Department of Pure and Applied Chemistry

K^+ AS A PRIVILEGED FACILITATOR OF ELECTRON TRANSFER REACTIONS?

by

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A thesis submitted to the Department of Pure and Applied Chemistry, University of Strathclyde, in part fulfillment of the regulations for the degree of Doctor of Philosophy in Chemistry.

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DECLARATION OF Ownership

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: Date:

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ABBREVIATIONS

Acac	Acetylacetonate
APCI	Atmospheric Pressure Chemical Ionisation
Aq.	Aqueous
Ar	Aryl
ATR	Attenuated Total Reflectance
cat.	Catalyst
DAT	Deuterium Atom Transfer
DIBAH	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DFT	Density Functional Theory
4-DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMEDA	*N*,*N*′-Dimethylethylenediamine
Dppe	1,2-Bis(diphenylphosphino)ethane
EDA	Electron donor-acceptor complex
EI	Electron Ionisation
EPR	Electron Paramagnetic Resonance
ESI	Electrospray ionisation
FLP	Frustrated Lewis Pair
FT	Fourier Transform
GC	Gas-phase Chromatography
HAT	Hydrogen Atom Transfer
hv	Irradiation
hνCT	Charge-transfer band
HMPA	Hexamethylphosphoramide
HNESP	High Resolution Nano-Electrospray
ICR	Ion cyclotron resonance
IPA	Isopropanol

KDMS	Potassium bis(trimethylsilyl)amide
KIE	Kinetic Isotopic Effect
*t*Bu	*tert*-butyl
LED	Light Emitting Diode
LDA	Lithium diisopropylamide
LTMP	Lithium tetramethylpiperidide
Liq.	Liquid
MD	Molecular Dynamics
MOF	Metal Organic Framework
mp	Melting Point
Ms	Mesyl (methanesulfonyl)
MS	Mass Spectrometry
MTBE	Methyl *tert*-Butyl Ether
ND	Not Determined
NMP	*N*-Methyl-2-pyrrolidone
ppm	Parts Per Million
q	Quartet
RT	Room Temperature
s	Singlet
sat.	Saturated
SCE	Saturated Calomel Electrode
SED	Super Electron Donor
SET	Single Electron Transfer
SHE	Standard Hydrogen Electrode
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t	Triplet
TDAE	1,1,2,2-Tetra(dimethylamino)ethene
OTf	Triflate (trifluoromethanesulfonate)
TLC	Thin Layer Chromatography
TBAB	Tetrabutylammonium bromide
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine

TTF	Tetrathiafulvalene
UV	Ultra-Violet
Vis	Visible
vs	Versus
μw	Microwave

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LIST OF PUBLICATIONS

(1) **KO*t*Bu: A Privileged Reagent for Electron Transfer Reactions?**
Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, *138* (23), 7402–7410.

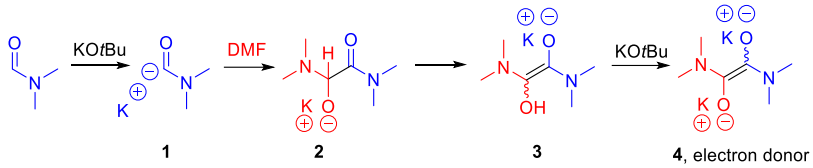
(2) **Electron Transfer Reactions: KO*t*Bu (but not NaO*t*Bu) Photoreduces Benzophenone under Activation by Visible Light**
Nocera, G.; Young, A.; Palumbo, F.; Emery, K. J.; Coulthard, G.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2018**, *140* (30), 9751–9757.

(3) **Dual Roles for Potassium Hydride in Haloarene Reduction: CS_NAr and Single Electron Transfer Reduction via Organic Electron Donors Formed in Benzene**
Barham, J. P.; Dalton, S. E.; Allison, M.; Nocera, G.; Young, A.; John, M. P.; McGuire, T.; Campos, S.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2018**, *140* (36), 11510–11518.

(4) **Special K^+? Reductive Coupling of Benzene by Potassium Metal, Facilitated Specifically by Potassium Salts**
Nocera, G.; Turner, O.; Young, A, G.; Pang, J. H.; McGuire, T.; Chiba, S.; Tuttle, T.; Murphy, J. A. *manuscript in preparation*

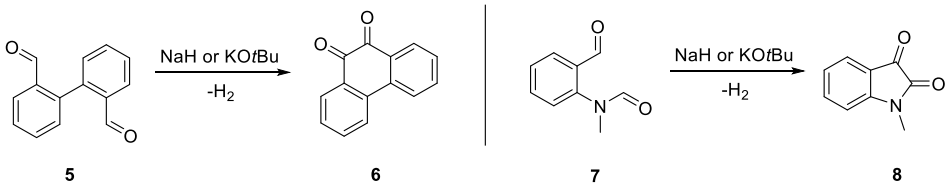
ABSTRACT

The first part of these studies examines the role of KO*t*Bu in electron transfer reactions when DMF is the solvent. Here, deprotonation of DMF leads to carbamoyl anion **1**, which has been previously suggested to be an electron donor; in contrast, this thesis proposes the formation of the DMF dimer dianion **4** as the electron donor, based on experimental investigations.[1]



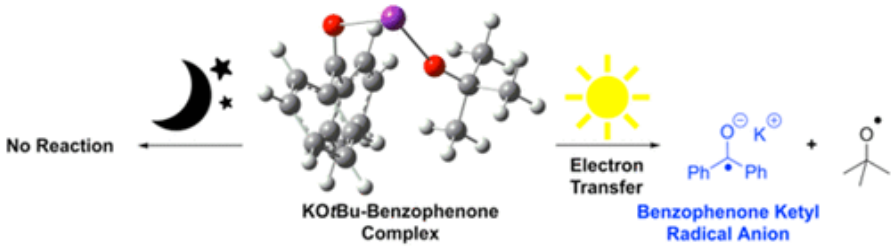
Scheme 1. KO*t*Bu-mediated DMF dimerisation and electron donor formation.[1]

An extension of the capability for KO*t*Bu to act as a powerful base is illustrated with deprotonation of aromatic and aliphatic aldehydes and formamides such as **5** and **7**. This reaction type could be important for understanding the process which underpins formation of carbohydrates in the prebiotic era.



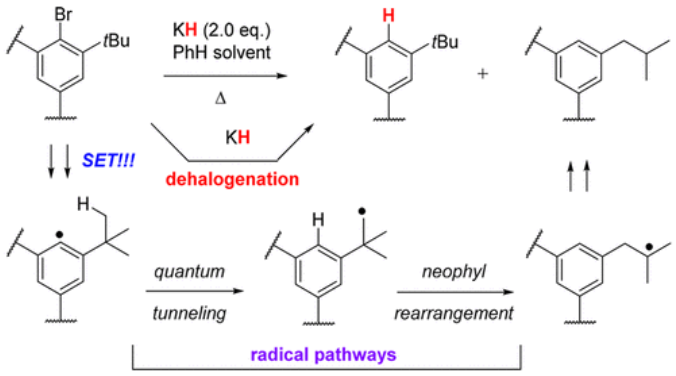
Scheme 2. C-C bond formation promoted by strong bases.

Long-standing controversial reports of electron transfer from KO*t*Bu to benzophenone have been studied and resolved. These results now establish that a complex is formed between the two reagents, with the potassium ion providing the linkage. Photoactivation at room temperature by irradiation at defined wavelength (365 or 400 nm), or even by winter daylight, leads to the development of the blue colour of the potassium salt of benzophenone ketyl anion, whereas no reaction is observed when the reaction mixture is maintained in darkness or when NaO*t*Bu is used.[2]



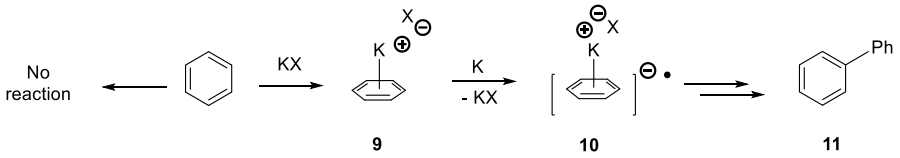
Scheme 3. Photoreduction of benzophenone by KO*t*Bu.[2]

The second part of this study deploys KH in electron transfer reactions. Whilst in THF, KH promotes a concerted nucleophilic aromatic substitution, in benzene it promotes electron transfer reactions via organic electron donor formation. Here, again KH was found to have unique properties, different from NaH.[3]



Scheme 4. Example of radical pathways triggered by KH in benzene as solvent.[3]

The last part of this study reveals an unprecedented reactivity of K metal with benzene in presence of π-activators. Potassium cation is found to be more effective than sodium cation, promoting SET and reductive coupling of benzene leading to coupled product **11**. The reaction in the absence of any cation source shows no reaction.



Scheme 5. K metal determines homocoupling of benzene in presence of selected additives.

PREAMBLE

This work will refer to many coupling reactions where transition metals are involved and, in these cases, the reactions will be named, as in the literature, as "cross-coupling reactions." Other examples will refer to transition metal-free arylations of aryl halides. Many differences exist between these two types of reaction in term of mechanism, substrates, selectivity and effectiveness. For simplicity, the transition metal-free arylations of aryl halides will be named "transition metal-free cross-coupling reactions". Therefore the difference of the two reactions will only be represented by the presence and absence of transition metal.

1 INTRODUCTION

Cross-coupling reactions have been studied since the 19th century. The first discoveries on the use of transition metals, their salts and complexes, as catalysts for these reactions allowed efficient C-C or C-X bond formations to be achieved.[4] A flood of reports has emerged in the last decade, where arylation reactions of haloarenes were achieved under transition metal-free conditions. In fact, it was discovered that organic compounds under particular conditions are able to promote C-C bond-forming reactions, acting as additives but no-catalysts, leading to the formation of initiators. Despite the fact that the selectivity achieved under transition metal-free conditions is not as good as the selectivity achieved in the presence of a metal catalyst, in many cases the yields are comparable. The cross coupling in the absence of a transition metal is only selective with one coupling partner whereas in transition metal-catalysed reactions, the selectivity is extended to both reacting partners. This difference is remarkable when we open the discussion towards the reaction scope which, of course, is greater in the case where transition metals are present.

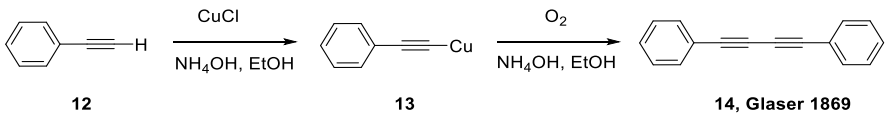
This review will focus on the progressive development of metal-catalysed cross-coupling, which then will be followed by the more recent findings on metal-free cross-coupling reactions. Initiation of some of the transition metal-free cross-coupling reactions may be brought about by benzyne, and so this review also contains a limited section on benzyne, touching upon its early development but focusing more on the role played in cross-coupling reactions.

1.2 Literature Review

The formation of C-C and C-X bonds is central to the development of modern organic chemistry. A great deal of research has been done in the last century on cross-coupling reactions mediated by transition metals. With time, these discoveries inspired chemists worldwide to find new reagents and conditions, improving the applications, yields and selectivity. These discoveries have had a great impact on academic research, the development of new drugs and materials, and are used in many industrial chemical processes for the synthesis of pharmaceuticals and other biologically active compounds. Despite the effectiveness and benefits of cross-coupling mediated by transition metals, costs, sustainability and toxicity limit their use.

1.2.1 Historical Metal-Catalysed Cross-Coupling Reactions

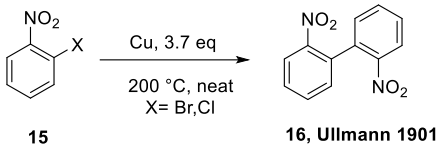
Transition metal-catalysed cross-coupling reactions have a rich and intriguing history, commencing in the 19th century. A lot of chemists worked in this particular field of organic chemistry and many actively contributed to its development. One of the first protagonists of this development was Glaser,[5] who reported the homocoupling of copper acetylides **13**, as an example of bond formation between two sp-carbons to afford **14** (Scheme 6).



Scheme 6. Homocoupling proposed by Glaser.[5]

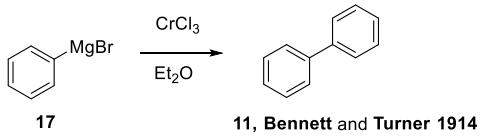
Glaser achieved the dimerisation of copper phenylacetylide to give the diphenyldiacetylene **14** in an open flask. One of the disadvantages of this reaction was the explosive character of the acetylene intermediate **13**. Nevertheless, this method has been used quite often in the last century. A famous example of its use is in the synthesis of indigo by Baeyer in 1882.[6]

In 1901, Ullmann extended the copper-catalysed homocoupling reaction to sp^2-sp^2 bond formation. Differently from Glaser, he underlined how substrates with a carbon atom bearing a halogen are much more activated and ready for a cross-coupling reaction. One of his masterpieces was the dimerisation of 2-bromo- and 2-chloronitrobenzenes **15** promoted by the use of super-stoichiometric copper sources to afford biaryl **16** (Scheme 7).[7]



Scheme 7. Homocoupling reported by Ullmann.[7]

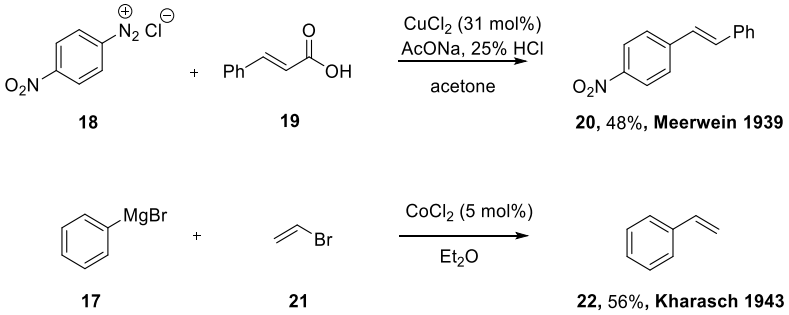
Since Ullmann, the concept of the use of halogen-substituted carbon atoms as activated centres for cross-coupling reactions became established. The use of activated substrates meant that it became possible to use milder catalysts. Bennett and Turner, in 1914, described the first dimerisation of organomagnesium compounds such as **17** through the use of stoichiometric quantities of chromium(III) chloride,[8] as shown in Scheme 8, affording biphenyl **11**. A few years later Krizewsky and Turner showed that copper chloride ($CuCl_2$) promoted similar coupling reactions on organomagnesium compounds.[9]



Scheme 8. Bennett and Turner reaction.[8]

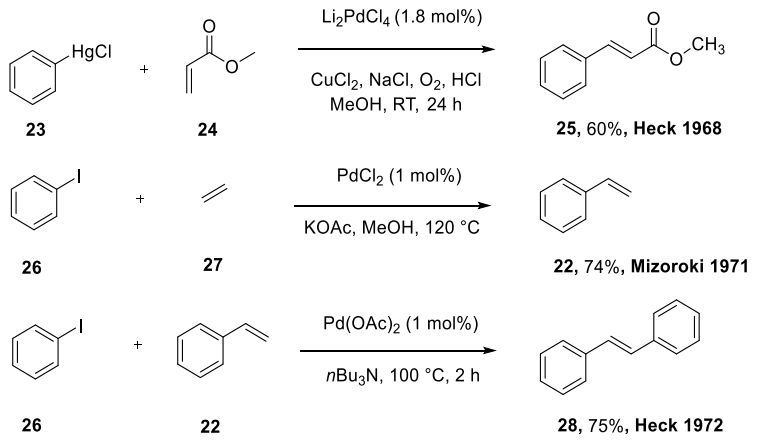
The early use of non-selective metals as cross-coupling promoters forced the use of stoichiometric quantities of metal in the reaction mixture, which caused side-reactions. In 1939, Meerwein first reported the effect of copper (II) salts as a catalyst in the coupling of

arenediazonium salts **18** with alkenes **19** (Scheme 9),[10] although this was limited to only particular substrates. In 1943, Kharasch published the first example of sp^2-sp^2 cross-coupling of vinyl bromide **21** with arylmagnesium species **17** mediated by cobalt chloride as shown in Scheme 9.[11] Meerwein and Kharasch's reports represent the earliest two successful studies of a cross-coupling product composed of different coupling partners *via* the use of metal salts in catalytic amounts. However, the use of these metal salts as catalysts often entails low selectivity and yields, with homo-coupled and hetero-coupled product ratios being substrate-dependent.[10,11]



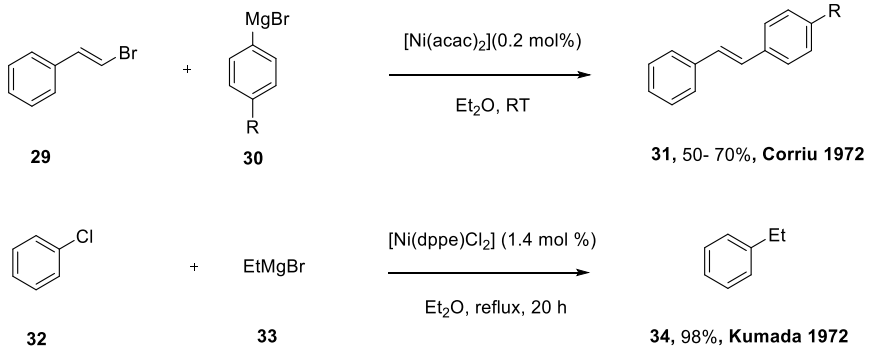
Scheme 9. Meerwein and Kharasch reactions.[10,11]

One of the first findings, in terms of cross coupling reactions mediated by palladium, was reported by Heck in 1968 when he described the coupling of an organo-mercury reagent **23** with alkenes in the presence of catalytic amounts of $Li_2[PdCl_4]$ (Scheme 10).[12] Given the toxicity of organomercury reagents, in the following years, Mizoroki in 1971[13] and Heck in 1972,[14] developed the possibility to couple aryl halides, such as iodobenzene **26**, benzyl and styryl halides with various alkenes such as **22** and **27**, employing palladium catalysis, which then evolved to the now-named Mizoroki-Heck reaction.



