) v (cm^{-1})



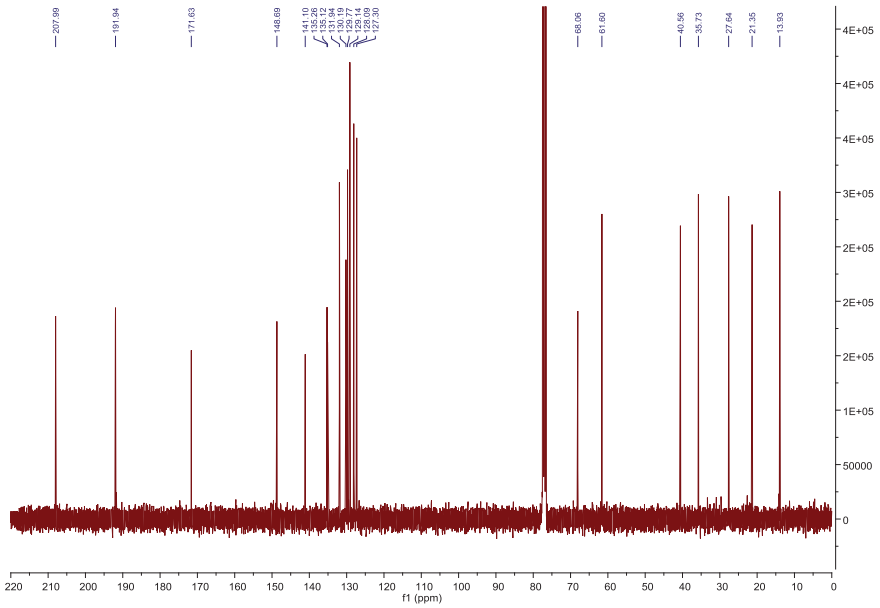
ethyl 1-(4'-formyl-[1,1'-biphenyl]-2-yl)-2-oxocyclohexanecarboxylate



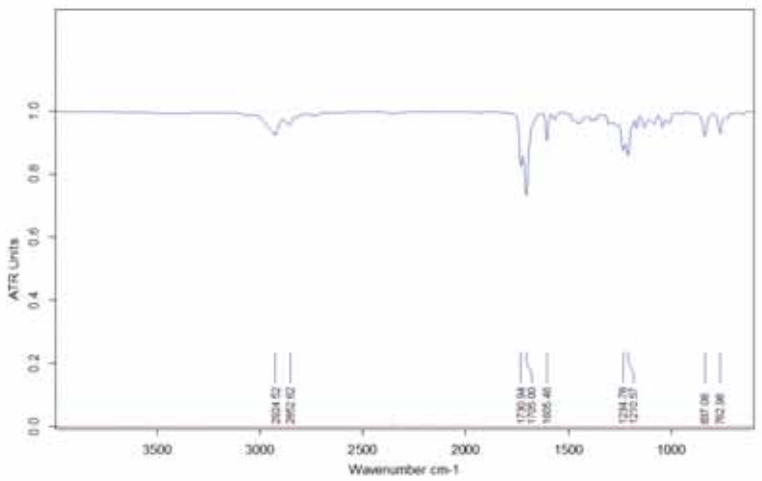
^{1}H NMR (360 MHz, $CDCl_3$)



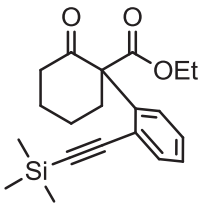
^{13}C NMR (91 MHz, $CDCl_3$)



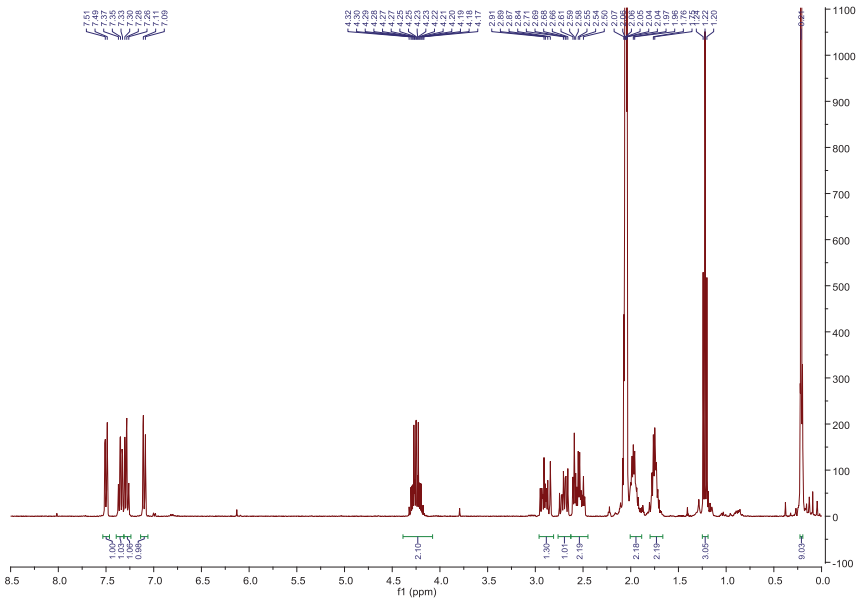
IR (ATR) v (cm^{-1})



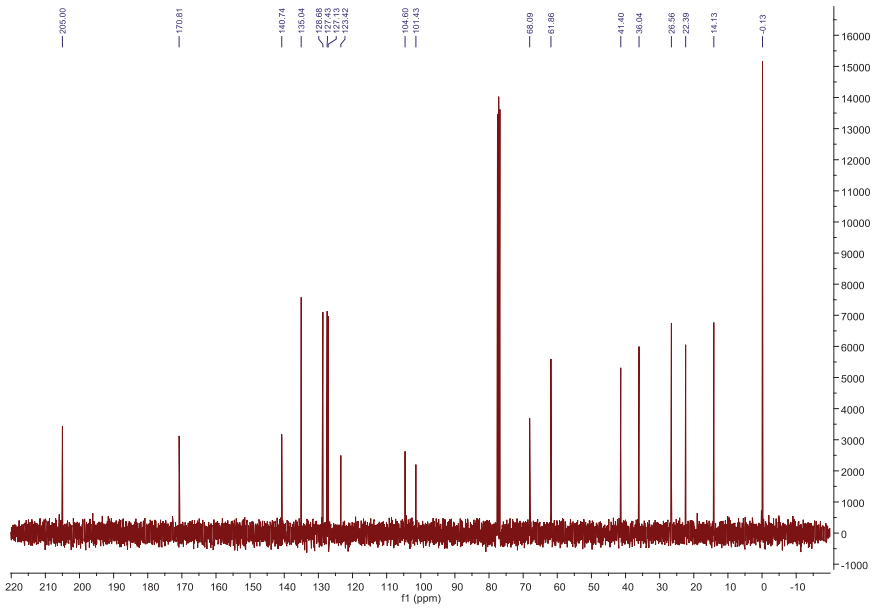
ethyl 2-oxo-1-(2-((trimethylsilyl)ethynyl)phenyl)cyclohexanecarboxylate



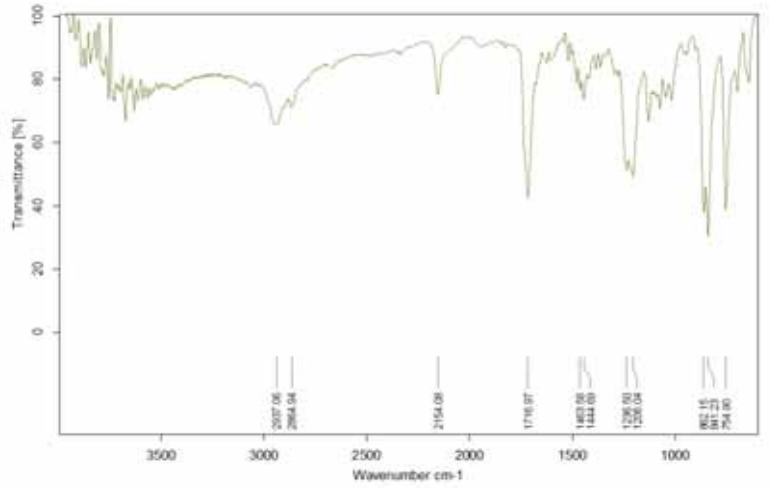
^{1}H NMR (360 MHz, $CDCl_3$)



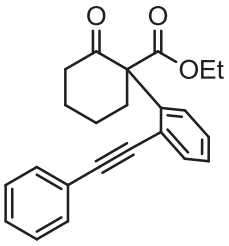
^{13}C NMR (91 MHz, $CDCl_3$)



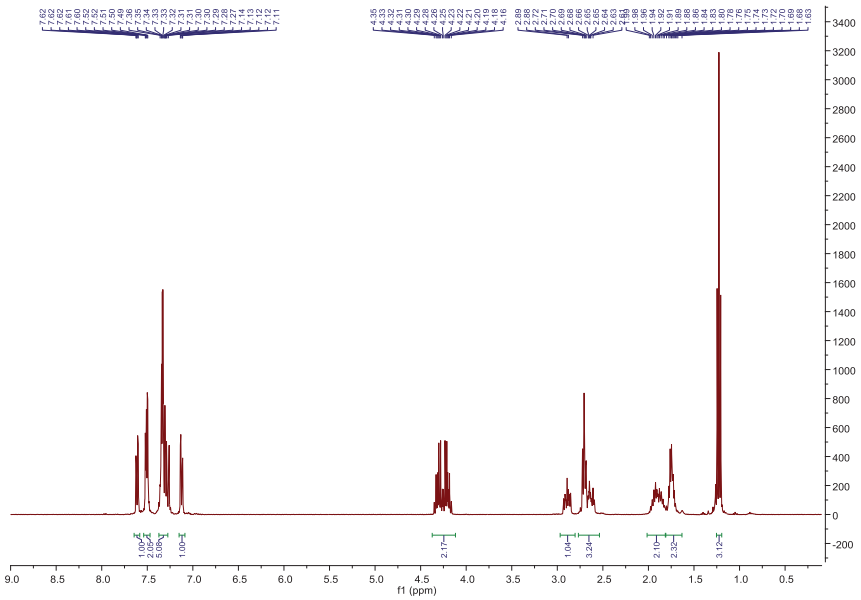
IR (ATR) ν (cm^{-1})



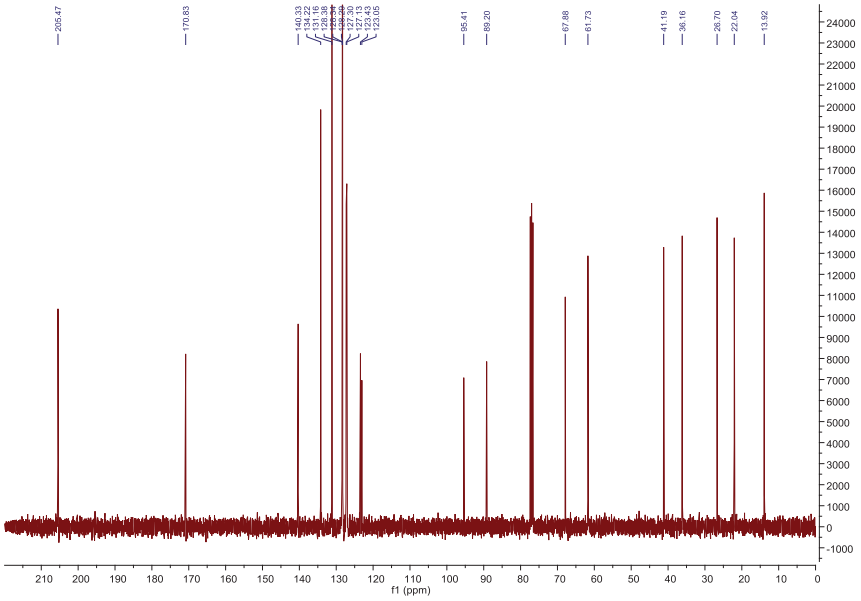
ethyl 2-oxo-1-(2-(phenylethynyl)phenyl)cyclohexanecarboxylate



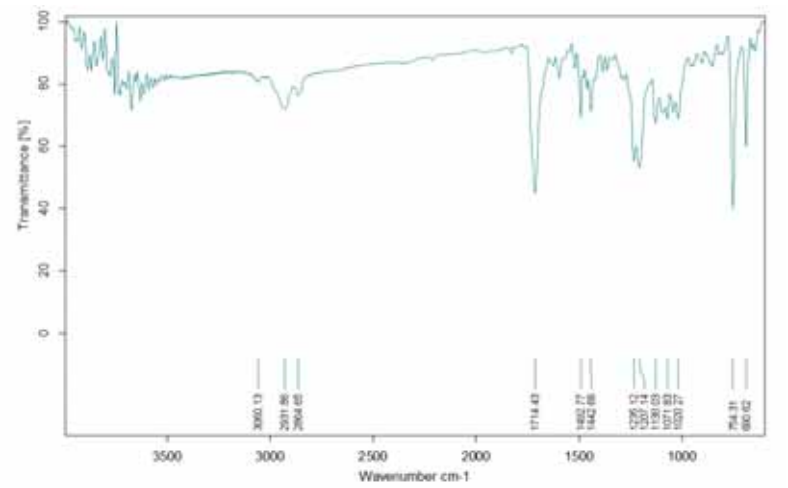
^{1}H NMR (360 MHz, $CDCl_3$)



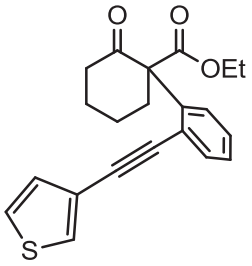
^{13}C NMR (360 MHz, $CDCl_3$)



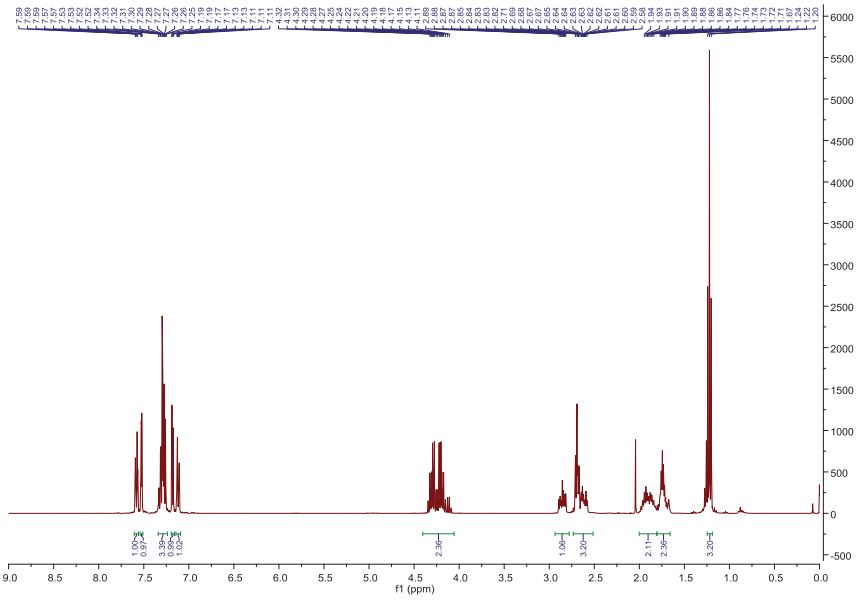
IR (ATR) v (cm^{-1})



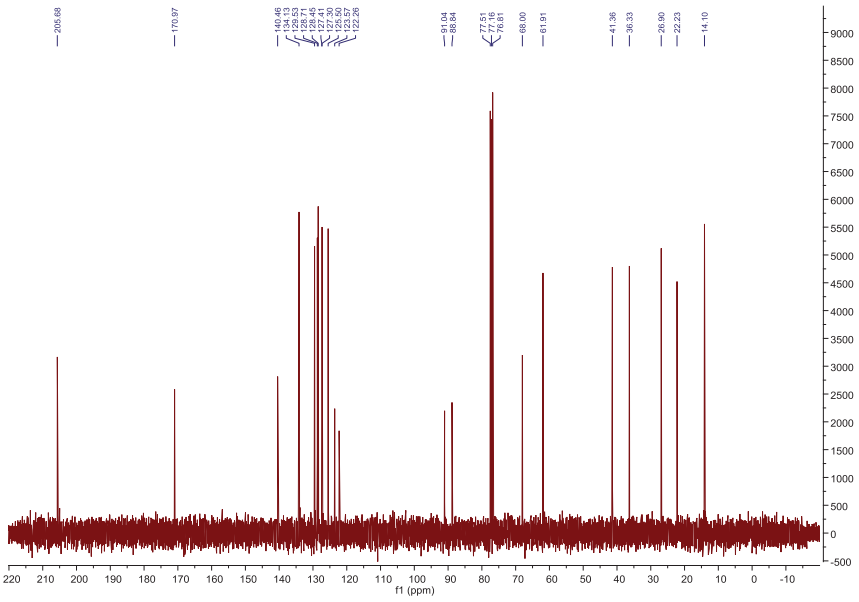
ethyl 2-oxo-1-(2-(thiophen-3-ylethynyl)phenyl)cyclohexanecarboxylate