Scheme 10. Heck and Mizoroki reactions.[12–14]

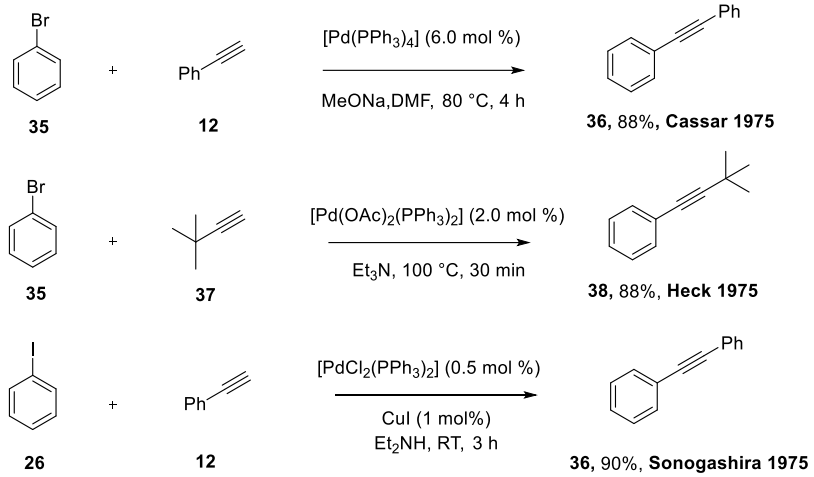
Meanwhile, two other chemists separately reported on nickel-catalysed cross-coupling reactions using Grignard reagents in 1972. Particularly Corriu[15] worked on alkenyl halides **29** while Kumada[16] worked on aryl halides such as chlorobenzene **32** to obtain respectively **31** and **34** (Scheme 11). Interestingly, Kumada introduced the use of phosphine ligands to regulate the reactivity of the metal, a procedure used also during later cross-coupling research.



Scheme 11. Corriu and Kumada reactions.[15,16]

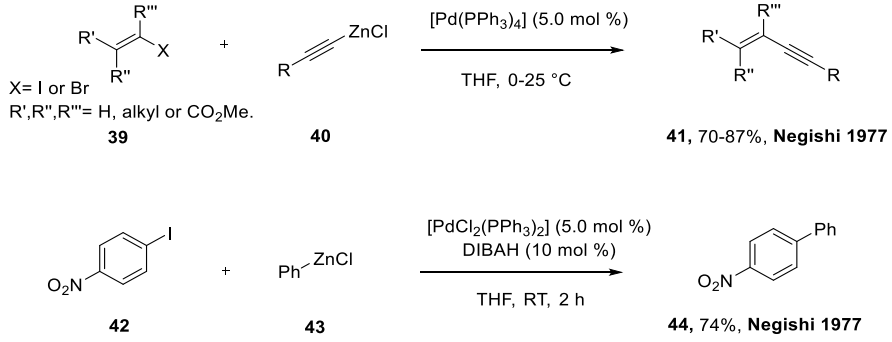
During these years, the use of palladium catalysts was propagated. Particularly Sonogashira,[17] Cassar[18] and Heck,[19] independently, reported on the 1975 palladium-catalysed coupling of acetylenes such as **12** and **37** with aryl halides (Scheme 12). The Sonogashira coupling reaction requires a copper salt as co-catalyst, and this combination

makes the reaction conditions considerably milder than the non-cocatalysed Heck and Cassar reactions and the Castro-Stephens coupling reaction,[20] where stoichiometric amounts of copper and high temperatures are needed.



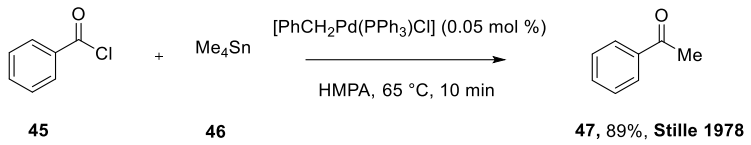
Scheme 12. Cassar, Heck and Sonogashira reactions.[17–19]

Meanwhile, other authors were exploring the organometallic coupling partners for metal-catalysed cross-coupling reactions. Negishi in 1977[21] reported the reaction of alkyl- and aryl-zinc derivatives **40** and **43** with vinyl and aryl halides **39** and **42** in the presence of a catalytic amount of a Ni or Pd catalyst to afford the coupled products **41** and **44** as shown in Scheme 13. Subsequently, Negishi reported the use of zinc reagents and organoaluminium intermediates as coupling partners, showing that magnesium and lithium are not strictly required.[22] Therefore, Negishi and co-workers carried out a metal screening study to identify the best coupling partners.[23]



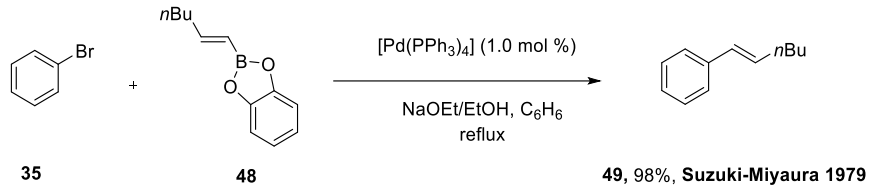
Scheme 13. The Negishi cross-coupling reaction.[21,22]

After some initial reports of Eaborn and Migita, Stille in 1978[24] achieved the palladium-catalysed ketone synthesis *via* coupling between aroyl chlorides **45** and organostannanes, such as **46** as shown in Scheme 14.



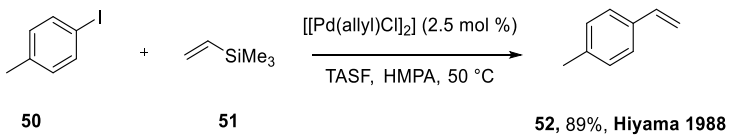
Scheme 14. The Stille reaction.[24]

In 1979 Suzuki[25] discovered a very powerful C-C bond forming process using more stable and manageable reagents such as organoborane **48** to afford the coupled product **49**, as well as milder conditions as shown in Scheme 15. Nowadays, this reaction is well known and commonly used in both industry and academia.



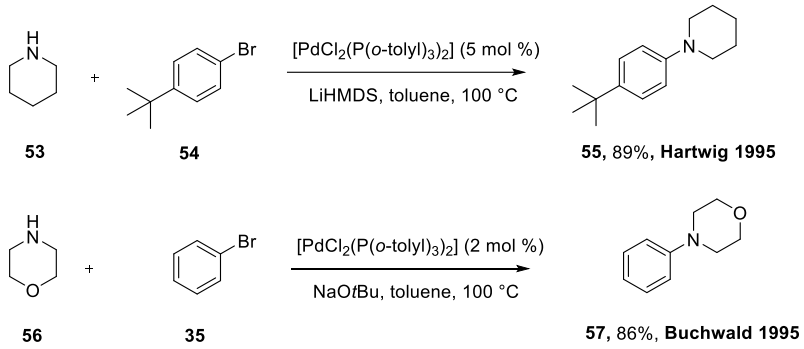
Scheme 15. The Suzuki-Miyaura reaction.[25]

Hiyama, a few years later presented a new and safer type of cross-coupling between organosilanes **51** (more environmentally friendly than organoboron, organozinc and organostannane reagents) and aryl halides **50** or triflates catalysed by either nickel or palladium and a source of fluoride such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) or CsF.[26]



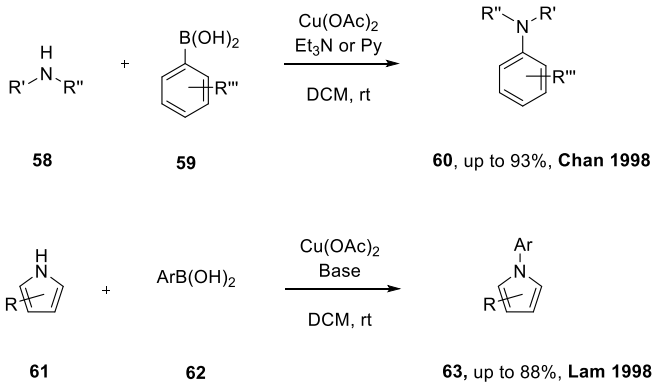
Scheme 16. The Hiyama reaction.[26]

Many other studies have been performed on heterocoupling reactions between a carbon and a heteroatom, such as the work shown by Buchwald and Hartwig in 1995 where they reported the coupling between an amine such as **53** or **56** and bromobenzenes **35** and **54** in the presence of a palladium catalyst and strong base (Scheme 17).[27,28]



Scheme 17. Hartwig and Buchwald reactions.[27,28]

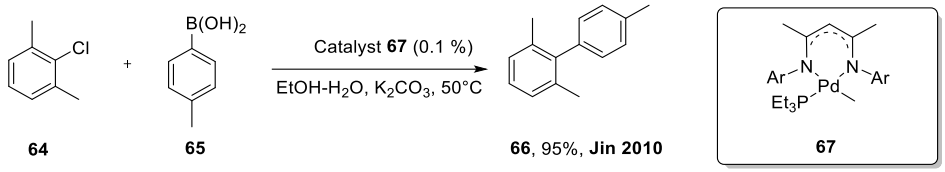
Later, Chan[29] and Lam [30] discovered an aryl-heteroaryl C-N bond cross-coupling reaction *via* the arylboronic acid **59** and **62** and cupric acetate arylation of N-H containing compounds, such as amines, anilines, amides, imides, ureas, carbamates, and sulfonamides *etc* (Scheme 18). The reaction only requires mild conditions such as room temperature, and the presence of air often does not affect the reaction.



Scheme 18. C-N cross coupling promoted by copper acetate, discovered by Chan and Lam.[29,30]

Over the years, many extremely active catalysts were discovered, able to trigger the coupling reaction of normally unreactive aryl chlorides under mild conditions. One example **67**, was

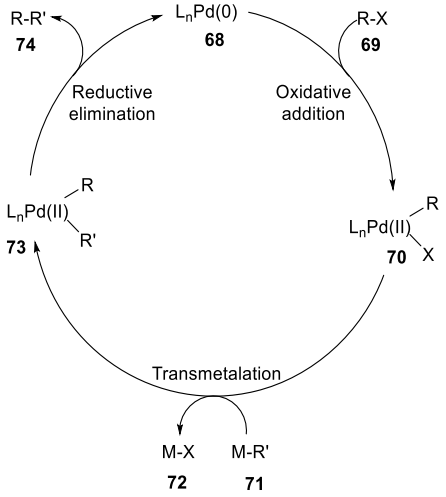
published by Jin in 2010 where different chloroarenes, such as chloro-*m*-xylene **64**, were coupled with boronic acid **65** *via* Suzuki cross-coupling and great yields were obtained (Scheme 19).[31]



Scheme 19. An example of recent advances on Suzuki cross coupling.[31]

The metal-catalysed cross-couplings have been greatly studied in the last century and many advances were presented in these years and more are likely in future because of the benefits these reactions have brought to both industry and academia. Despite many studies, the mechanisms are still not perfectly defined. In all these reactions the metal, ligand or substrate *etc*. used can vary, so the mechanism can be slightly or significantly different. Nevertheless, it is not the aim of this thesis to discuss these mechanisms. The many accepted interpretations for the mechanisms will be minimised to only a general combined discussion.

As Scheme 20 shows, the entire process is typified by 3 (or more for many cases) different steps. The first is an *oxidative addition* where a substrate such as vinyl or aryl halide **69**, adds to a palladium(0) compound **68** to form a palladium(II) complex **70**. The latter species undergoes a *transmetalation* with a different metal, for example organozinc in the Negishi reaction, a Grignard reagent in the Kumada reaction, an organostannane (normally unsaturated) in the Stille reaction, an organoboron species in the Suzuki coupling, *etc*.; where an exchange happens between the two metals: the palladium receives an organic moiety whereas the other metal receives the halide in its place. The final step is the *reductive elimination* of **73** where the two organic moieties bonded to palladium couple and leave the complex forming a C-C bond affording **74** and reducing the palladium back to Pd(0), which then catalyses another cycle.

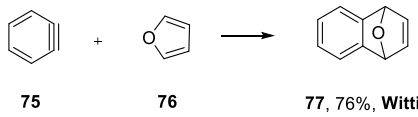


Scheme 20. Generic mechanism of a transition metal-catalysed cross-coupling reaction.

1.2.2 Benzyne-Mediated Cross-Coupling Reactions

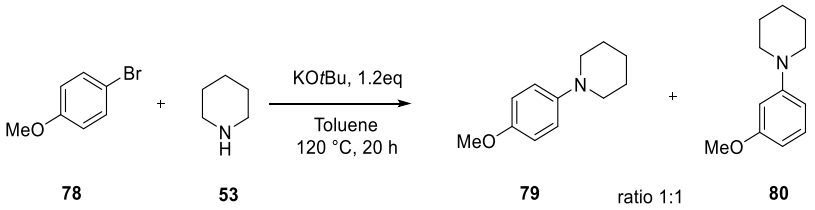
An important chapter in organic chemistry arrived when the species C_6H_4 was discovered. This species was found to be an intermediate for a wide selection of reactions, among them cross-coupling reactions.

Benzyne was first noticed in 1927 by Bachmann and Clarke when they investigated the mechanism of the Wurtz-Fittig reaction where chlorobenzene and sodium were refluxed to give rise to benzene, biphenyl, *o*-diphenylbenzene, triphenylene and *o,o′*-diphenylbiphenyl.[32] The reaction mechanism for the formation of the latter three species comes through benzyne **75** or "*free phenylene*" formation. Afterwards, an interesting result was obtained by Georg Wittig in 1942, who afforded biphenyl from the reaction between halobenzenes and phenyllithium.[33] In the following decades, many trapping experiments were carried out with the aim to explain the formation of this unstable species.[34] One of the most famous trapping reactions was achieved by Wittig, who reported the first Diels-Alder reaction of benzyne **75** with furan **76**, affording 76% yield of the adduct **77** (Scheme 21).[35]



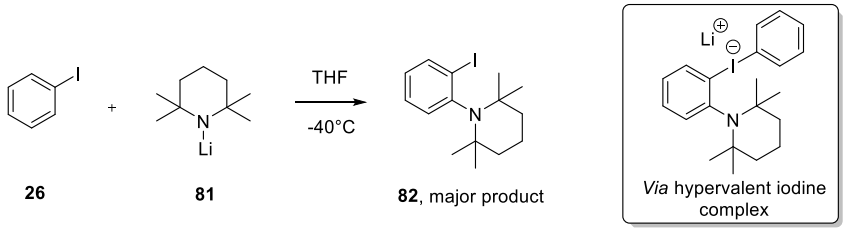
Scheme 21. Trapping experiment between benzyne **75** and furan **76** discovered by Wittig.[35]

Benzynes are widely applied in organic synthesis. One, more recent, observation of the benzyne-mediated cross-coupling reaction was shown by Djakovitch in 1999, with his work on amination of aryl bromides such as **78**, catalysed by supported palladium. When he carried out the reaction in the absence of supported metal, he noticed the formation of two regioisomers **79** and **80** when he forced the reaction to proceed at higher temperatures. Moreover he found that the amination *via* benzyne intermediates was favoured by the presence of electron-withdrawing groups on the aromatic ring, and also the use of a weaker base such as NaO*t*Bu was less effective.[36]



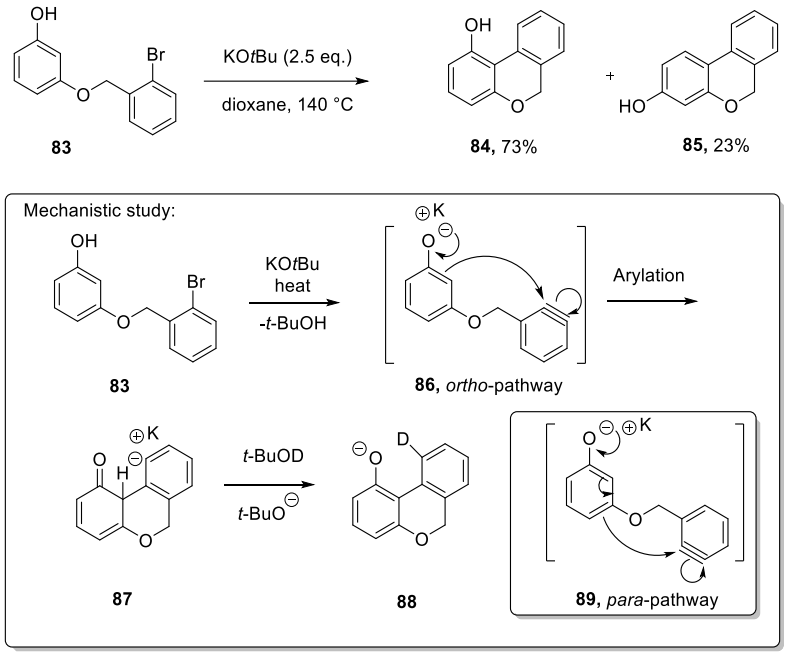
Scheme 22. Benzyne-mediated cross-coupling by Djakovitch.[36]

Another report was published by Durst *et al.* who generated benzyne from iodobenzene and lithium tetramethylpiperidide (**81**, LTMP) in THF at -40 °C (Scheme 23).[37]



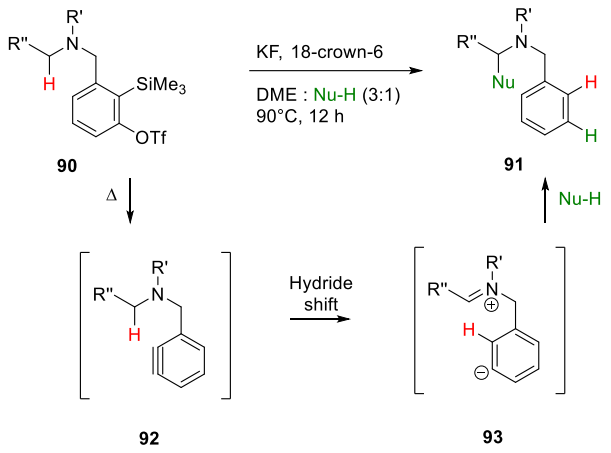
Scheme 23. Benzyne generation from iodobenzene.[37]

A compelling study was carried out by Daugulis and Bajracharya in 2008, who obtained a base-mediated intramolecular arylation of phenols by simply using 2.5 eq. of KO*t*Bu in dioxane at 140°C. The phenol **83** was chosen for this test and the two products **84** and **85** were obtained, the first coming from the *ortho* attack **86**, whereas **85** came from the *para*-attack as shown for **89**, on the benzyne intermediate. During the optimisation of the reaction, they noticed that weaker bases were less effective or totally ineffective. Moreover, they elegantly proved that the proton source was *tert*-butanol. When they carried out the reaction adding an excess of *t*BuOD, they noticed the incorporation of deuterium into the products, whereas in using dioxane-d_8, the products were found to be non-deuterated.[38]



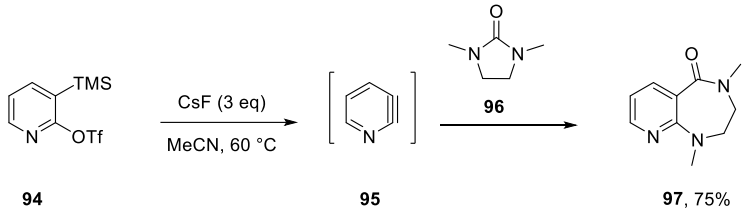
Scheme 24. Daugulis and Bajracharya mechanistic study on benzyne intermediate.[38]

A recent C-H functionalisation of amines using arynes was reported by Jones and co-workers.[39] The formation of the aryne **92** allows a hydride to shift onto the aryne and the resulting iminium cation can be functionalised by a pro-nucleophile such as CH_3CN (Scheme 25).



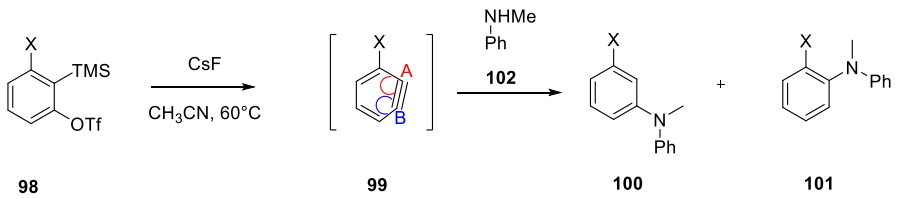
Scheme 25. α-C-H functionalisation of amines reported by Jones.[39]

Garg *et al.* have expanded the aryne formation towards the formation of pyridyne **95** and other arynes.[40] Pyridyne can be trapped with a series of different nucleophiles such as **96** to form more complex products such as **97**.



Scheme 26. Pyridyne intermediate proposed by Garg *et al*.[40]

Garg *et al.*'s investigation moved towards the study of the regioselectivity in aryne reactions with unsymmetrical arenes.[41] In particular, they studied computationally the reactivity of 3-halobenzyne **98** and what they found was that the bigger "aryne distorsion Δ" there is between angle "A" and "B" the more regioselective the reaction will be. The extent of the distortion Δ depends on the electronegativity of the halogen (F>Cl>Br>I) whereas the size of the substituent does not change the distortion significantly (Table 1). More computational predictions (*via* DFT calculations) were performed on disubstituted benzynes and substituted indolynes. Benzyne is normally represented as 1,2-dihydrobenzene, but isomeric didehydrobenzene are also known.[41]



X	A	B	Δ	100:101 Ratio
OMe	120°	135°	15°	100:0
F	118°	135°	17°	100:0
Cl	121°	132°	11°	20:1
Br	122°	132°	10°	13:1
I	124°	130°	6°	9:1

Table 1. Study of the regioselectivity of the halobenzyne and experimental ratios.

Benzynes are dehydrobenzenes, they are widely applied in synthesis and also into drug active molecules. New chemotherapeutic drugs are based on enediynes such as the antibiotic Lidamycin (**102**, Figure 1). The anticancer activity of the enediynes is apparently due to their capacity to interact and damage DNA through radical-mediated hydrogen abstraction. Lidamycin contains this enediyne core which generates *para*-benzyne biradical, and this intermediate abstracts hydrogens from the DNA sugar backbone, dismembering the entire structure.[42]

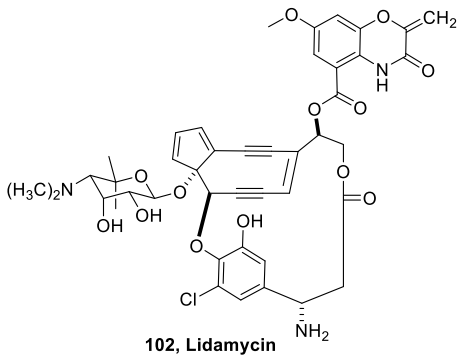
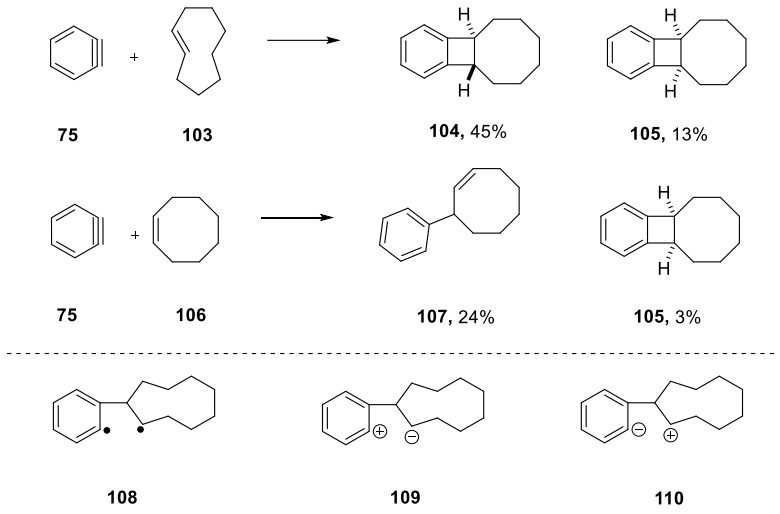


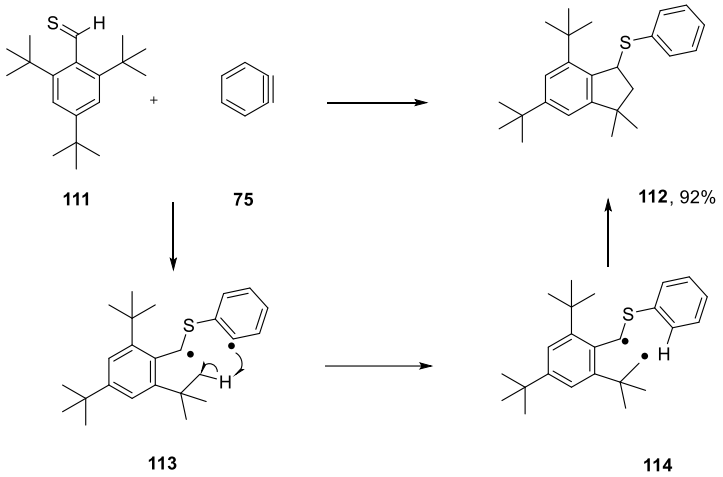
Figure 1. Structure of Lidamycin.[42]

An interesting point which needs to be discussed is the capability of benzyne to act as a *o*-diradical. Gassman and Benecke in 1969 reported a nice piece of work on the evidence of the formation of diradical intermediate in [2 + 2] addition of benzyne to olefins (Scheme 27).[43] In particular, they demonstrated the outcome of the products coming from the reaction of benzyne with *trans*-alkene **103** and they provided evidence that the generation of the two products **104** and **105** must come from a 2-step mechanism. The initial hypothesis on the possible isomerisation of alkene **103** was ruled out with the experiment performed with *cis*-alkene **106** which gave mainly product **107** (not observed in the first experiment) and a small amount of **105**. Since no isomerisation occurs, the two products *trans*-**104** and *cis*-**105** ought to come from one of the proposed intermediates **108**-**110**. Gassman asserts that **109** is a too unstable species and, therefore, its formation is precluded. The formation of zwitterion **110** can also be excluded since the reaction was studied in THF, benzene and acetonitrile and similar ratio was obtained in all cases. If a polar intermediate such as **110** were being formed, it ought to be stabilised by the more polar solvent and therefore, the intermediate lifetime ought to be prolonged with the consequent more rotation of the intermediate. This event would conclude with a different ratio of the ring-fusion products **104** and **105**, in favour of the production of *cis* product **105**. This evidence did not occur, therefore, the diradical intermediate **108** is the most plausible intermediate for this reaction which suggests that benzyne can act as a *o*-diradical.[43]



Scheme 27. Evidence for diradical intermediates in the [2 + 2] addition of benzyne to olefins reported by Gassman and Benecke.[43]

Another example where benzyne was reported to act as an *o*-diradical was given by Okuma and coworkers.[44] They suggested that when benzyne reacts with congested compounds such as thioaldehyde **111**, a thioaldehyde-benzyne adduct **112** forms. The mechanism proposed by Okuma sees the formation of diradical **113** in which phenyl radical abstracts a hydrogen from a *t*-butyl substituent, with a resulting diradical **114**, from which adduct product **112** forms (Scheme 28).



Scheme 28. Reaction of sterically hindered thioaldehyde with benzyne reported by Okuma.[44]

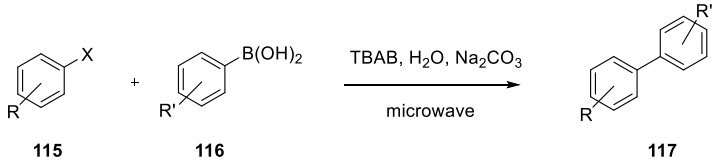
In the following section, transition metal-free cross coupling reactions will be discussed as well as the involvement of benzyne.

1.2.3 Transition Metal-Free Cross-Coupling Reactions (TMF-CCR)

Cross-coupling reactions were known to work with the transition metal catalyst as *conditio sine qua non*, until some experiments were performed, revealing that transition metals were not needed.

1.2.3.1 Development of TMF-CCR

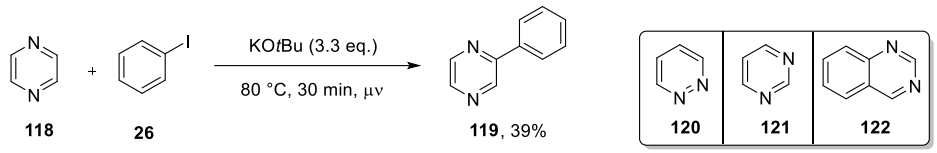
Leadbeater and Marco in 2003 were studying a Suzuki reaction with arylboronic acid **116** and aryl halides **115**, using water as solvent and under microwave conditions.[45] During these attempts, they noticed that the product **117** was formed also in the "blank" reaction (Scheme 29) without palladium as catalyst. They repeated the reaction with both new glassware and reagents, and the product was found to be contaminated with palladium levels down to 0.5-1.0 ppm.



Scheme 29. Leadbeater and Marco experiments.[45]

Further studies from the same authors, later, revealed that a very low concentration (around 50 ppb) of palladium was present in the Na_2CO_3 (although the nature of the complex present was not proved) and this low concentration was responsible for the reaction success. For this reason, they tested the reaction adding 100 ppb, 250 ppb and 2.5 ppm of $Pd(NO_3)_2$ and they discovered that the reaction yield was not constant but increased with the addition of catalyst. After these results, their conclusion was that the reactions were running with ultra-low palladium concentration and not under metal-free conditions, and so they published a reassessment of their "transition metal-free" Suzuki-type coupling reaction.[46]

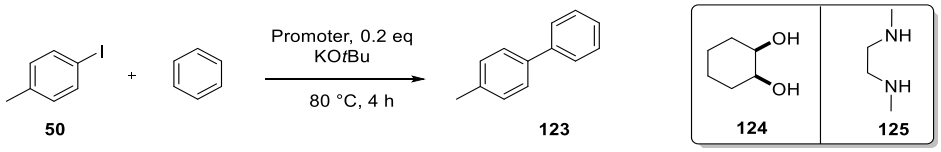
However, a few years later, Itami *et al.* in Japan discovered that the biaryl coupling of electron-deficient nitrogen heterocycles and iodoarenes, normally conducted in the presence of iridium catalysts, can be promoted by KO*t*Bu alone, without the addition of any exogenous transition metal species. This finding was pursued, performing a "blank" reaction with iodobenzene **26** and pyrazine **118** without iridium catalyst, a metal for which they were studying the catalytic activity (Scheme 30).[47]



Scheme 30. The metal-free cross- coupling reaction of Itami *et al.*.[47]

Considering that, a few years before, transition metals were found to be present in the base used by Leadbeater,[46] all the reagents were purified, including sublimation of KO*t*Bu. The quantitative elemental analysis on the base revealed that only Si, Al and Ca were present with a detectable value, whereas Pd, Rh and Ru were not found with any values above the detection limit (Pd: <0.06 ppm, Rh: < 0.20 ppm, Ru: <0.30 ppm). Itami *et al.* found that pyridazine **120**, pyrimidine **121** and quinazoline **122** were all able to couple with iodobenzene **26** in moderate yields. Moreover, they found that radical scavengers such as TEMPO, galvinoxyl or acrylonitrile were capable of shutting down the reaction. This suggested that a radical-based process was driving the reaction. Additionally, various coupling attempts between different disubstituted iodoarenes and pyrazine **118** showed no regioisomer formation from the reaction, which excluded a benzyne-mediated process.

Soon afterwards, other research groups published new advances on Itami's discovery. Lei *et al.* discovered that some neutral compounds, used as additives in the reactions, were able to promote the transition metal-free cross-coupling. In one of his reports, Lei showed how some reagents, such as **124** and **125** together with KO*t*Bu were able to promote the coupling of 4-iodotoluene **50** and benzene,[48] as shown in Scheme 31.

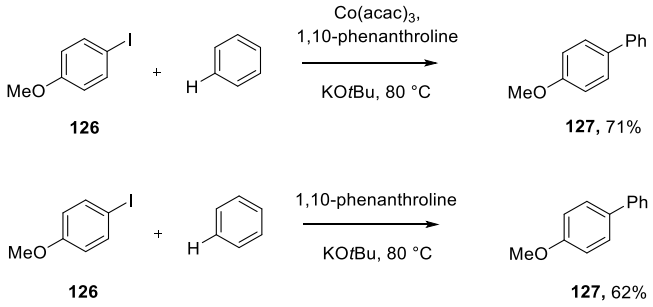


Scheme 31. Lei discovered the role of some neutral compounds as promoters.[48]

Curiously, only KO*t*Bu and alcohols such as **124** and diamines such as DMEDA **125** were noticed to be effective for these reactions. Moreover, radical scavengers shut down the

reaction in a similar vein as in Itami's reaction. Nevertheless, at this stage it was still difficult to think about a mechanism for these transformations.

In 2010 two different works were published about the use of "catalytic" 1,10-phenanthroline derivatives as additives in metal-free cross-coupling reactions with aryl iodides or bromides.[49] Shi *et al.* initially were working on a cobalt-catalysed cross-coupling between 4-iodoanisole **126** and benzene in the presence of ligands capable of promoting the coupling (Scheme 32). Without any expectation, when they tested the reaction in the absence of the "catalyst", a comparable yield was also achieved. Therefore, Shi *et al.* proposed that a radical is formed from the aryl halides by KO*t*Bu, and that 1,10-phenanthroline might facilitate the radical generation.