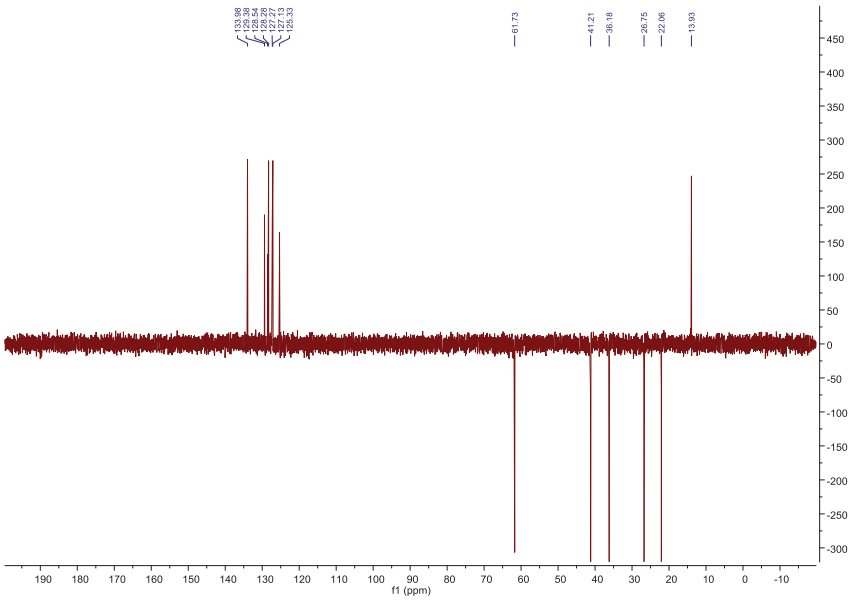
^{1}H NMR (360 MHz, $CDCl_3$)



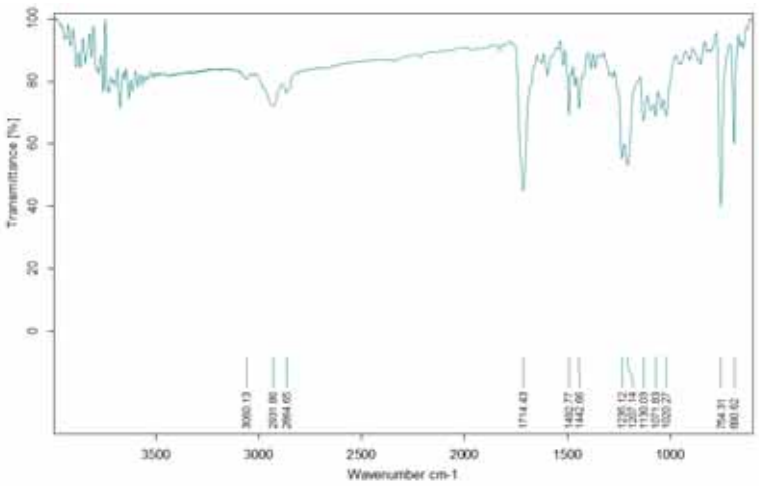
^{13}C NMR (91 MHz, $CDCl_3$)



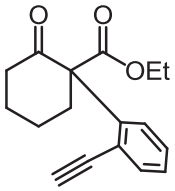
DEPT 135 (91 MHz, $CDCl_3$)



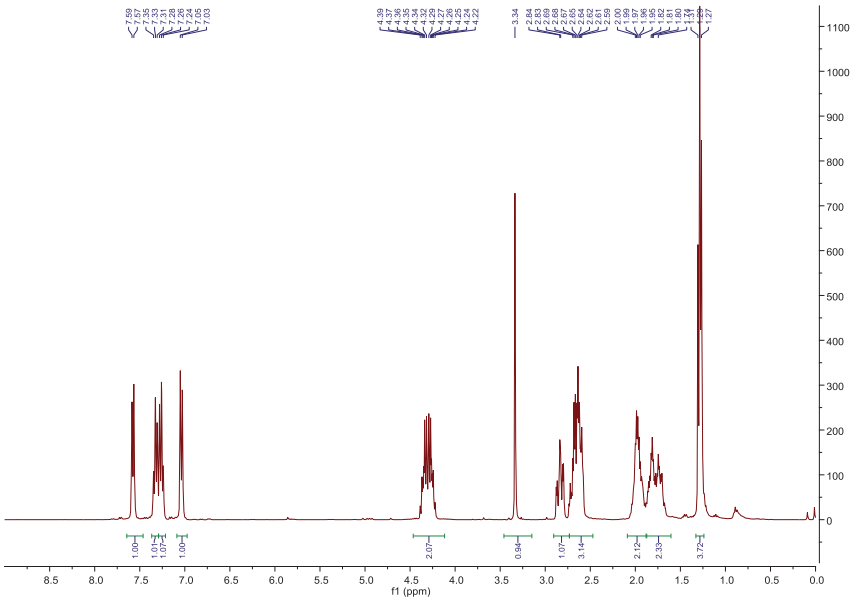
IR (ATR) v (cm^{-1})



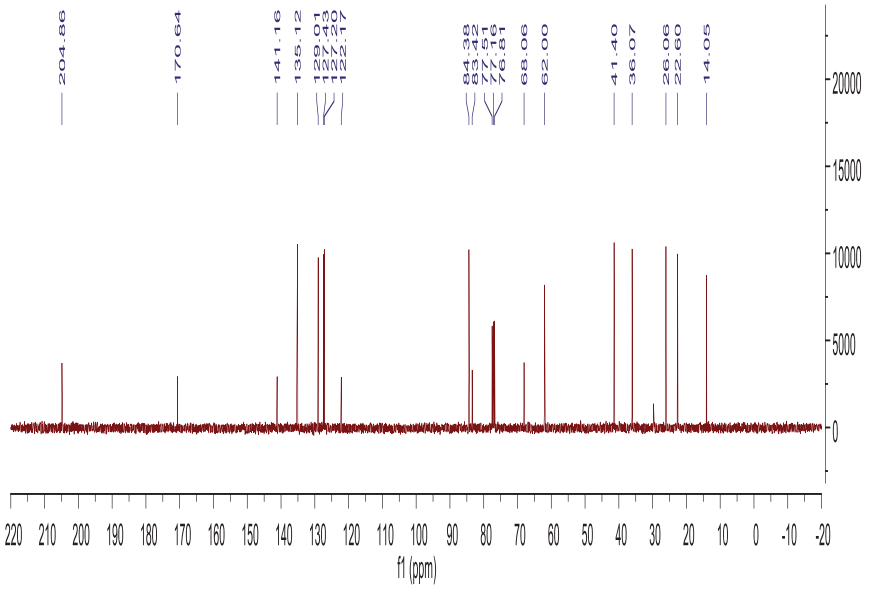
ethyl 1-(2-ethynylphenyl)-2-oxocyclohexanecarboxylate



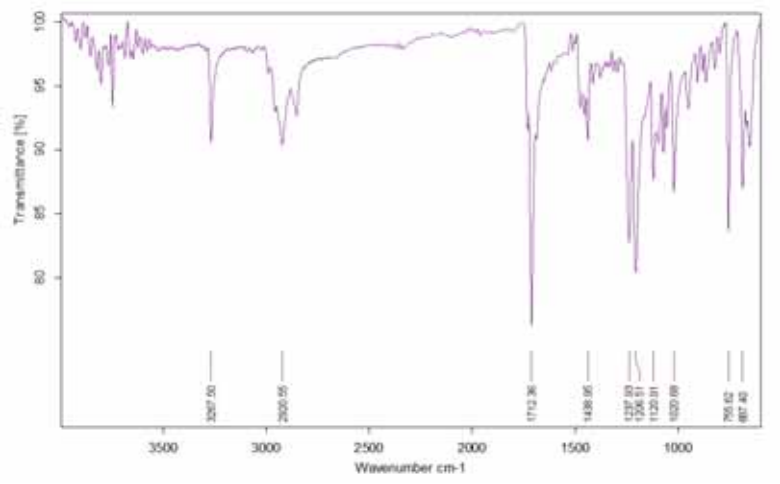
^{1}H NMR (360 MHz, $CDCl_3$)



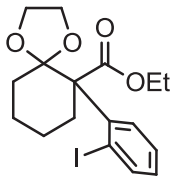
^{13}C NMR (91 MHz, $CDCl_3$)