Scheme 32. Comparing the reaction in the presence and absence of transition metal by Shi.[49]

They further proposed that both 1,10-phenanthroline and a potassium ion might interact with arenes *via* π,π-stacking and ion–π interaction respectively, to promote their reactivity as shown in Figure 2; however this was not based on any experimental or computational evidence.

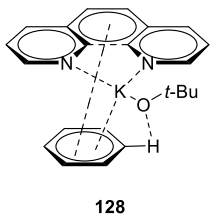
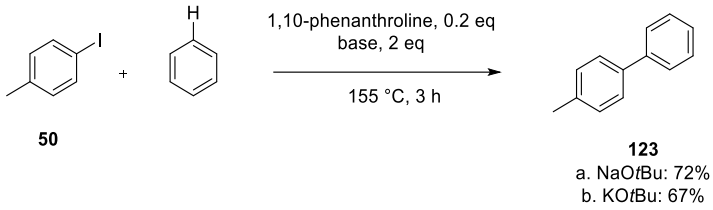


Figure 2. Interaction between 1,10-phenanthroline, KO*t*Bu and arenes proposed by Shi *et al.*[49]

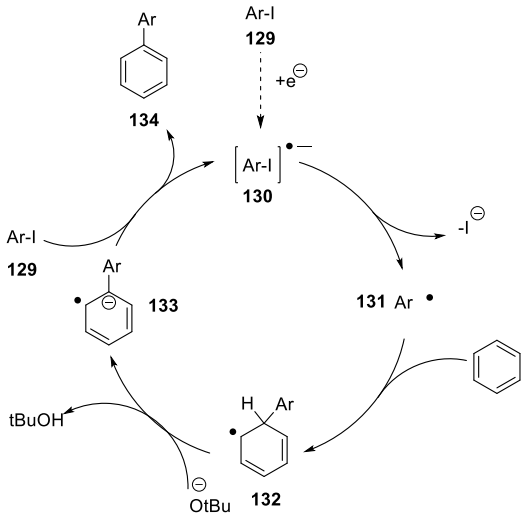
Simultaneously, Hayashi in Japan revealed the NaO*t*Bu-mediated coupling between aryl halide **50** and benzene in the presence of a small amount of 1,10-phenanthroline (Scheme 33).[50] This study finally showed that the choice of the base is not strictly limited to KO*t*Bu. But that NaO*t*Bu can promote these types of reactions as well.



Scheme 33. Coupling reaction mediated by 1,10-phenanthroline and alkoxides as proposed by Hayashi.[50]

Another curious point of his work was the formation of 3- and 4-butoxytoluenes (ratio 1:1) derived from the aryne intermediate when they tested *p*-bromotoluene. This suggests that that at higher temperatures, benzyne is formed.

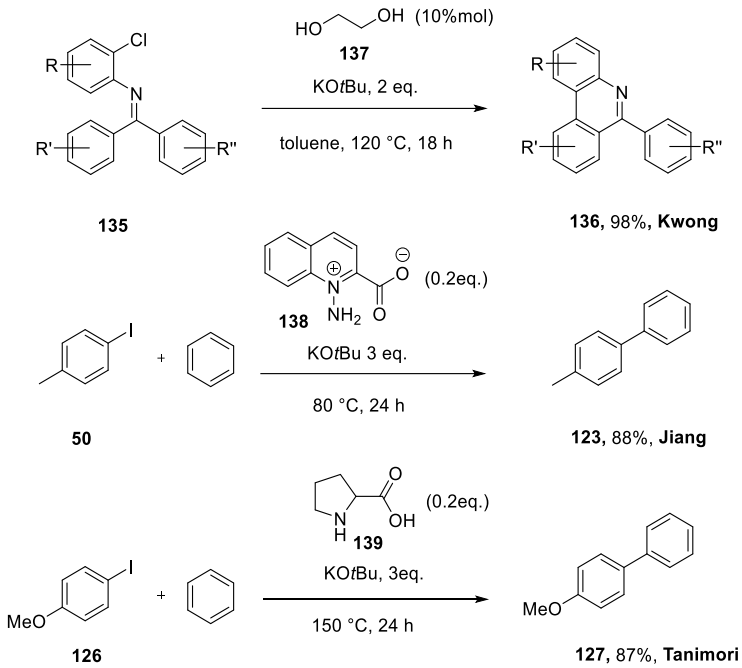
An interesting overview, published by Studer and Curran in 2011, summarised what Itami, Shi and Hayashi had previously developed. However, Studer and Curran also proposed a plausible mechanism for these transition metal-free arylations that they named as Base-promoted Homolytic Aromatic Substitution (BHAS) reactions.[51] In their proposal, they described the formation of the biaryl radical anion **133**, a powerful reducing agent and keystone of the entire process. The radical species **131** derives from the radical anion **130** formed from iodoarene **129**; radical **131** then couples with benzene to form the cyclohexadienyl radical species **132**, which undergoes deprotonation by the strong base to afford **133**. This latter radical anion species is able to propagate the process by donating an electron to another iodobenzene producing the coupled product **134** (Scheme 34). The weak point of this mechanism is the initiation step, which still needed to be clarified. The two scientists stated that presumably additives such as 1,10-phenanthroline and DMEDA **125** may play a crucial role on this stage.



Scheme 34. Base-promoted Homolytic Aromatic Substitution (BHAS) proposed by Studer and Curran.[51]

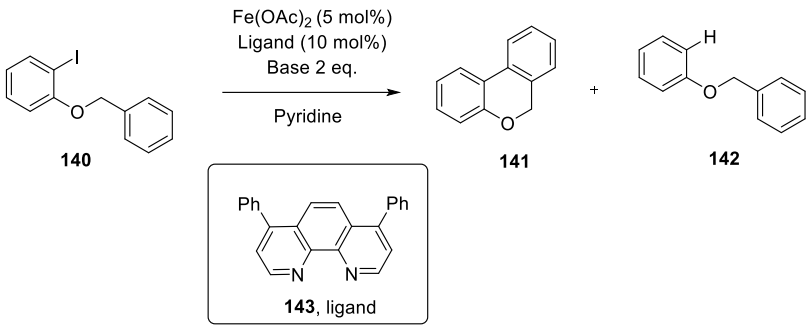
In the following years, other authors published many papers showing how neutral organic compounds could be used as additives, capable of promoting the BHAS. Kwong *et al.* achieved an intramolecular arylation of aryl chloride **135** in the presence of ethylene glycol **137** and KO*t*Bu, giving rise to various phenanthridines such as **136** (Scheme 35).[52] Curiously, other ligands such as DMEDA and 1,10-phenanthroline were much less efficient. Jiang, almost simultaneously, discovered another effective system constituted by KO*t*Bu and quinoline-1-amino-2-carboxylate **138** for promoting transition metal-free BHAS cross-coupling reactions.[53] This additive can chelate the K^+ cation, forming a 6-membered ring in the vein of 1,10-phenanthroline forming a 5-membered ring, as suggested by Shi *et al.*[49] Furthermore, they investigated the effects of traces of transition metals in the reactions. They tested the same reaction conditions in the presence of metals capable of promoting cross-coupling reactions such as CuI and $Fe(acac)_2$, which cut down the coupling yields, suggesting that the transition metals do not participate in the coupling processes. These tests decreased the concerns, started by Leadbeater in 2003,[45] about the possibility that traces (ppm or ppb) of transition metals can promote these "apparently" transition metal-free coupling reactions. This conundrum was faced again by Leadbeater in 2010 who raised the question about the presence of metals within his cross-coupling: "When is free really free",[54] and it is still an object of discussion by many scientists in the world.

Furthermore, in 2012 Jiang *et al.* disclosed how also a MOF (Metal Organic Framework) constructed from Al^{3+} and 2,2′-bispyridine-5,5′-dicarboxylate was able to promote transition metal-free cross-coupling reactions (not shown in scheme), whereas further introduction of Al^{3+} does not affect the yield.[55] Tanimori *et al.* in 2012 tested several amino acids and, among them, proline **139** was found to be the best additive for C-H arylations of unactivated arenes *via* transition metal-free cross-coupling (Scheme 35).[56]



Scheme 35. Arylation reactions by Kwong, Jiang and Tanimori. [52,53,56]

Charette in 2011 reported a regioselective cyclisation of aryl ethers, amines, and amides mediated by KO*t*Bu under microwave irradiation. A route to optimisation was pursued: the reaction gave rise to cross-coupling using the iodoarene **140** as substrate, with 1,10-phenanthroline-type ligands **143**, KO*t*Bu and $Fe(OAc)_2$ (Entry 1, Table 2); nevertheless, a comparable result was obtained in the absence of $Fe(OAc)_2$ (Entry 2). Furthermore, the use of only KO*t*Bu and pyridine, under microwave conditions (Entry 3, 160 °C, 10 min) gave rise to a significant yield, whereas the weaker base NaO*t*Bu was found to be ineffective (entry 4).[57]



Entry	$Fe(OAc)_2$	Ligand	Conditions	Conversion (%)	141 (%)	142 (%)
1[a]	yes	L1	KO*t*Bu	99	80	9
2[a]	none	L1	KO*t*Bu	88	79	4
3[b]	none	none	KO*t*Bu/µw	80	50	18
4[b]	none	none	NaO*t*Bu/µw	0	0	0

Table 2. Charette's studies on 1,10-phenanthroline. [a] Reaction conditions: 80 °C, 16 h. [b] Reaction conditions: 160 °C, 10 min.[57]

Charette and coworkers added radical scavengers which shut the reaction down. A benzyne-type pathway was ruled out since no butoxide anion-trapped products were detected, even if the temperature of the reaction could have allowed it. The mysterious absence of an electron donor, apparently, in entry 3 still needed to be explained.

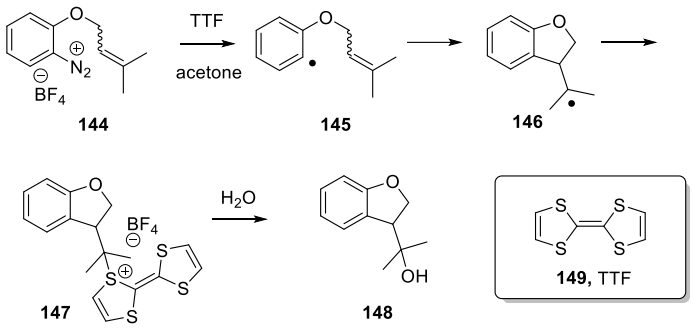
Inspired by all the previous works, in particular where heterocycles were employed either as additives or as solvent, the Murphy group carried out a great deal of research on transition metal-free cross-coupling and many noteworthy findings were revealed.

1.2.3.2 Organic Electron Donors: the first findings

Organic Electron Donors (OEDs) are neutral, ground state organic molecules able to reduce substrates by single electron transfer. The common characteristics for this new class of molecules include the presence of an electron-rich alkene moiety, with the ability to donate

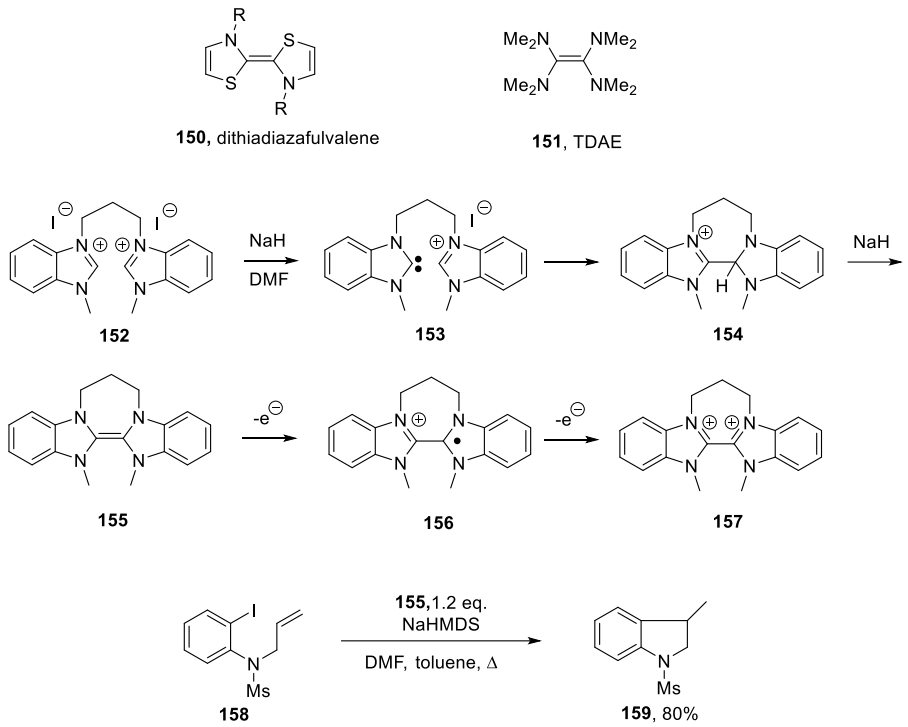
one or more electrons to different substrates and featuring charge delocalisation and/or aromatic stabilisation as a driving force for oxidation.

Murphy initially reported a new behaviour for tetrathiafulvalene (**149**,TTF) in mediating radical cyclisation and nucleophilic displacements through single electron transfer.[58] The reaction was proposed to proceed *via* electron transfer, dediazotisation of **144** and radical cyclisation of **145** to afford the radical intermediate **146**, which then gave rise to the alcohol **148** through the trapped intermediate **147**.



Scheme 36. The Murphy group reported TTF **149** as an electron donor in organic synthesis.[58]

After this work, Murphy *et al.* focused their attention on how to design a stronger organic electron donor and they prepared a series of molecules, such as diazadithiafulvalenes **150**,[59,60] tetrakis(dimethylamino)ethylene (**151**, TDAE),[61,62] tetraazafulvalene **155,**[63,64] that were able to trigger electron transfer on different substrates. This first wave of compounds from Murphy's discoveries led the group to important conclusions. While the first two compounds were not able to reduce iodoarenes, compound **155** was, as shown in the radical cyclisation of substrate **158** in Scheme 37. The mechanism of the activation of the tetraazafulvalene **155** is shown in Scheme 37 and since this compound is very reactive even with molecular oxygen, then it can only be stored under inert atmosphere. Considering that the oxidation potential of TDAE ($E^1_{½}$ = -0.78 V; $E^2_{½}$ = -0.61 V vs SCE in MeCN) and tetraazafulvalene[65] ($E^1_{½}$ = -0.82 V; $E^2_{½}$ = -0.76 V vs SCE in MeCN) are very similar, the reason for the increased reductive power of **155** over **151** could rely on the better stacking of **155** with iodoarenes. Nevertheless, the power of the electron donors was improved further with subsequent discoveries. One important common element of the electron donation is the aromatisation step, which drives the donation process.[66]



Scheme 37. First generation of organic electron donors developed by the Murphy group.

Following the abovementioned principles, the Murphy group discovered a second generation of more powerful organic electron donors **160**-**163** (Figure 3).

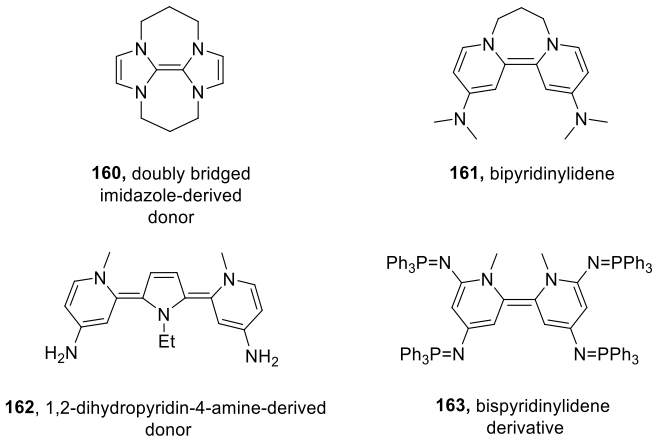
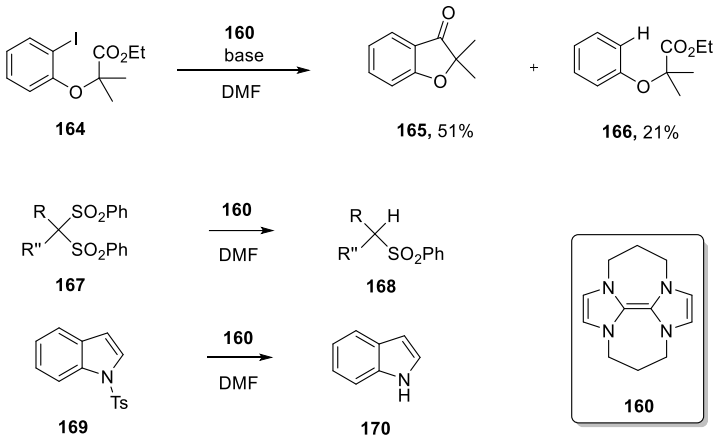


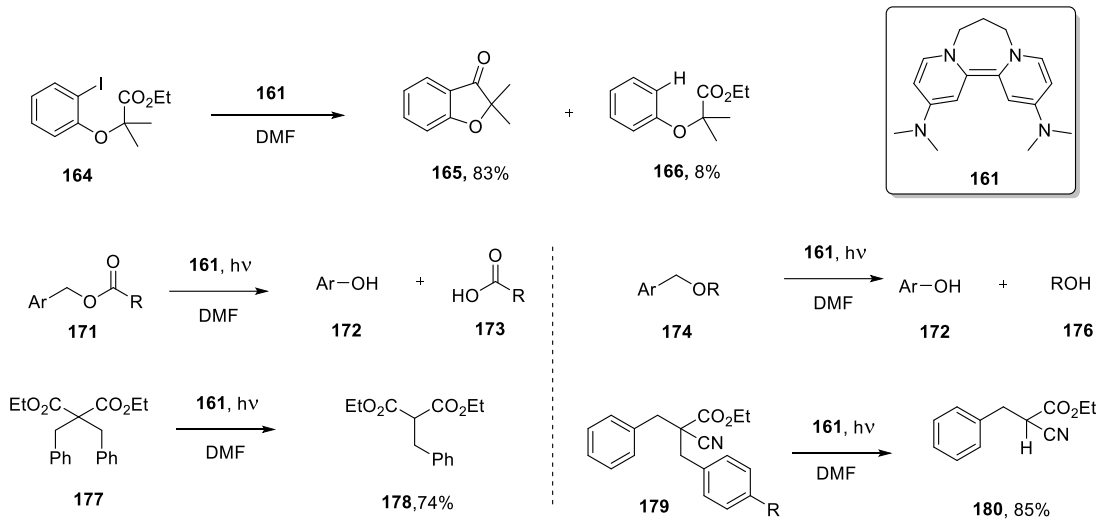
Figure 3. Second generation of organic electron donors reported by the Murphy group.