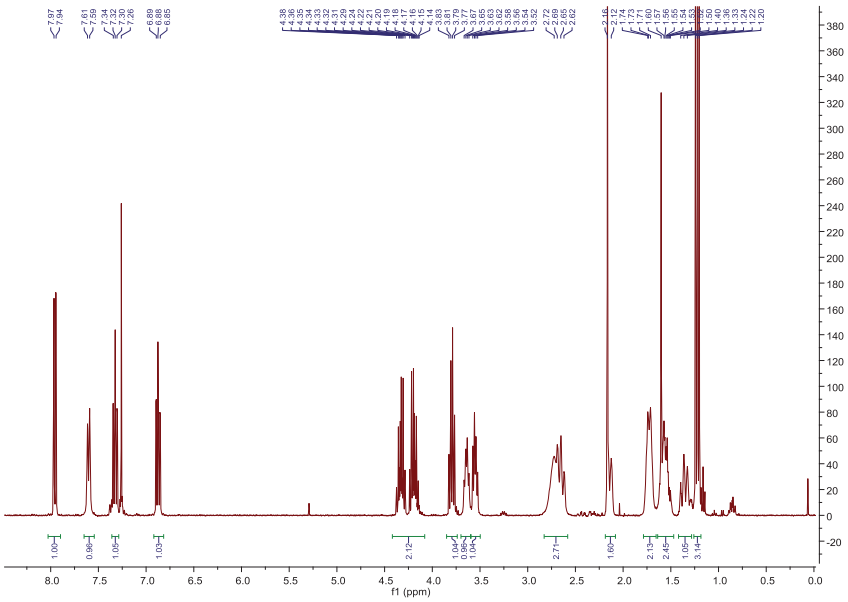
IR (ATR) ν (cm^{-1})



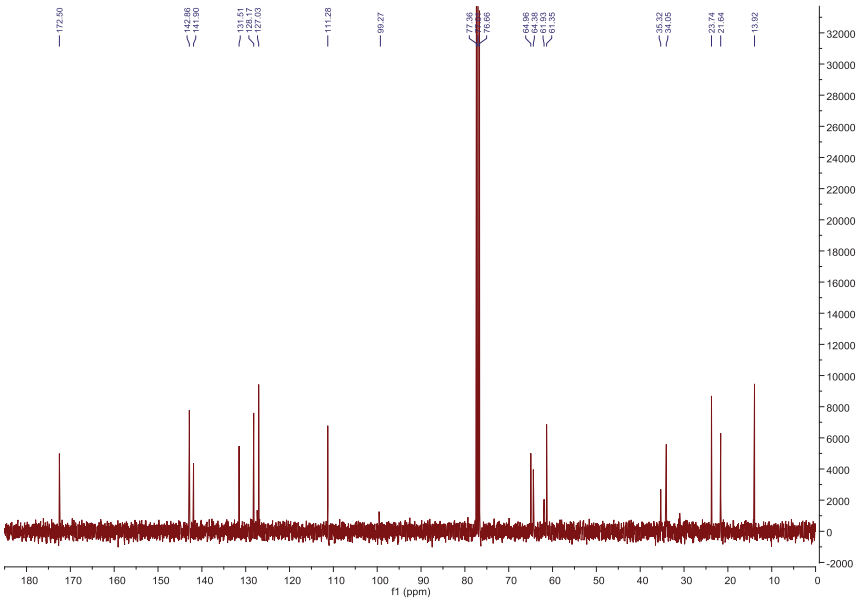
ethyl 6-(2-iodophenyl)-1,4-dioxaspiro[4.5]decane-6-carboxylate



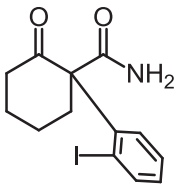
^{1}H NMR (360 MHz, $CDCl_3$)



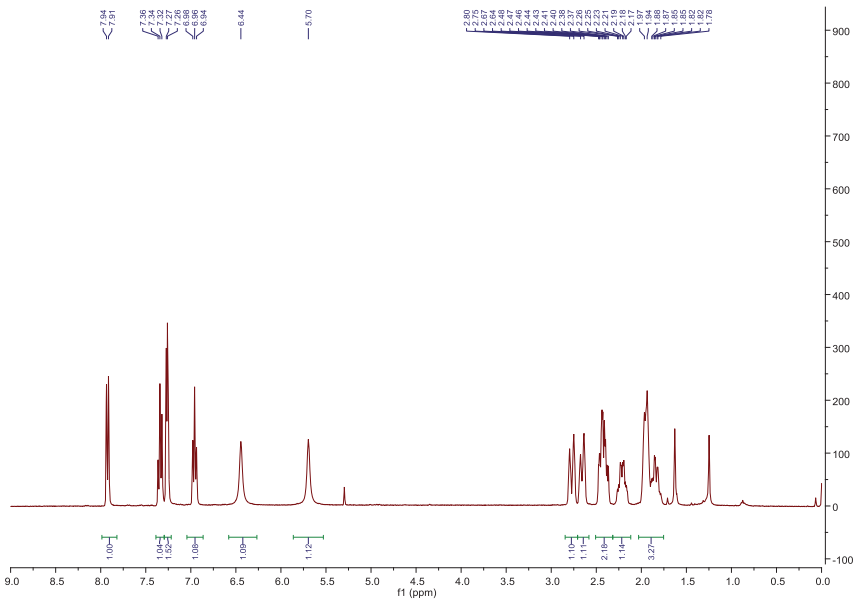
^{13}C NMR (91 MHz, $CDCl_3$)



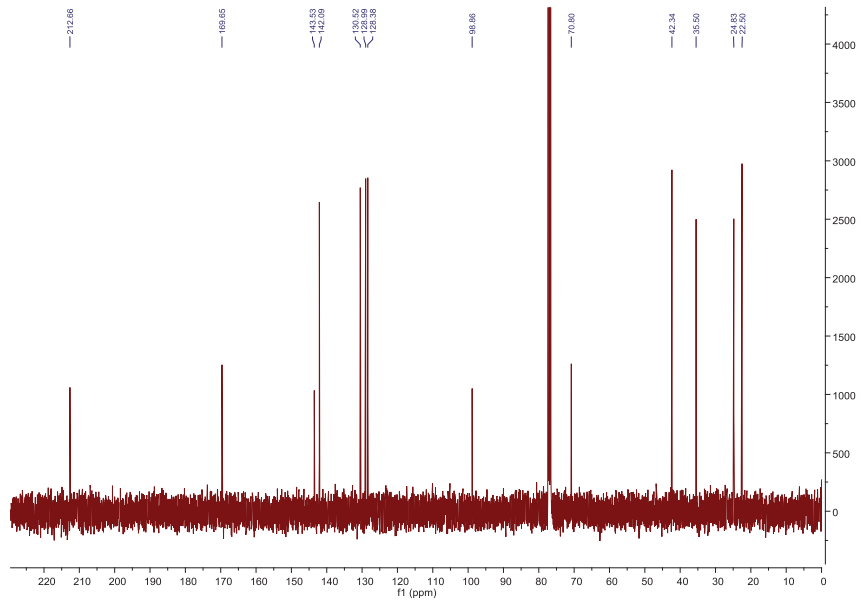
1-(2-iodophenyl)-2-oxocyclohexanecarboxamide



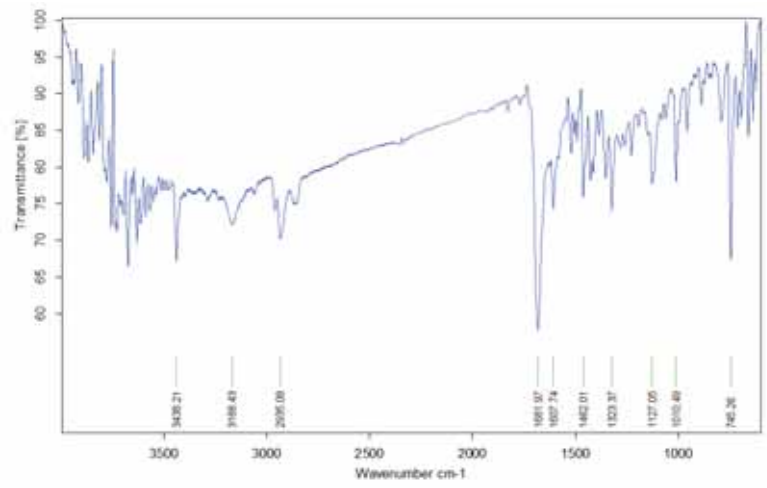
^{1}H NMR (360 MHz, $CDCl_3$)



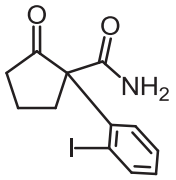
^{13}C NMR (101 MHz, $CDCl_3$)



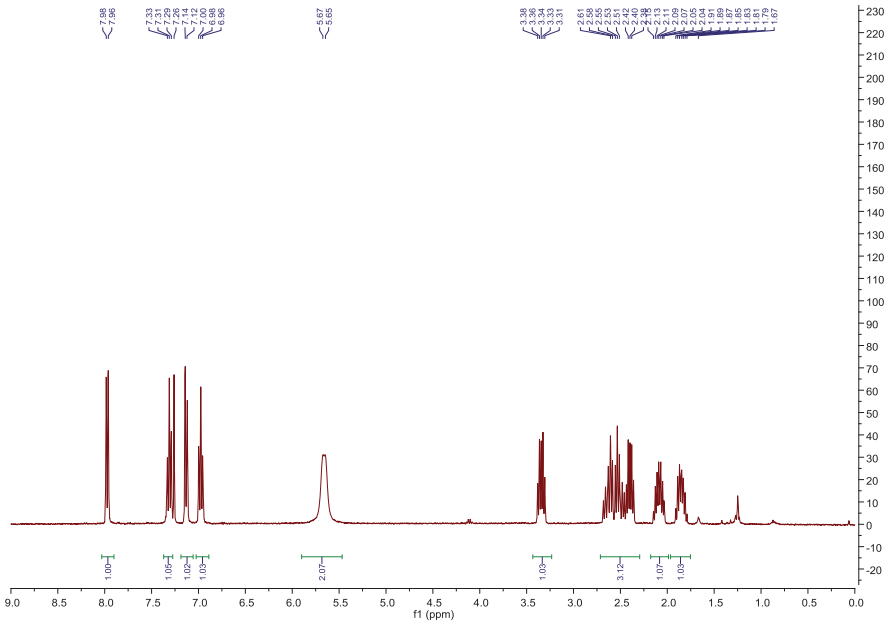
IR (ATR) v (cm^{-1})



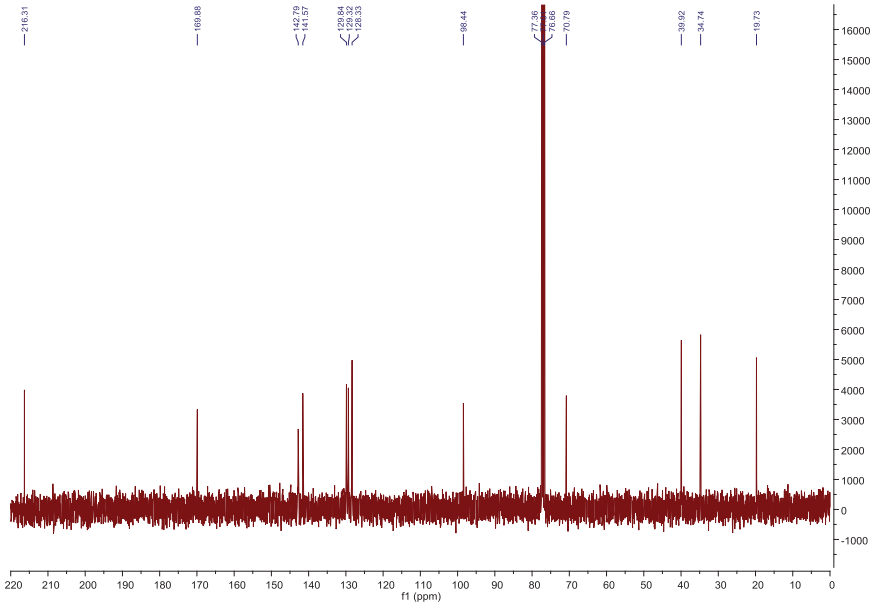
1-(2-iodophenyl)-2-oxocyclopentanecarboxamide



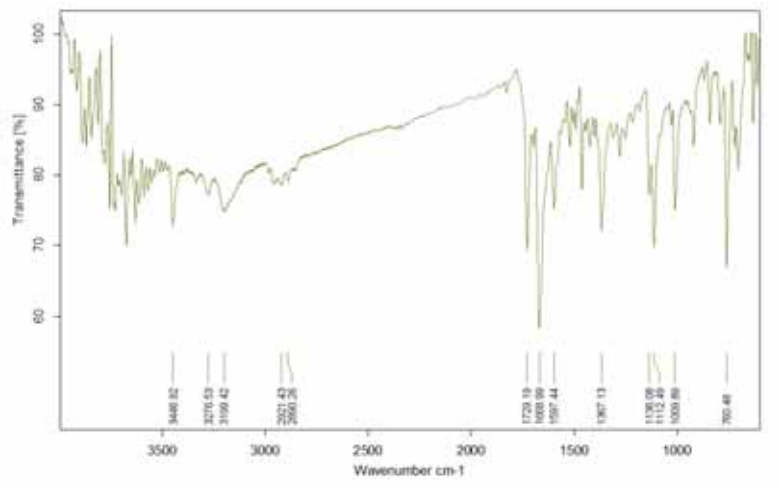
^{1}H NMR (360 MHz, $CDCl_3$)



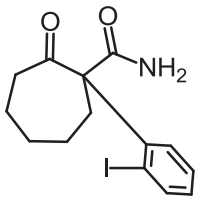
^{13}C NMR (91 MHz, $CDCl_3$)



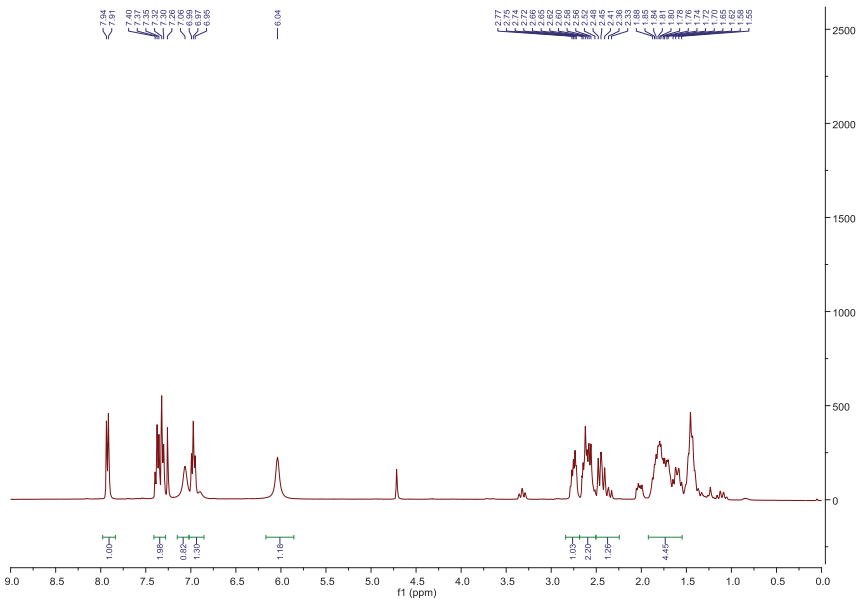
IR (ATR) v (cm^{-1})



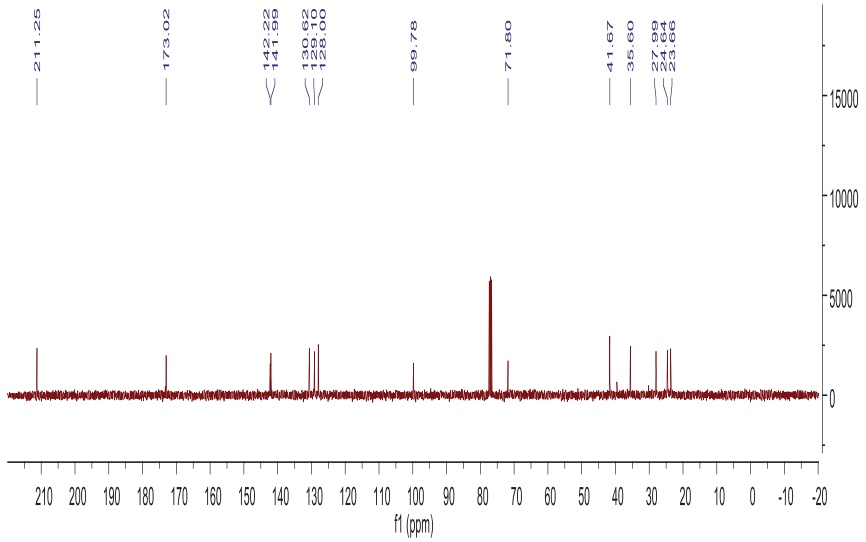
1-(2-iodophenyl)-2-oxocycloheptanecarboxamide



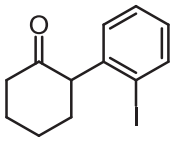
^{1}H NMR (360 MHz, $CDCl_3$)