The "doubly bridged" imidazole derivative donor **160** was found to be more powerful than tetraazafulvalene donor **155**.[63,66] When substrate **164** was tested with donor **160**, indanone **165** and the de-iodinated product **166** were both isolated. The production of product **166** relies on the fact that this more powerful donor is able to donate two electrons to an iodoarene forming the aryl anion and not merely the aryl radical, therefore the anion will get protonated giving rise to product **166**.[66] Furthermore this donor was also able to promote reductive cleavage of arylsulfones **167** and arylsulfonamides **169**.[67]



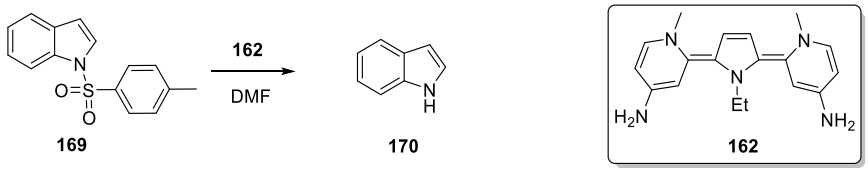
Scheme 38. Reducing power of the imidazole donor **160**.

Another great reagent for electron transfer reaction was bipyridinylidene **161**. This latter is capable of donating two electrons to iodoarenes; therefore the reaction with substrate **164** gave rise to product **165** in a very good yield and **166** as minor product (see Scheme 39). Further tests have been done on the activation of these substrates by photoactivation, enhancing the reductive power of the electron donor, therefore the resulting activated donor was found to promote reductive cleavages of benzylic esters **171** and ethers **174.**[68] Moreover, Murphy *et al.* achieved the chemoselective reduction of benzyl groups over malonates and cyanoacetates in substrates such as **177** and **179**.[69] This clearly proved that the donor-acceptor π-stacking interaction plays an important role with these transformations with this reducing agent, overturning the chemoselectivity of other reagents (favouring ester or nitrile reduction) known in the literature.[69]



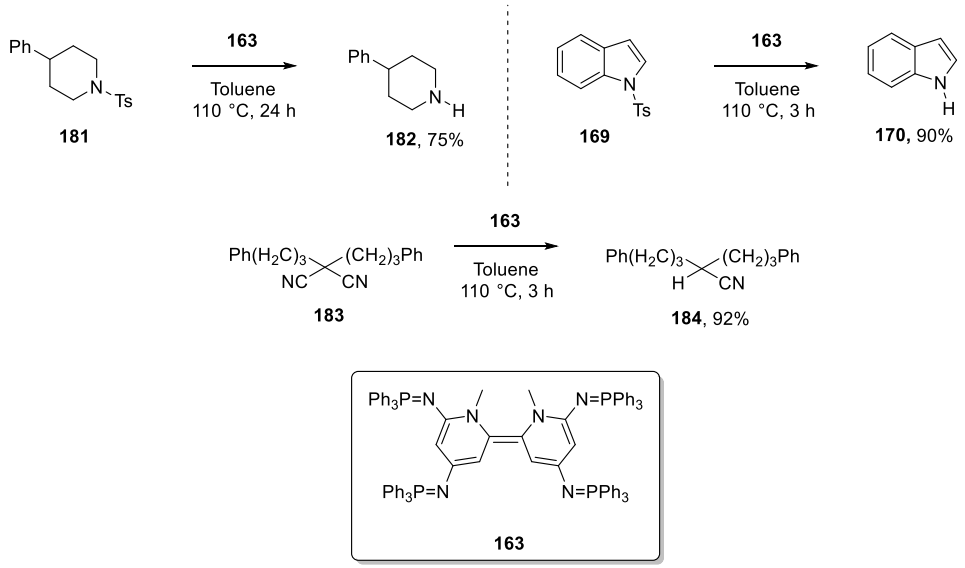
Scheme 39. Reducing power of bipyridinylidene **161**, in this case the major product is the coupled product.[69]

Another very powerful organic donor **162** was found to be very reactive in the ground state. This donor boasts the fact that it can achieve a triple aromatisation after oxidation, acting like a very powerful reducing agent capable of reducing appropriate tosylamides such as **169** (see Scheme 40).[70]



Scheme 40. Reduction of tosylamide **169** by **162**.

The electron donor **163**, a bipyridinylidene derivative, is even more powerful than the **161** and **162**. CV measurements revealed a very low redox potential ($E_{1/2}$ = -1.70 V vs SCE) which makes this donor able to induce the reductive S-N bond cleavage of *N*,*N*-dialkylsulfonamides **181** and *N*-arylsulfonamides **168** as well as malonitriles **183** without photoexcitation.[71]



Scheme 41. Many examples of cleavages reported by Murphy.[71]

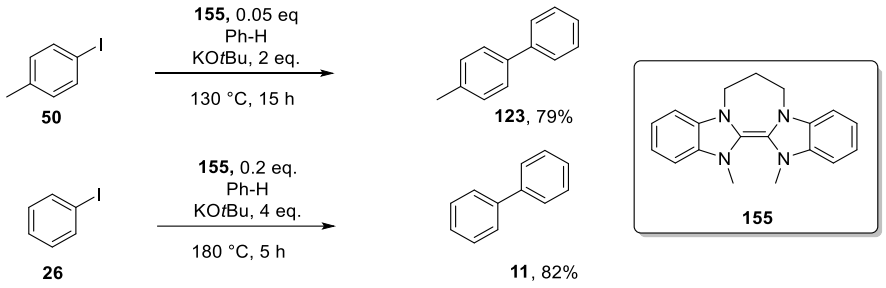
After these first findings on the power of organic electron donors, the Murphy group worked on some of the applications of this class of compounds.

1.2.3.3 Organic Electron Donors as valid initiators for transition metal-free cross-coupling reactions

Since it is possible to generate an aryl radical from an iodoarene using organic electron donors, the Murphy group started to evaluate the possibility that some of their electron donors might promote the arylation of aryl halides in the presence of KO*t*Bu. If an electron donor could be formed *in situ* then it ought to behave as promoter of the initiation step of the Base-

induced Homolytic Aromatic Substitution, the mechanism was partially described by Studer and Curran in 2011 (Scheme 34).[51]

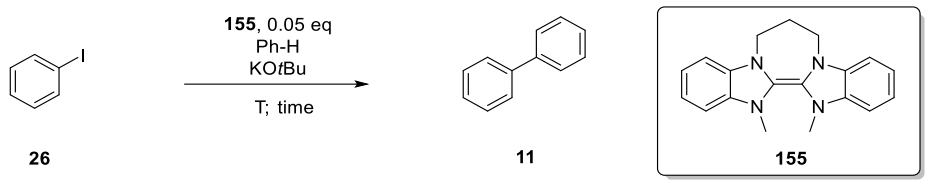
Test reactions were then performed in benzene as solvent using electron donor **155** and different iodoarenes such as **26** and **50**. As shown in Scheme 42, the yields obtained *via* this new approach were very satisfying, although when bromoarenes were tested instead, lower yields were achieved, mirroring the previous results with electron donors.[72]



Scheme 42. The role of benzimidazole-derived donor **155** in mediating cross-coupling reactions.[72]

Moreover, to evaluate how important the amount of donor used is, different tests with progressively decreasing amounts of electron donor were performed and it was found that the yield of the coupled product was concentration-dependent (Table 3). This underlined that the donor **155** is able to trigger the radical process (BHAS).

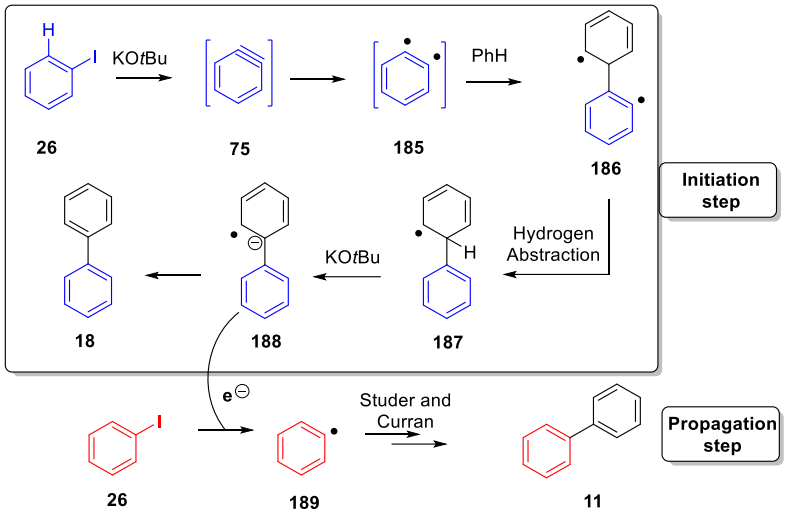
The role of temperature was also investigated and the reaction was found to be strictly dependent on; in fact when the temperature was decreased, either in the presence or absence of the donor **155**, the reaction yield dropped (Entries 1-2 and 4-5, Table 3).



Entry	155 (eq.)	KO*t*Bu (eq.)	Reaction conditions	11 (%)
1	0.05	2	130 °C; 3.5 h	80
2	0.05	2	110 °C; 3.5 h	47
3	0.025	2	110 °C; 3.5 h	27
4	none	2	130 °C, 3.5 h	30
5	none	2	110 °C, 3.5 h	27
6	none	4	185 °C, 14 h	48

Table 3. Evaluating the presence of **155** as additive in different conditions.

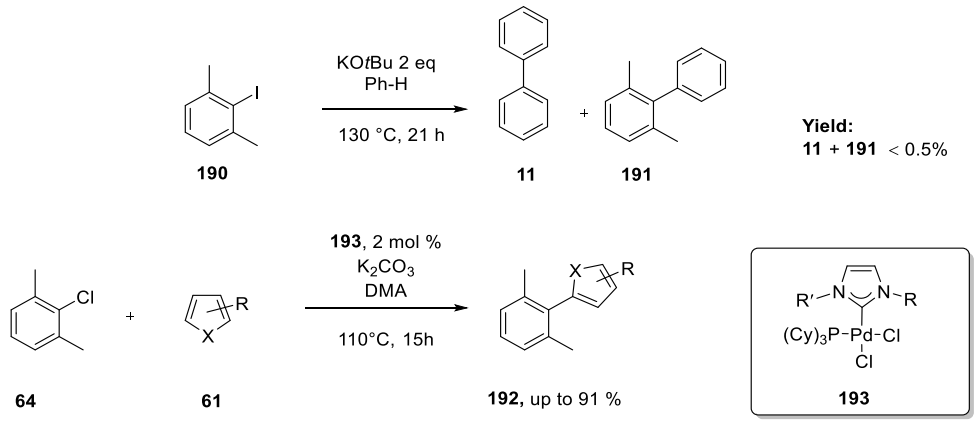
When the temperature was raised to 185°C for 14 h in absence of the donor, the product yield was found to be 48%.[72] The reason for this correlation between temperature and yield in the absence of electron donor lies in the possible benzyne-mediated initiation (see Scheme 43). The possibility of forming benzyne using iodoarenes and strong base has been previously shown by Djakovitch *et al*.[36]



Scheme 43. Initiation promoted by the benzyne intermediate proposed by the Murphy group.[72]

As proposed by the Murphy group, benzyne plays a role in the initiation steps for a radical chain, but not in the propagation. As shown in Scheme 43, the benzyne intermediate **75** can act as *o*-diradical **185**,[43,73] as already described in Chapter 1.2.2. This latter couples with benzene to afford **186**; the normal fate of this species may be to undergo 4-membered ring formation, but occasionally, an alternative process may occur, for example when the aryl radical in **186** abstracts a hydrogen, giving rise to **187**. This, afterwards, undergoes deprotonation by the base to form the radical anion species **188**, the electron donor species capable of donating an electron to iodobenzene, and then the propagation steps occur. Since the benzyne is involved in the initiation step and since this process affects only a small percentage of substrate, then it has been impossible to isolate the eventual benzyne trapping products formed.

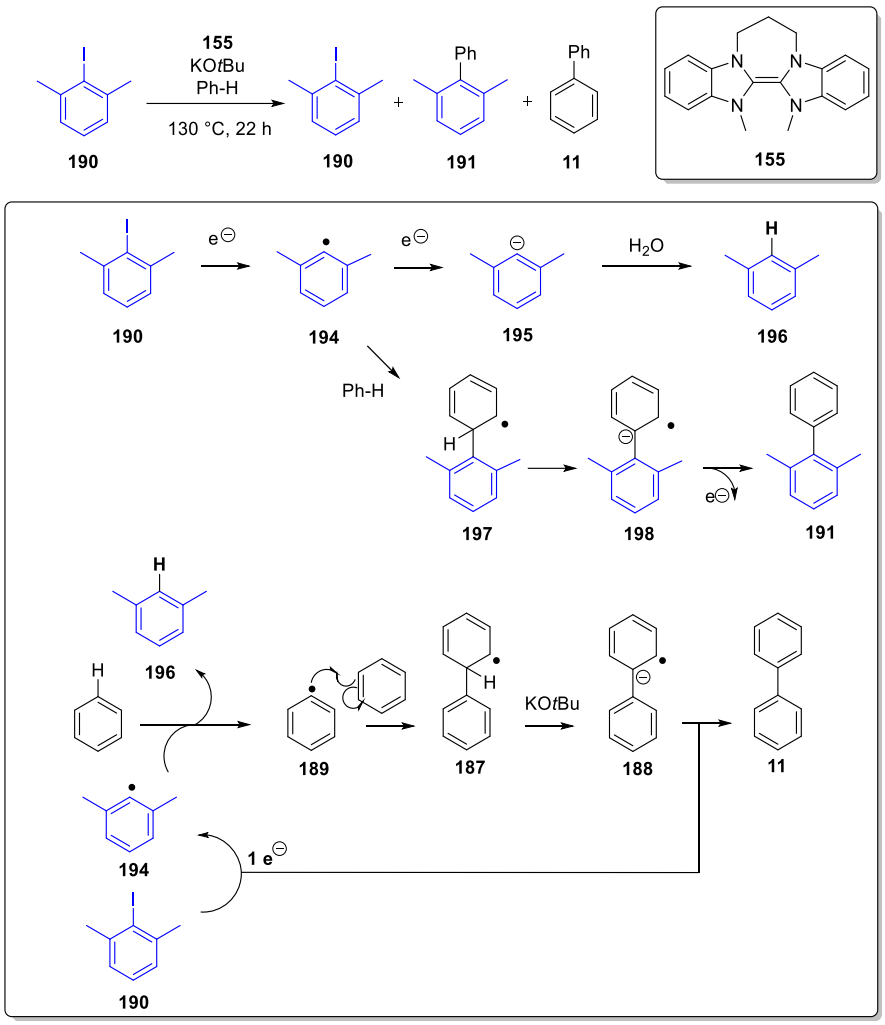
To prove the possibility that the benzyne initiation plays a crucial role in the "additive-free" cross-coupling reactions, the substrate iodo-*m*-xylene **190**, from which a benzyne intermediate analogous to **75** cannot form, was tested. As expected, when this substrate was reacted with KO*t*Bu in benzene, only a small amount (less than 0.5%) of mixture of coupled products, biphenyl **11** and 2,6-dimethylbiphenyl **191,** was observed (Scheme 44). This result supports the proposal of the benzyne-initiation process as well as the incapacity of KO*t*Bu to trigger a cross-coupling reaction from iodoarenes by direct electron transfer.



Scheme 44. No reaction was observed using iodo-*m*-xylene **190** as substrate.

In the literature, cross coupling of sterically congested aryl chlorides with heteroaromatics in the presence of the electron-rich Pd complex such as **193** has been reported (Scheme 44).[74] Therefore, it is likely that **190** undergoes coupling in the presence of appropriate Pd (or another transition metal) complexes. Since reagents are likely never to be completely free of Pd and other metals (even if the level might be ppb), we attribute the minute traces of coupled products in our reactions in the absence of organic electron donors to such contaminations.