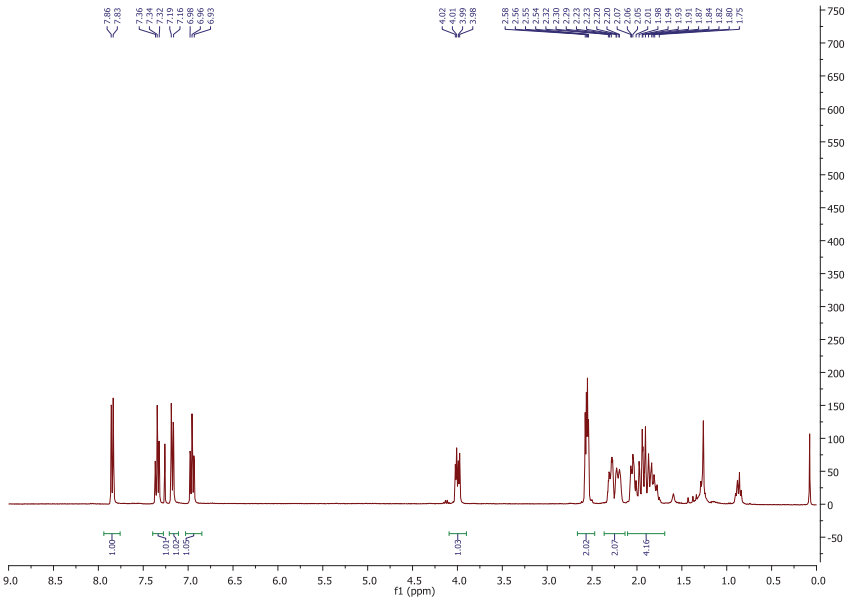
^{13}C NMR (91 MHz, $CDCl_3$)



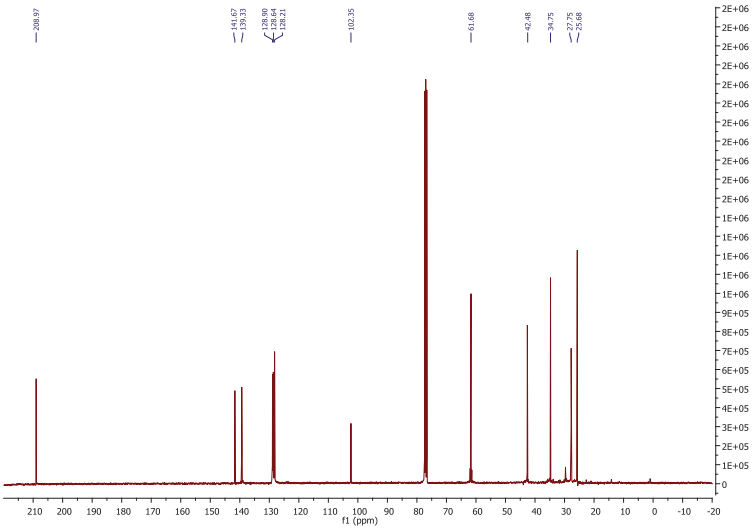
2-(2-iodophenyl)cyclohexanone



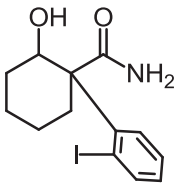
^{1}H NMR (360 MHz, $CDCl_3$)



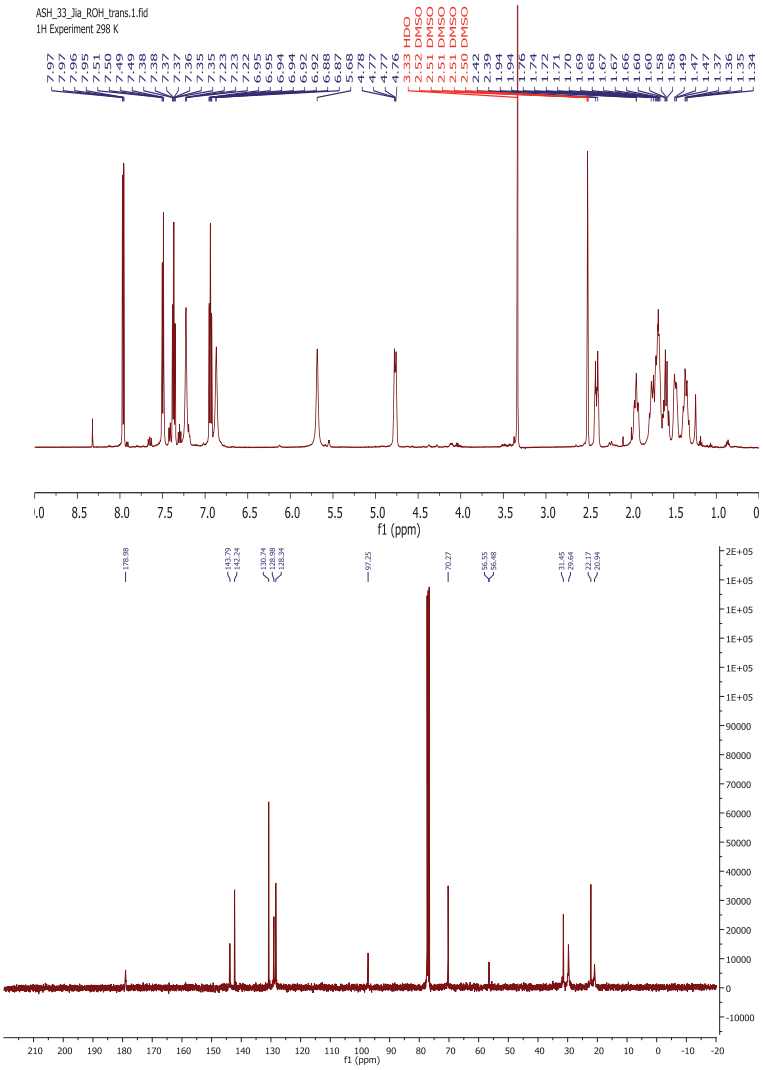
^{13}C NMR (91 MHz, $CDCl_3$)



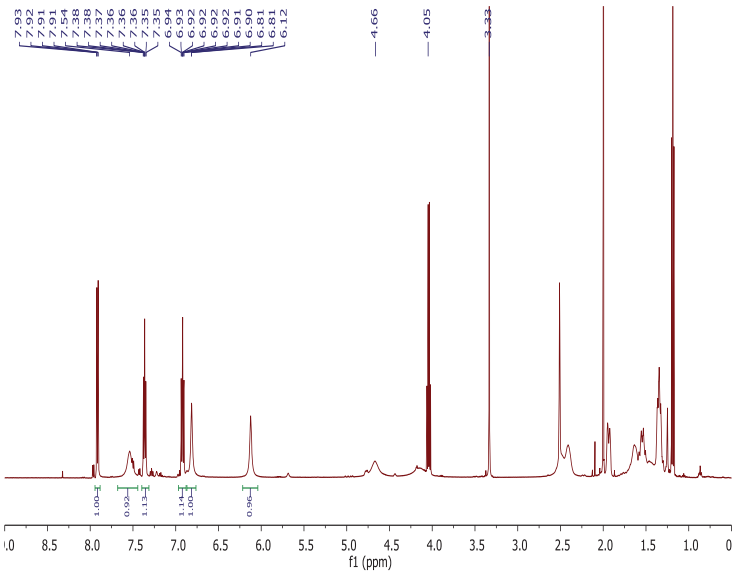
2-hydroxy-1-(2-iodophenyl)cyclohexanecarboxamide



Main product



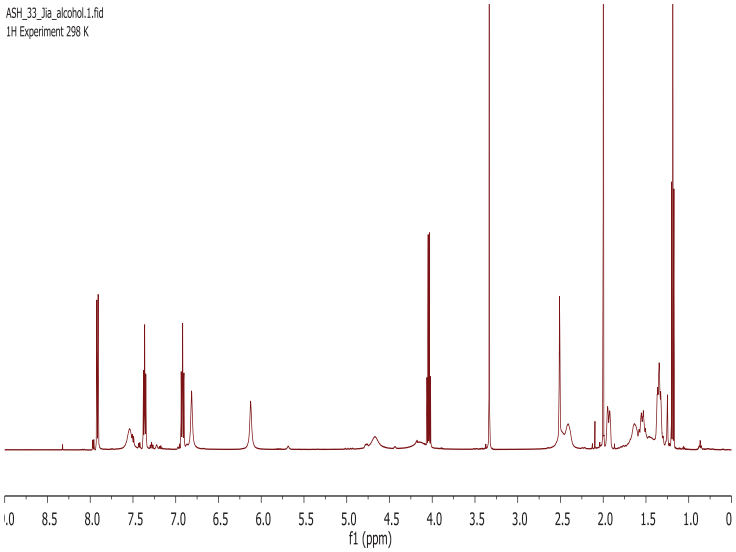
Side product: broad signals



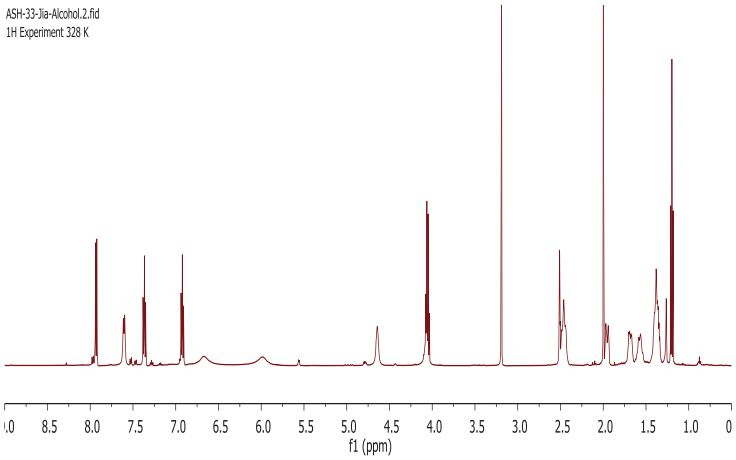
Due to the broadness of the signals in the spectrum of the “side product”, VT NMR was performed

Compare the 25 °C, 55 °Cand 125 °C spectra for side product (DMSO-d_6)

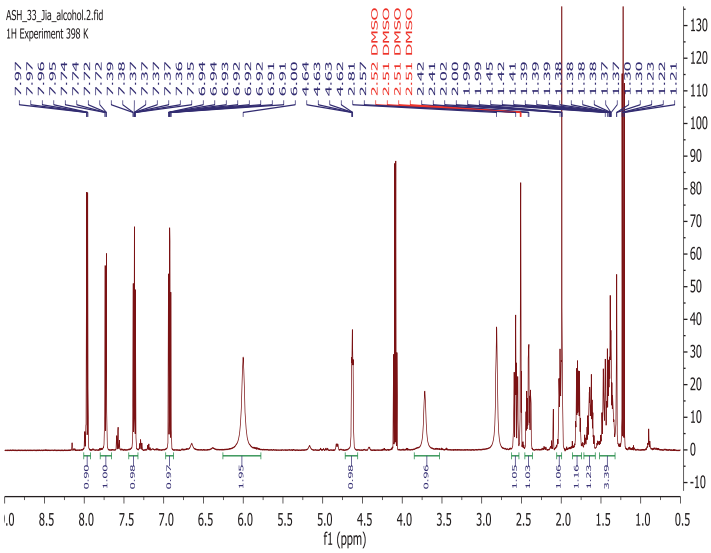
25 °C



55 °C



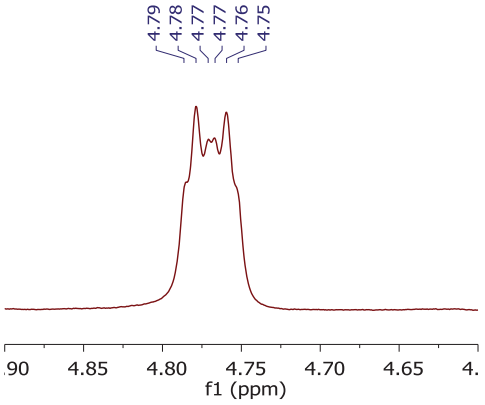
125 °C



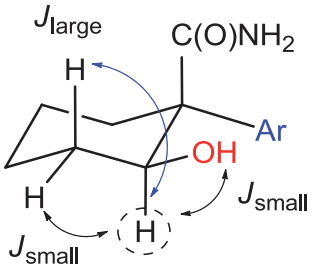
The High temp NMR helps establish the stereochemistry of the two products

The CH(OH) resonance is examined

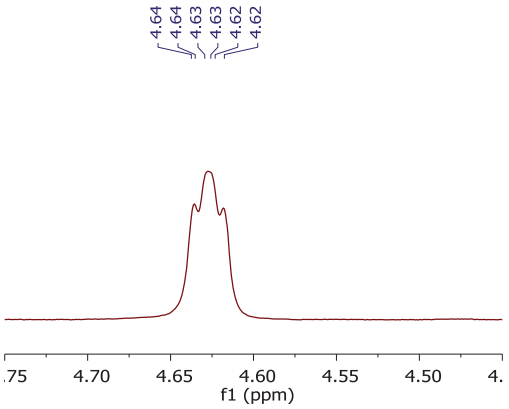
"Main product (room temp)"



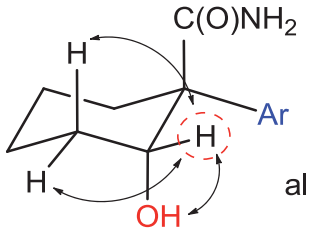
H axial: dt, J = 9.5 Hz, 3.8 Hz



"Side product (high temp)"

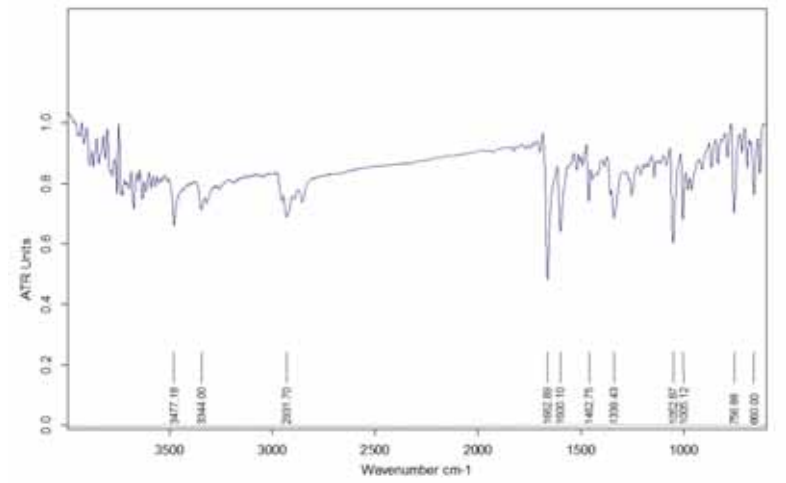


H eq:
appears as td, J = 4.1 Hz, 2.0 Hz
represents a ddd (three small J)

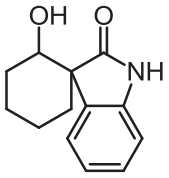


all J_{small}

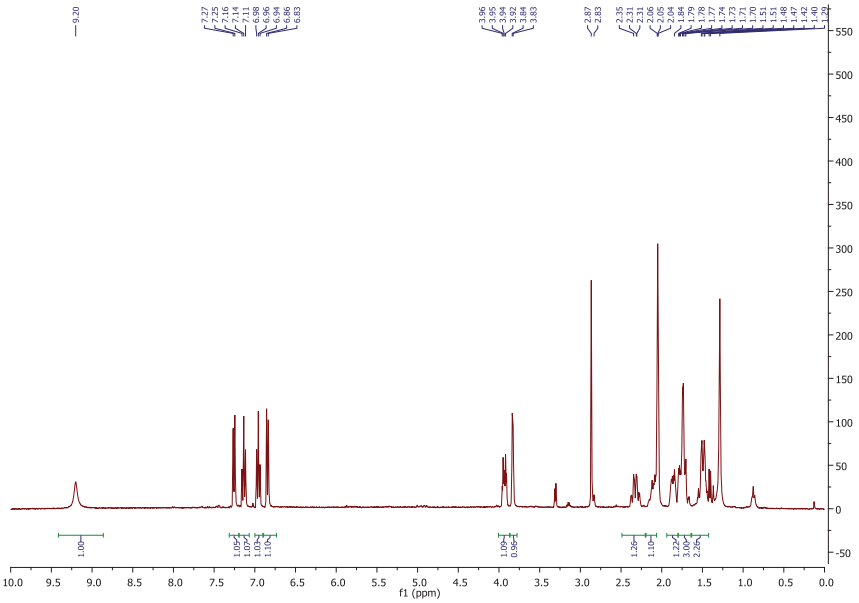
IR (ATR) v (cm^{-1})



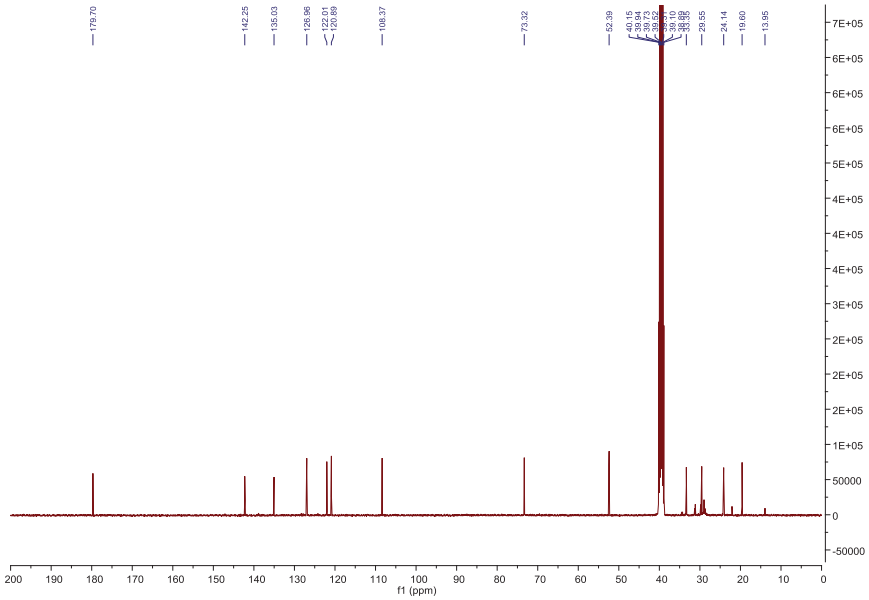
2-hydroxyspiro[cyclohexane-1,3'-indolin]-2'-one