The same reaction was repeated under the same conditions but in the presence of organic donor **155**. This reaction led to a fixed ratio of two coupled products which are representative for this substrate, 2,6-dimethylbiphenyl **191** (5%) and biphenyl **11** (19%), as well as to recovery of some starting material **190**. These interesting results show the capability of the *ortho*-disubstituted aryl halide to undergo cross-coupling reactions triggered by an additive; nevertheless, it shows also the somewhat low capability to couple with benzene. Logically, it would not be surprising that a process diverts in different pathways when very reactive species, such as radicals, are involved. The explanation for these interesting results, shown in Scheme 45, can be interpreted as described below.

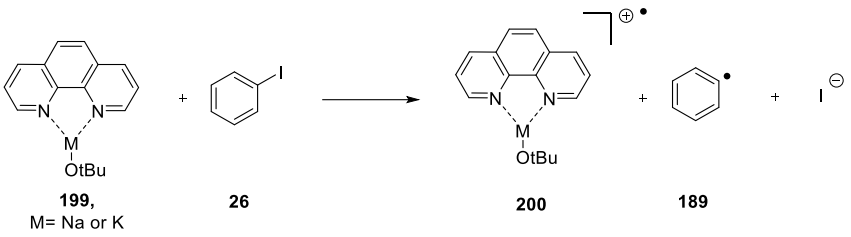


Scheme 45. Proposed mechanism for the formation of the two coupled products **191** and **11**.

The iodo-*m*-xylene **190** receives an electron from the electron donor **155** and then the radical species **194** can proceed through two different pathways. In one, radical **194** couples with benzene giving rise to the radical **197** and after deprotonation, radical anion **198**, which can propagate the process and promote the formation of 2,6-dimethylbiphenyl **191**. Secondly, the radical species **194** can abstract a hydrogen from benzene and form phenyl radical **189** which then follows the Studer and Curran mechanism[75] and forms biphenyl **11** as well as the volatile xylene **196**. Evidently, the second pathway progresses 3.5 times faster than the first pathway, likely because the radical species **194** is not an efficient coupling species due to its steric hindrance and then it prefers to abstract a hydrogen from the benzene and then generate the much more active coupling radical **189**. An interesting result is the constant ratio between

the two coupled products afforded using this coupling reagent; independently of the electron donor used, it is always ~3.5:1, with biphenyl **11** as the major product.

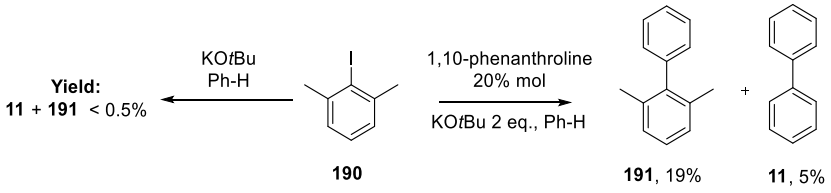
Analogously, further investigations were undertaken on the work described by Hayashi *et al*. in 2010.[50] Primarily, the thermodynamics for the electron transfer reaction between 1,10-phenanthroline complex **199** with alkali metal alkoxides and iodobenzene were evaluated (Scheme 46).



Scheme 46. Thermodynamics for this electron transfer for the reaction between 1,10-phenanthroline with alkali metal alkoxides and iodobenzene were calculated.

The calculated free energy change was found to be ΔG_{rel} = +63.9 kcal mol^{-1} for NaO*t*Bu and ΔG = +59.5 kcal mol^{-1} for KO*t*Bu.[72] These large values led the Murphy and Tuttle groups to conclude that the initiation step must involve the formation of other species instead.

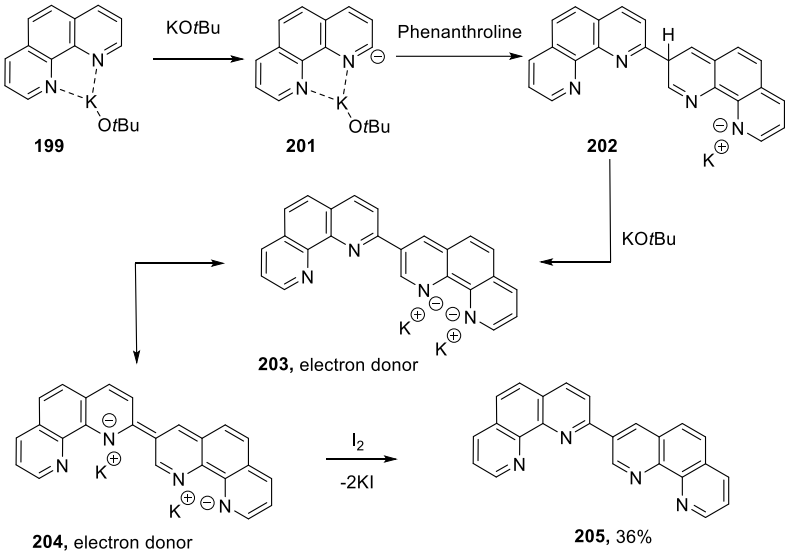
Therefore, a test of the coupling reaction between haloarenes and benzene under basic conditions using 1,10-phenanthroline as additive was performed. To avoid the benzyne-type process from occurring, iodo-*m*-xylene **190** was employed as shown in Scheme 47.



Scheme 47. The importance of the presence of an additive in metal-free cross-coupling reaction involving **190**.

Interestingly, the results obtained from this reaction mirrored the results displayed by the donor **155**. When phenanthroline was tested, a deep green-solid was afforded, and when this

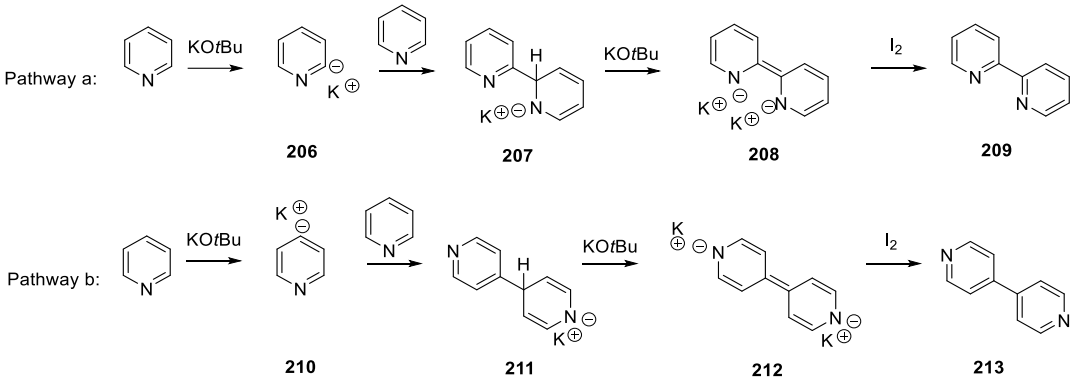
material was exposed to the air, it was very pyrophoric in a similar vein to the organic electron donors, *e.g.* **155** and **160**. To prove the actual formation of an electron donor, the reaction between phenanthroline and KO*t*Bu was repeated and quenched with iodine, an electron acceptor, affording 2,3′-bis-phenanthroline (**205**, 36%). Murphy *et al.* then proposed a possible mechanism for this observation, as shown in Scheme 48. The phenanthroline **199** undergoes deprotonation by KO*t*Bu, and the resulting anion then nucleophilically attacks a neutral phenanthroline to afford the species **202** which, after further deprotonation, forms **203** and, upon oxidation by iodine, gives rise to the dimer **205**. The dianion, **203**, proposed for this mechanism seems to have the canonical form of an active electron donor, whose charge can be delocalised through the entire molecule (**204**), starting from an electron-poor molecule **199**. The dianions **203** (= **204**) will then be able to promote the initiation step proposed by Studer and Curran, donating an electron to the iodoarene and triggering the radical cycle.[72]



Scheme 48. Formation of dimer **159** derived from the electron donor species **158**.[72]

With a similar approach, the conditions described by Charette[57] were evaluated and some tests were pursued. Thus, pyridine was reacted with KO*t*Bu and the reaction was quenched with iodine to afford 2,2′-bipyridine **163** and 4,4′-bipyridine **167**, as the major and minor products respectively. The mechanism proposed by Murphy *et al.* for the formation of the two products dealt with the possibility of deprotonation by the strong base in the two

positions, 2- (pathway a) and 4- (pathway b), of pyridine (see Scheme 49). The anions **206** and **210** then attack a neutral molecule of pyridine, and then further deprotonation affords the dianion species **208** and **212**, electron-rich molecules derived from the electron-poor pyridine. These species would be able to act as electron donors and promote the initiation step for the cross-coupling as has been seen with related electron donors. The quench with iodine allowed isolation of two different dimers **209** and **213**. Certainly, the low yield obtained from these test reactions can be explained by the fact that deprotonation of pyridine in the 2-position occurs more slowly (less favoured either kinetically or thermodynamically) than in phenanthroline, since the additive-base complex is stabilised by only one nitrogen with pyridine, whereas by two nitrogens with phenanthroline.[72]



Scheme 49. Pyridine dimerisation from which form the electron donors **208** and **212**.[72]

In light of these findings, the Murphy group investigated the possible role that aminoacids, alcohols and 1,2-diamines have in metal-free cross-coupling reactions. The approach used was fundamentally the same. Iodo-*m*-xylene **190** was selected as substrate to avoid benzyne initiation, and a series of neutral organic compounds, which act as precursors for electron donors, was selected and tested. As reported in a recent paper, Murphy *et al.* list many precursors that are effective for these types of transformations.[76] A short list is shown in Figure 4.

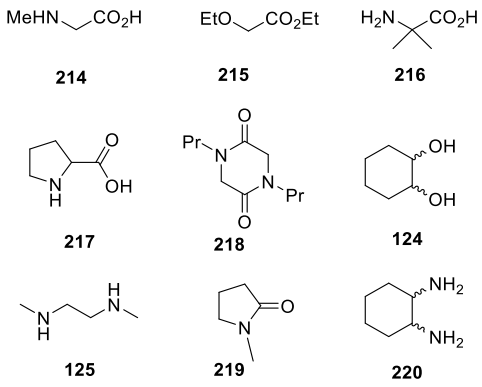
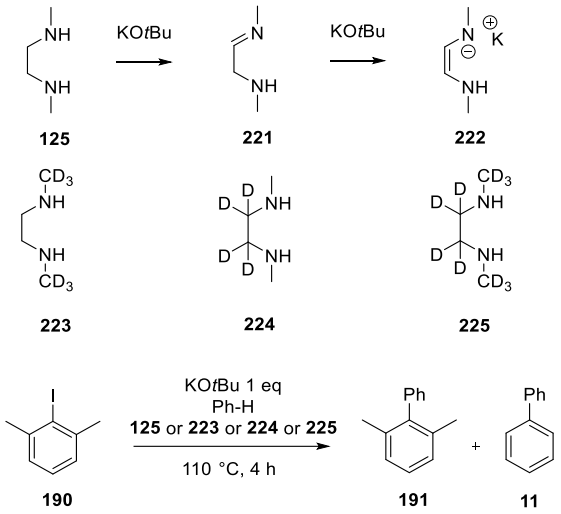


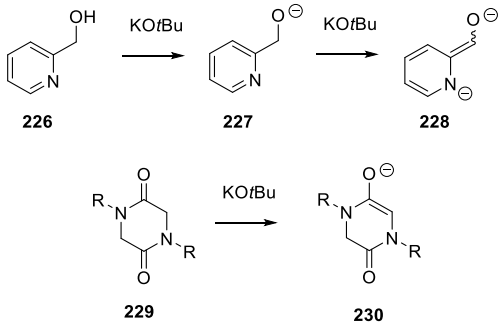
Figure 4. List of neutral compounds which act as precursors of electron donors.[76]

It was previously demonstrated by Koster *et al.* in 1972 that deprotonation of a diamine such as **125 (Scheme 50)** can occur with strong bases.[77] A compelling study has been done on the 1,2-diamine **125,** an organic precursor intensively studied also by Jiao *et al.* recently.[78] The mechanism proposed by Murphy for the electron donor formation from this precursor consists of formation of imine **221** through the loss of hydride (a possible rate-determining step) and this could undergo further deprotonation by the base to afford enamine salt **222**, an electron-rich candidate to act as electron donor for the initiation step. To prove the possible formation of the enamine **222**, polydeuterated analogs **223**, **224** and **225** were synthesised, with the hypothesis that if the mechanistic proposal was right, the presence of deuterium could retard the formation of the imine, due to the kinetic isotopic effect, and therefore retard the initiator formation. All the additives were tested side-by-side using identical and specific conditions. The reaction time was shortened to give just about half of the normal conversion when the unlabeled diamine **125** was used. The product yields agree, with the presence of a primary deuterium isotopic effect, such that the yields decrease in the order **125** > **223** > **224** > **225** (16%, 10%, 0.5%, traces, respectively).[76]



Scheme 50. Electron donor formation from 1,2-diamines and a study of its isotopomers.[76]

Once more, the Murphy group showed how the presence of a simple neutral precursor led to initiation in transition metal-free haloarene-arene coupling. A recent advance is the use of pyridinols such as **226**, which is a precursor of a very powerful electron donor **228,** able to initiate the cross-coupling very effectively.[79] Also structures such as the diketopiperazines **229** can act as initiators in transition metal-free haloarene-arene coupling in presence of KO*t*Bu.[80,81]



Scheme 51. Pyridinols **226** and diketopiperazines **229** as organic precursor of electron donors.[79–81]

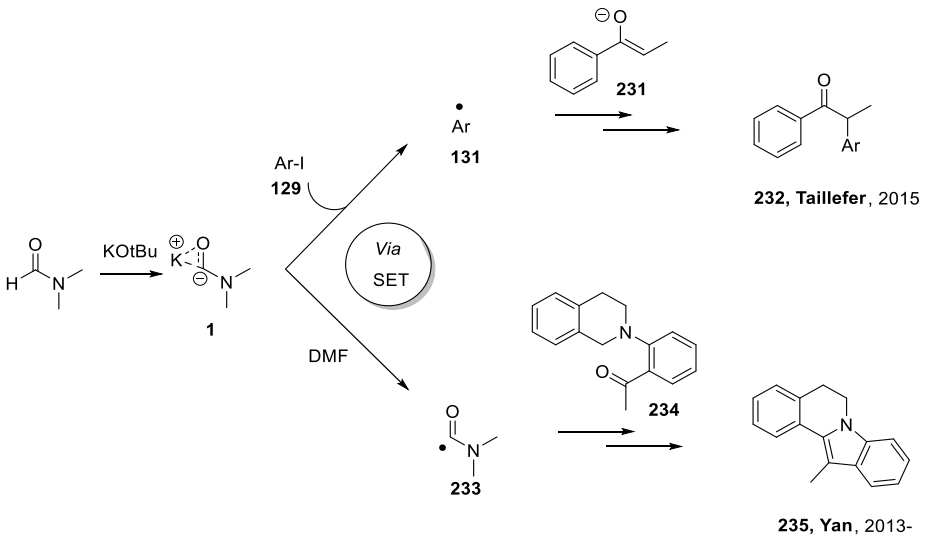
These recent reports of the Murphy group have a great resonance in the field of transition metal-free cross-coupling reactions. Since the first evidence about the possibility to trigger a

cross coupling reaction without the employment of transition metals, many points are becoming clearer. Despite the complexity of mechanism and the presence of many unresolved points, many scientists are convinced that the effectiveness (yield, selectivity etc.) obtained with a transition metal will be achieved by the use of transition metal-free conditions.

1.2.4 Recent Proposals on the Role of Alkoxides in Single Electron Transfer Reactions

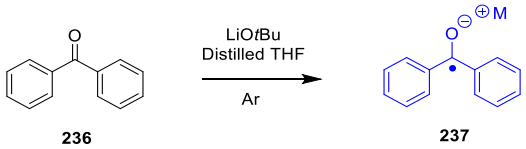
Following the investigation by the Murphy group into understanding the role of additives as possible organic electron donors in many types of reactions, in particular, on the transition metal-free base-induced cross-coupling reactions, many other works raised particular interests within the group.

The role of alkoxides in the field of single electron transfer reaction is still not well known from screening the different ideas reported in the literature. Recent publications address the use of KO*t*Bu in DMF for many different applications.[82–88] Many authors reported that this system is responsible of the formation of the carbamoyl anion **1** and proposed that this is directly responsible for SET reactions. Taillefer *et al.*, for example, proposed a direct electron donation from carbamoyl anion **1** to an aryl halide **129** to afford aryl radical **131**, which then triggers a particular radical process [87] (it will be shown later); on the other hand, many reports published by Yan *et al.* proposed that carbamoyl anion **1** donates an electron to neutral DMF to afford the DMF radical **233**, which then triggers the reaction [82] (it will be shown later). Nevertheless, to our knowledge, while the formation of the carbamoyl anion **1** has been reported,[89–91] no experimental support reported it acting as an electron donor.



Scheme 52. SET from carbamoyl anion as proposed be Yan and Taillefer.[82,87]

Some authors[88,92] proposed a direct electron transfer from the base referring back to the original proposal from Ashby.[93,94] In his hypothesis, alkoxides were capable of donating an electron to aromatic ketones such as benzophenone **236**; he observed the blue colour of the ketyl anion **237** and monitored radical formation by EPR spectroscopy.