^{1}H NMR (360 MHz, Acetone-d_6)



^{13}C NMR (101 MHz, DMSO-d_6)



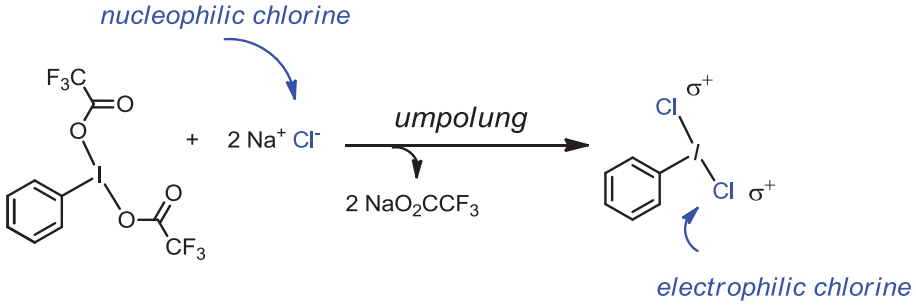
5. Thesis Conclusions and Summary

Chapter 1. The present thesis was focused on the preparation and application of hypervalent iodine reagents. A brief introduction to the field of hypervalent iodine reagents, with a special emphasis on their application and characterization, is given in chapter 1 of this manuscript. After a general overview, a emphasis in the latter part pf the chapter is given to the chemistry of diaryl λ^3iodanes, and to their ability to act as aryl transfer agents in the oxidative arylation processes.

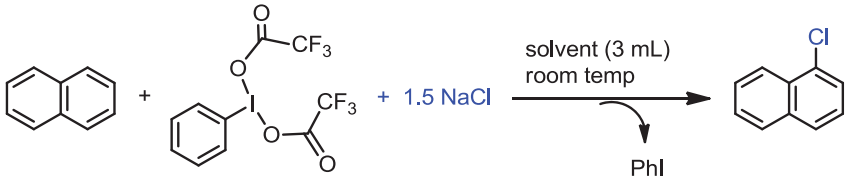
Chapter 2. In this chapter the goal of the present doctoral thesis are outlined. The thesis' aim is to provide new synthetic application of the phenyliodinebis(trifluoroacetate) and related compounds in oxidative CH bond functionalization.

Chapter 3. The use of PIFA in combination with a halide source was found to serve as a promising system in the *umpolung* halogenation of aromatic molecules and α-halogenation of carbonyl species.

a) The method operate through the incorporation of a halide into coordination sphere of the iodane. Thus, the reversal (*umpolung*) in reactivity is due to the transformation from a negativelycharged Cl^- to an iodine-bound Cl atom bearing a partial positive charge.



b) The PIFA/NaCl combination was found effective in the chlorination of aromatic compounds.



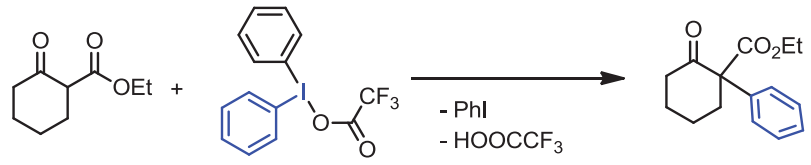
c) Despite some progress in using other halides (Br, I) further work will be required for these to be incorporated in an efficient manner. No incorporation of fluoride could be achieved.

d) Some progress in the *unpolung* halogenation of β-ketoesters has been achieved.

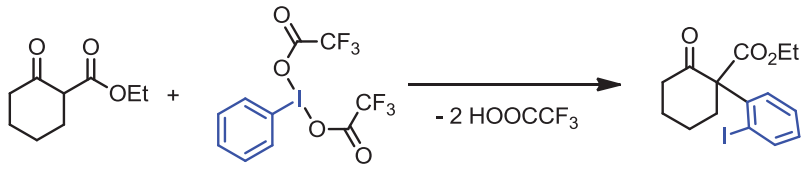
It should also be mentioned that the concept of the *unpolung* introduction of other anions using PIFA [or other iodine(III) reagents] is a highly promising one, and future development of this approach will like make this method highly versatile for a variety of transformations.

Chapter 4. In this final chapter a newly discovered method for the α-arylation of the activated ketones is described. Unlike protocols employing diaryliodonium salts, in this new process the arylation takes place directly from a monoaryliodane, specifically PIFA. A unique feature is the transfer of a (2-iodophenyl) group rather than a simple phenyl. Thus, the final products retains an iodine atom o*rtho* to the newly formed C-C bond.

classical arylation

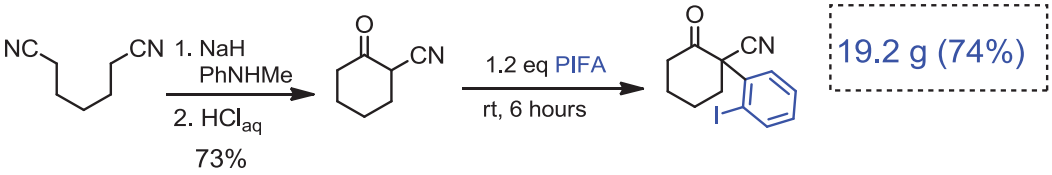


new 2-iodoarylation)

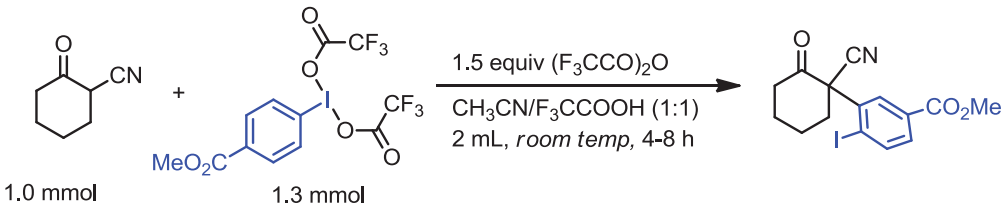


a) The reaction was found to be favoured by acidic conditions and have been performed in a mixture of the trifluoroacetic acid and acetonitrile.

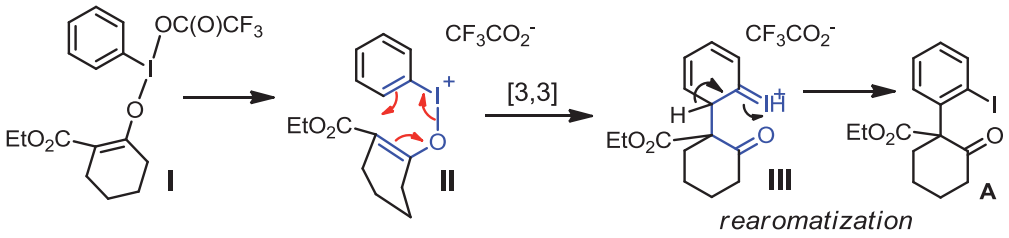
b) The β-ketoesters, β-diketones and α-cyanoketones were all suitable substrates for this process. Best yields are obtained using cyclic cyanoketones, and the reaction cn be carried out on a multigram scale.



c) In addition, a range of substituted iodoarylbis(trifluoroacetates) have been prepared and applied to the synthesis of the more highly substituted arylketones.



d) The reaction is proposed to proceed through a Claisen-type rearrangement of an iodonium enolate intermediate, that is, a [3,3] sigmatropic rearrangement This mechanism helps explain the uniquely selective formation of the o*rtho*-iodoregioisomer. In addition, the unusually facile rearrangement (1-6 h, room temp) has been rationalized by the positive charge build up at the bridging iodine atom, allowing for the known *charge-accelerated Claisen rearrangement*.



It should be mentioned that all of the arylation product reported in this work have been synthesized for the first time. This may be taken as evidence for the scarcity of methods to prepare such *ortho*-halogenated aryl ketones. In addition, the method has proved highlypromising, having opened the door to several new research lines currently underway.