Scheme 53. Formation of benzophenone ketyl radical anion **237** *via* SET proposed by Asbhy *et al.*[94]

The direct electron donation to iodoarenes from alkoxides ought to be an unlikely process. Jutand and Lei, recently, measured the oxidation potential of *tert*-butoxide anion (from KO*t*Bu) as +0.10 V vs. SCE in DMF[95] and showed by cyclic voltammetry that it does not directly reduce aryl halides (ArI, E^p = -2.0 V vs. SCE in DMF). Moreover the reduction potential of benzophenone **236** is also known in the literature $E^1_{½}$ = -1.78 V vs. SCE in DMF. [96]

With this premise, a deep investigation of the real role of KO*t*Bu in electron transfer reactions was pursued. In the following chapters, aims, results and discussions and proposal for future works will be discussed.

2 PROJECT AIMS

Preamble

In the following chapter, aims, results and discussion and future work will be found. The projects are divided as follows:

Macroproject A: the role of KO*t*Bu in electron transfer reactions;

Macroproject B: K^+ triumphs over Na^+ in electron transfer reactions.

Each macroproject is subdivided in projects; macroproject A includes 3 projects (A1, A2 and A3) whereas macroproject B includes 2 projects (B4 and B5).

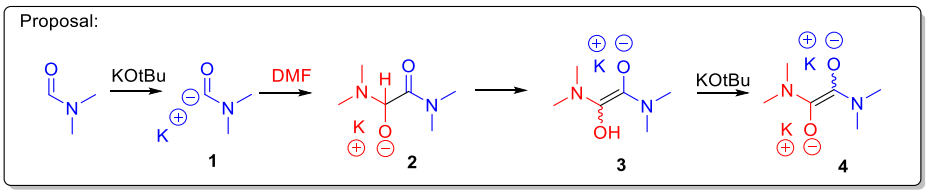
2.A Aims: the role of KO*t*Bu in electron transfer reactions

KO*t*Bu is a widely used reagent in electron transfer reactions. A lot of reports in the last decade cite KO*t*Bu as a facilitator in electron transfer reactions. However, a small number of chemists believe that KO*t*Bu can act as a direct electron donor towards substrates such as haloarenes and that it would trigger radical chemistry directly.

My studies aimed to find a clear answer to . Is KO*t*Bu only a facilitator or a direct electron transfer reagent in electron transfer reactions?

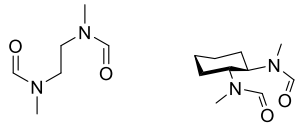
The reader will find different projects in which KO*t*Bu will be involved.

A1 The 1st project discloses the role of the system KO*t*Bu/DMF in electron transfer reactions. After the great exploration of the role of alkoxides with organic additives such as 1,10-phenanthroline and pyridine by the Murphy group,[72] the idea that this approach might apply also with DMF was investigated. In particular, if deprotonation of DMF occurs, as it has been previously demonstrated,[89–91] then carbamoyl anion **1** will act as a nucleophile to a neutral DMF.[97–99] Therefore the resulting anion **2** could give rise to an enolate-type species **3** which would act as electron donor; otherwise it can form the dianion **4**, after further deprotonation, an even stronger electron donor.



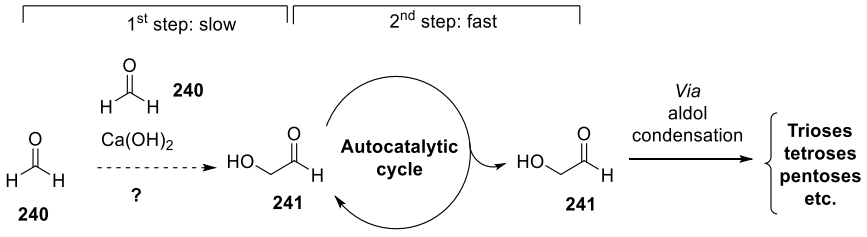
Scheme 54. DMF dimerisation promoted by KO*t*Bu and formation of the electron donors **3** and **4**.

This idea was supported by the fact that DMF carbamoyl anion **1** was previously found to act as a nucleophile, and promote different reactions to selected electrophiles.[97–99] To evaluate this idea, two different diformamides **238** and **239** were prepared and tested.



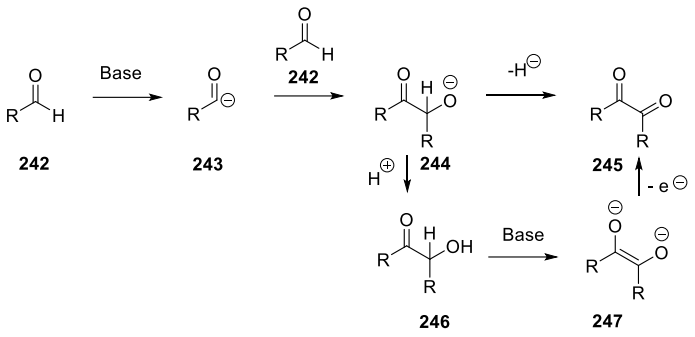
Scheme 55. Diformamides chosen to evaluate the dimerisation process.

A2 The 2nd project arose as a follow-up to the first project. After studying the deprotonation of diformamides, a new series of deprotonations was to be investigated. Particular attention was paid to non-enolisable aldehydes. Searching in the literature for the possible dimerisation of aldehydes, interestingly, many different topics were found to be related. In particular, in the fascinating hypothesis for which formaldehyde **240** is the keystone of the origin of life, the famous "formose reaction" is relevant (Scheme 56); in this process, carbohydrates are formed from formaldehyde dimerisation.



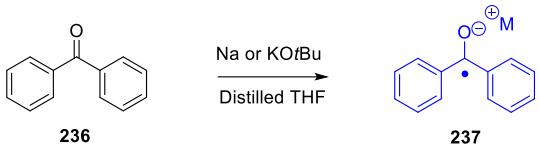
Scheme 56. The formose reaction proposed by Breslow.[100]

Many different theories on the first step have been proposed but the mechanism is still not resolved, and so the deprotonation of various non-enolisable aldehydes **242** with a strong base such as KO*t*Bu was to be explored.



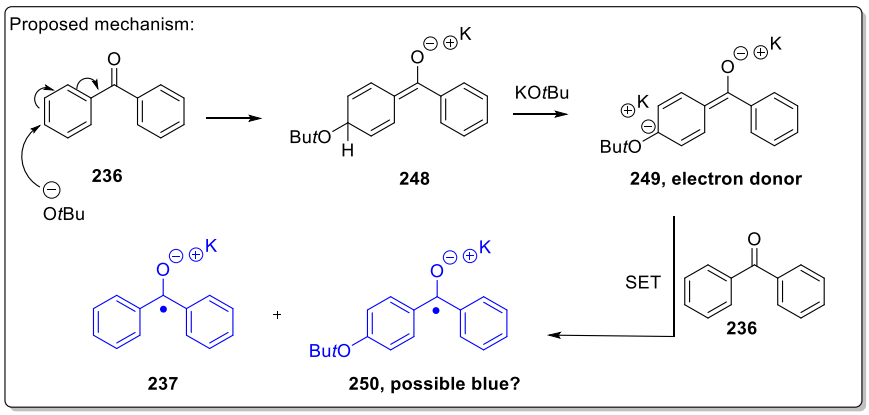
Scheme 57. Exploring the deprotonation of aldehydes **242** (counterions are omitted).

A3 In the 3rd project, the reduction of benzophenone **236** by alkali metals and alkali metal butoxides reported by Ashby *et al.* was to be explored.[93,94] In particular, it is known that the ketyl radical **237** forms by using alkali metals as reducing agents, giving a distinctive blue coloration of the solution (normally with distilled THF as solvent); nevertheless the proof for alkali metal butoxides acting as reducing agents lacks evidence.



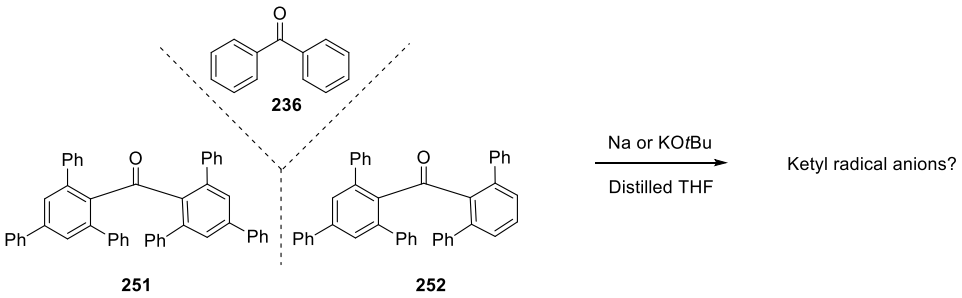
Scheme 58. Formation of ketyl radical **237** from benzophenone.

For this case another reactivity of KO*t*Bu was initially proposed, in particular, butoxide anion acting as a nucleophile attacking the *para*- or *ortho*- (not shown) position of benzophenone **9**. The resulting anion **248** can undergo further deprotonation to form the dianion **249**, which could act as an organic electron donor and donate an electron to benzophenone **236** to generate the ketyl radical anion species **237** and **250**.



Scheme 59. Proposed mechanism for generation of the enolate-type donor **249**.

Many different substituted benzophenones, such as **251** and **252** were to be prepared and tested, qualitatively and quantitatively, under different conditions.



Scheme 60. Evaluating the reduction of benzophenone and benzophenone derivatives **251** and **252**.

2.B Aims: K^+ triumphs over Na^+ in electron transfer reactions

The role of MO*t*Bu in the BHAS cycle is well represented in the literature. Its capability of triggering the process has been widely discussed in the introduction. A few reports consider NaO*t*Bu as a valid supporter in such a mechanism, but not enough to compete with the KO*t*Bu primacy. The second part of the Results and Discussion will explore an unprecedented case where KH is capable of triggering the BHAS cycle and some new

behaviour of KO*t*Bu in electron transfer reactions. Two other examples where K^+ triumphs over Na^+ will be given alongside the project discussions.

B4 The 4th project is an evaluation of the properties of KH in electron transfer reactions, in particular KH was found to promote radical processes with benzene as solvent, whereas NaH was ineffective. An accurate understanding of the role of KH with different haloarenes will be explored.

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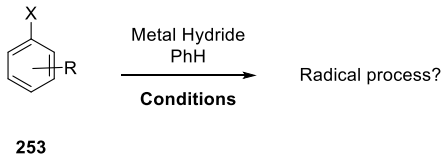
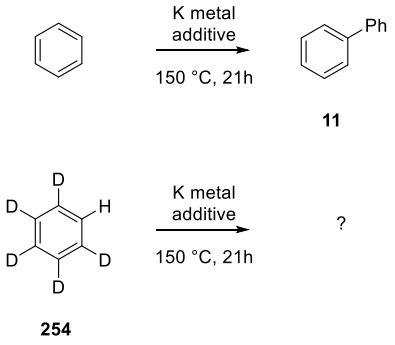


Scheme 61. KH mediated reactions of haloarene **253**.

B5 The 5th project speaks about the reduction of benzene and its reductive coupling. The role of alkali metal cations will be explored. In particular, different additives will be screened and a mechanistic study will be performed.



Scheme 62. Reductive coupling of benzene by the synergic activity of K metal and an additive.

3 RESULTS AND DISCUSSION

In this chapter, all the various projects **A** and **B** are presented. Every part (background, strategy, discussion of the results and conclusion and future work) of each project (**1**-**5**) will be shown subsequently.

3.A THE ROLE OF KO*t*BU IN ELECTRON TRANSFER REACTIONS

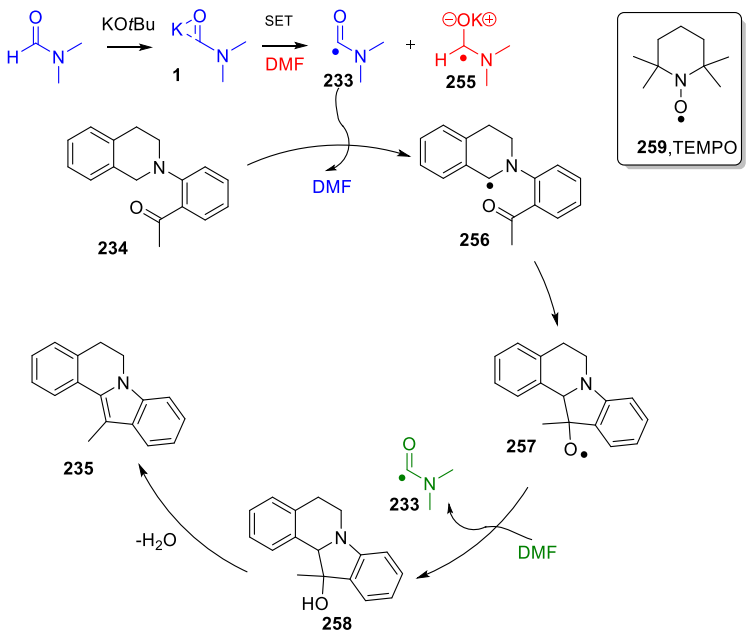
The use of alkoxides of alkali metals as powerful bases has always been widespread, however, in the last decade, alkoxides (mainly KO*t*Bu) have been employed in electron transfer reactions for the first time.[47–50,55,56,92,95,101] This led to controversial ideas of the role played by these bases. Most of the reports in the literature consider KO*t*Bu as a facilitator in electron transfer reactions; for instance, the base acts as a promoter for the formation of organic electron donors which trigger and propagate the BHAS mechanism. When the initiation process for this transformation was still unknown, many chemists started to believe that KO*t*Bu could itself act as an electron donor towards haloarenes. This idea arose from some observations reported by Ashby in 1981.[102] He believed that amides and alkoxides of alkali metals could reduce benzophenone by direct SET. This project now re-examines the role played by KO*t*Bu in electron transfer reactions, offering a new example where the base acts as a promoter for this transformation and, finally explains Ashby's observation unmasking the "urban legend" in which KO*t*Bu is believed to act as an electron donor to benzophenone.

3.A1 The Formation of Organic Electron Donors by Dimerisation from Formamides in the Presence of KO*t*Bu

3.A1.1 Background

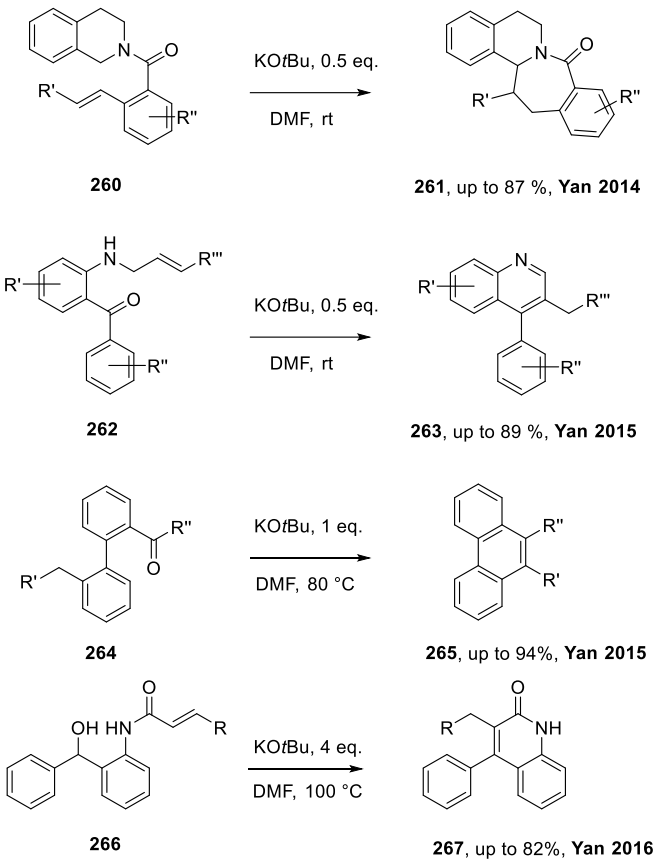
The literature presents a wide collection of reactions promoted by KO*t*Bu in DMF (as solvent) with regard to C-C bond formation, where similarities with our group's previous work led to our interest in these reactions.

The Yan group reported, in the past few years, a series of new applications of the KO*t*Bu-DMF system, such as an interesting new synthesis of indole derivatives *e.g.* **235** (Scheme 63). They reported an intramolecular dehydrative coupling of tertiary amines and ketones promoted by the proposed complex carbamoyl anion **1**. Deprotonation of DMF by a strong base such as LDA and KO*t*Bu has been previously reported.[89–91] Yan proposed that the carbamoyl anion **1** promotes the formation of DMF radical **233** *via* single electron transfer to a neutral DMF molecule. The DMF radical **233** abstracts a hydrogen atom from the carbon α to the nitrogen in substrate **234** and the radical species **256** generated, then attacks the carbonyl leading to a new radical species **257**. This then abstracts another hydrogen atom from neutral DMF and propagates the process, whereas the intermediate **258** undergoes elimination of water to afford product **235**.[82] Their explanation for a radical process was only based on the fact that the reaction is inhibited in the presence of either molecular oxygen or radical scavenger TEMPO **259**. Nevertheless, since no radical intermediates were trapped or isolated in the experiment with TEMPO, no radicals were proven to be involved in the reaction.



Scheme 63. Mechanism proposed by the Yan group.[82]

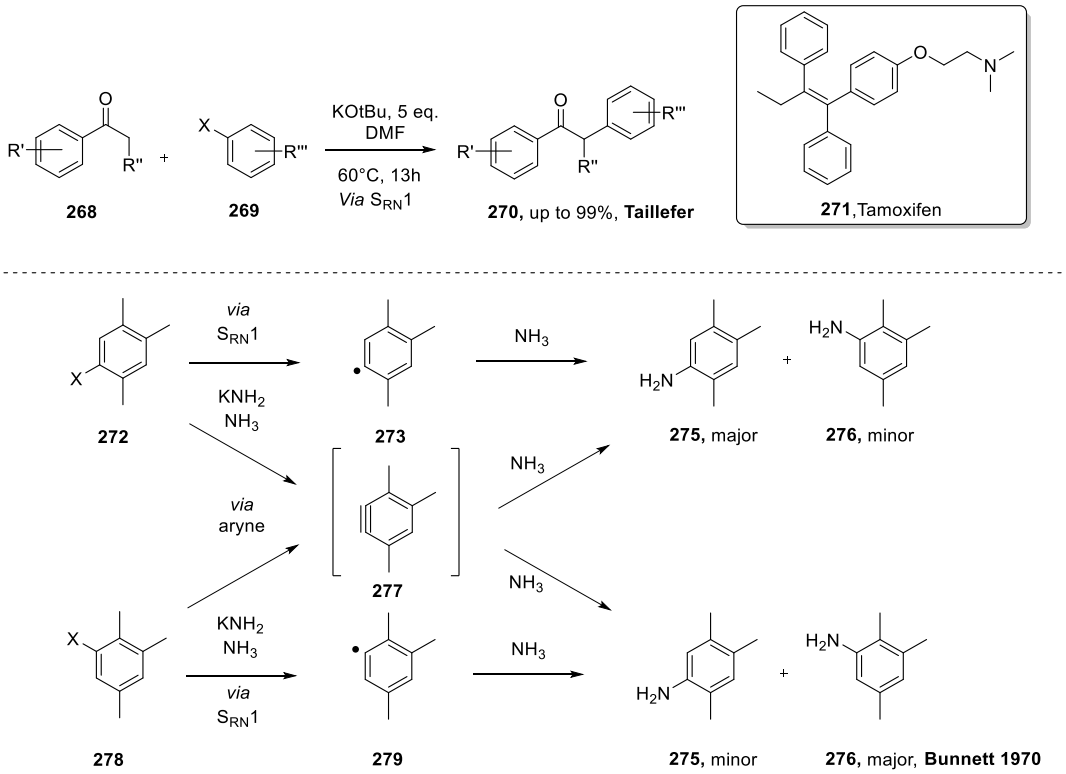
The Yan group, moreover, discovered that this system works also for the synthesis of 4-arylquinolines **263** [84] or tetrahydroisoquinoline derivatives **261**.[83] More recently they reported the ability of KO*t*Bu-DMF to promote intramolecular cyclisation of 1,1'-biphenyl aldehydes and ketones **264** to afford phenanthrenes **265** as well as intramolecular cyclisation of diarylmethanols and α,β-unsaturated amides *e.g.* **266** to afford 3,4-disubstituted quinolinones **267**.[85,86] Mechanisms were proposed for these transformations that feature radical intermediates; however, they will not be further discussed here.



Scheme 64. Some recent applications of the KO*t*Bu-DMF system proposed by Yan.[85,86]

An interesting study, published by Taillefer *et al.* in 2015,[87] disclosed a new example of transition metal-free α-arylation of enolisable aryl ketones **268** via $S_{RN}1$ (Radical-Nucleophilic Aromatic Substitution) mechanism. An application of this new method was the synthesis of large molecules like Tamoxifen **271** in only 3 steps and in 62% overall yield. The α-arylation of enolisable aryl ketones via $S_{RN}1$ was discovered in 1970 by Bunnett and Kim when they subjected 5- and 6-halopseudocumenes **272** and **278** to KNH_2 in liquid ammonia (Scheme 65). Bunnett and Kim observed formation of a mixture of products **275** and **276** with the *ipso*-substituted compounds as major product, according to the starting material used. The presence of both regioisomers indicates that an aryne intermediate **277** plays a role, but since the ratio is different than 1:1 at about 1.5:1, then a new mechanism likely competes with the aryne chemistry. Further studies on the exchange of halogen led them to rule out an S_NAr mechanism, inasmuch as iodoarenes are somewhat less reactive than the corresponding bromides and chlorides, whereas Bunnett and Kim noticed a better

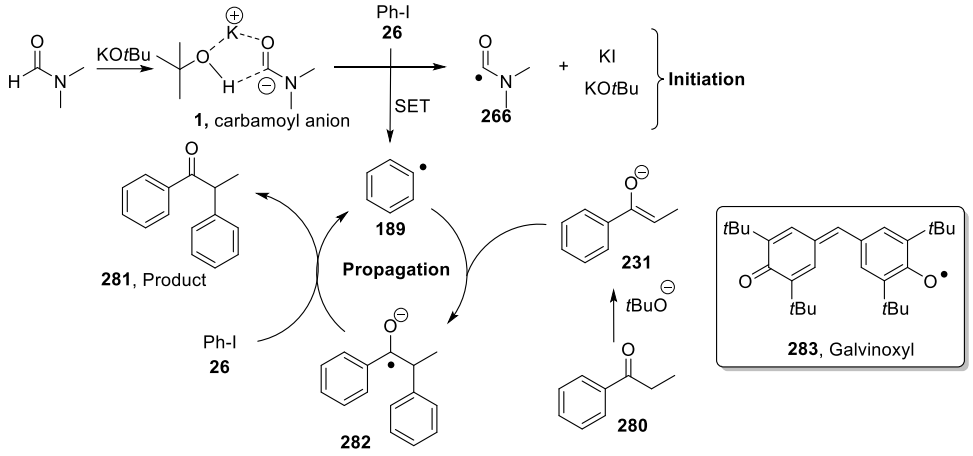
reactivity with iodo-substrates which would suggest a radical character of the process. Moreover, when they used radical scavengers such as tetraphenylhydrazine, the product ratio shifted towards the typical aryne ratio 1:1.[103] A few years later, Bunnett and Rossi reported that numerous ketones including acetone can be arylated in moderate to high yields.[104]



Scheme 65. $S_{RN}1$ examples reported by Taillefer and Bunnett.[87]

When Taillefer *et al.* performed a screening of organic solvents for this reaction, DMF was found to be unique in promoting this reaction. They proposed that the reaction proceeds *via* a radical process because the reaction was completely inhibited by radical scavengers such as galvinoxyl **283** and TEMPO **259**; nevertheless, they did not mention any radical intermediate trapped with the scavengers. Moreover, an alternative benzyne-mediated process was ruled out, since no regioisomers of the products were detected with substituted-iodobenenzene. With this perspective, Taillefer *et al.* suggested a possible mechanism for this transformation, supported exclusively by computational studies.[87] In this case they proposed that carbamoyl anion **1,** complexed and stabilised by the cation K^+ and *t*-butanol, behaves as an electron donor to iodobenzene **26**, generating iodide ion and phenyl radical

189 via $S_{RN}1$. The radical species couples with enolate **231** to generate the radical anion **282** which propagates the radical chain, giving rise to the α-phenylketone **281**.[87]

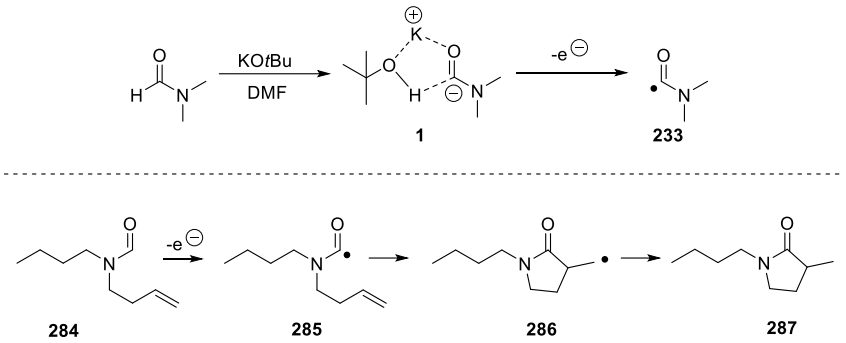


Scheme 66. Mechanism proposed by Taillefer.[87]

They used DFT calculations to evaluate their hyphothesis. However, the relative energies for two consecutive steps (ΔE_{rel} = 13.16 kcal mol^{-1} for the deprotonation and ΔE_{rel} = 15.86 kcal mol^{-1} for the SET) indicates that the reaction is thermodynamically unfavourable. From their study, the stabilisation of the carbamoyl anion **1** with *t*-butanol through hydrogen bonding is deduced to be favoured by the synergic effect of the cation K^+.[87] The direct electron donation by the carbamoyl anion **1** lacks evidence in the literature. The same Taillefer asserted his theory only by computational studies and therefore, a valid experimental investigation of the KO*t*Bu-DMF system was warranted.

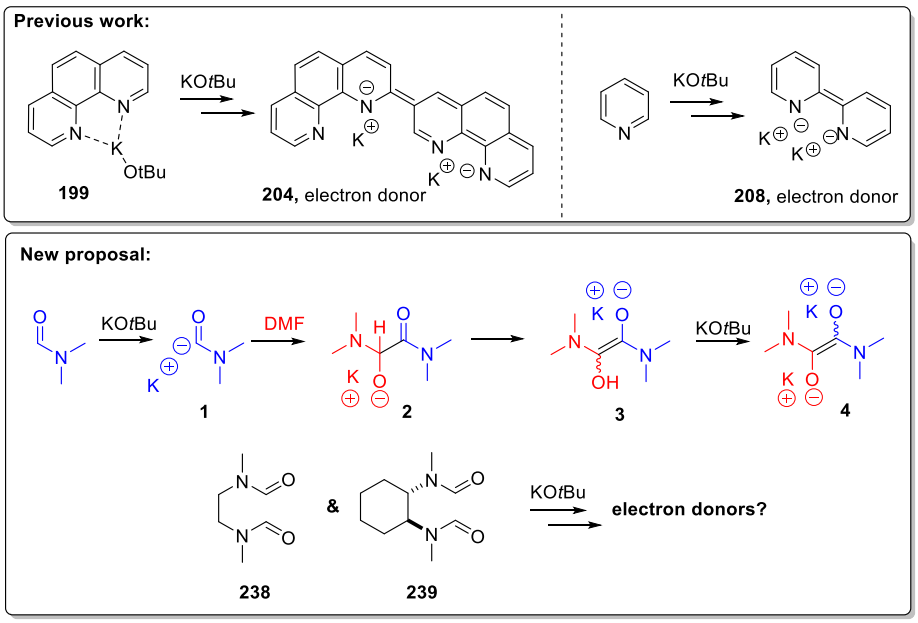
3.A1.2 Project strategy

The starting point was to design a trapping experiment for carbamoyl anion **1**, with the idea that if **1** donates an electron to a substrate, then the unpaired electron ought to be very reactive and cyclise intramolecularly with an alkene moiety of the test compound **284**, as shown in Scheme 67 and then afford the lactam **287**.



Scheme 67. Idea to probe Taillefer's mechanism.

Moreover, to check whether dimerisation of DMF anions can lead to an electron donor, in a similar vein to the dimerisation of 1,10-phenanthroline and pyridine to give the dimers **204** and **208**, different experiments were planned with DMF and diformamides **238** and **239**, to evaluate the effectiveness of this proposal. At a given concentration of diformamide, the formation of the electron donor should occur more easily with the diformamides rather than with twice this concentration of DMF, since the process occurs intramolecularly. Moreover, the more conformationally restricted diformamide **239** should be even more effective compared to the linear **238**.



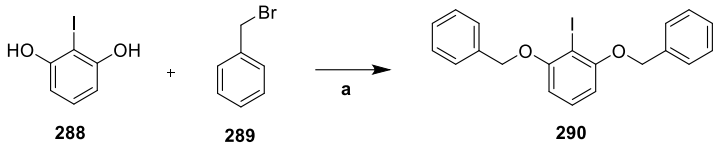
Scheme 68. Comparison between the previous work,[72] the new proposal and linear diformamide **238** and cyclic diformamide **239** as plausible electron donor precursors.

3.A1.3 Results and discussion

1. Investigation of the model reactions with KO*t*Bu and DMF

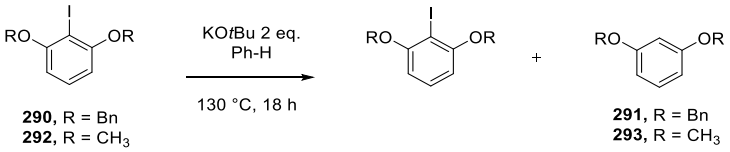
A series of reactions with different substrates was performed and the efficiency of KO*t*Bu in DMF, as a possible precursor to an organic electron donor, was evaluated.

2,6-Dibenzyloxy-1-iodobenzene **290** was prepared by reacting 2-iodoresorcinol **288** with benzyl bromide **289** in the presence of potassium carbonate as shown in Scheme 69.



Scheme 69. a. K_2CO_3**,** DMF, argon, 80 °C, 18 h, 66% yield.

The strategy adopted for these tests consisted of reacting substrates **290** and **292** with KO*t*Bu (2 eq.) with only a small amount of DMF (normally 1% v/v with the solvent) in benzene as solvent at 130 °C for 18 h. These conditions are equivalent to those used with cross-coupling reactions in the presence of additives in previous work from the Murphy group.[76]

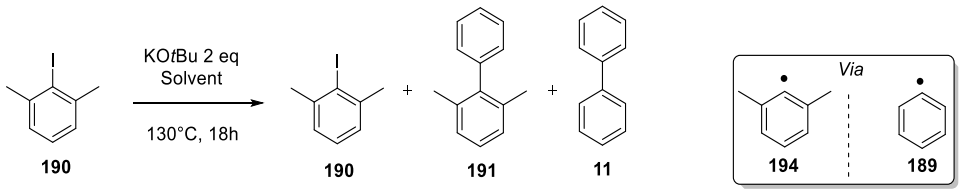


Entry	Substrate	Additive		Product 291 or 293 (%)
1	**290**	DMF	1% v/v[a]	80
2	**290**		-	10
3	**292**	DMF	1% v/v[a]	79
4	**292**		-	9

Table 4. The yields have been calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard. [a] Relative to benzene (v/v) as solvent.

The KO*t*Bu-DMF system was revealed to be very effective in reducing substrates **290** (Entry 1, Table 4) and **292** (Entry 3). The reaction in the absence of DMF gave rise to a low percentage (~10%) of the reduced product (Entries 2,4). Nevertheless, the deiodination of these iodoarenes is quite easy to achieve owing to the inductive effect *+I* of the two –OR substituents which allows the antibonding σ* orbital of the C-I bond to accept an electron quite readily. Moreover, the deiodination is a favourable process due to the steric release. On the other hand, the cross-coupling does not occur because of the steric hindrance of the substituents.

Afterwards, iodo-*m*-xylene **190** was tested to evaluate the cross-coupling efficiency of the KO*t*Bu-DMF system. This substrate possesses two relatively small substituents, facilitating the cross-coupling reaction and avoiding the benzyne mechanism at the same time. Therefore, the coupling products come only from the formation of the aryl radicals **194** and **189** (the mechanism that leads to the formation of the coupled products has been previously shown, Scheme 43 Chapter 1.2.3). Although the KO*t*Bu-DMF system is not very effective in triggering cross-coupling reactions, certain amounts of the typical coupled products **191** and **11**, obtained using an additive, were detected, in their typical ratio ~3.5:1 (Entry1, Table 5). The blank reaction also showed traces of coupled products, probably due to small traces of transition metal species present in the reaction (Entry 2).



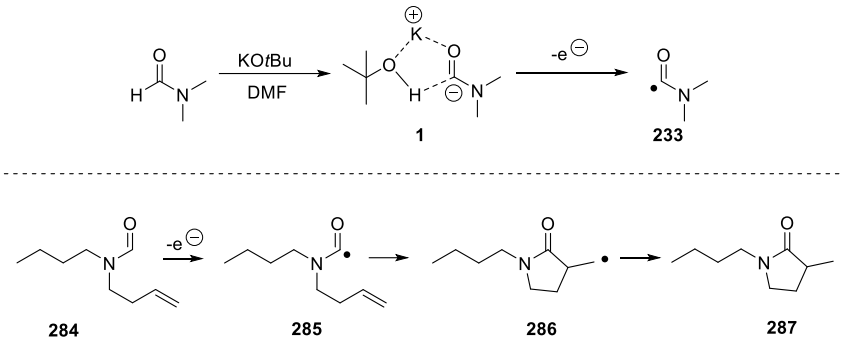
Entry	Solvent	190 (%)	191+11 (%)
1	Ph-H 99%, DMF 1%	51.5	2.8
2	Ph-H 100%	65.1	0.5

Table 5. The yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

A small activity of the system KO*t*Bu-DMF was therefore detected. The following study wants to test whether the mechanism proposed by Taillefer can be experimentally confirmed or not.

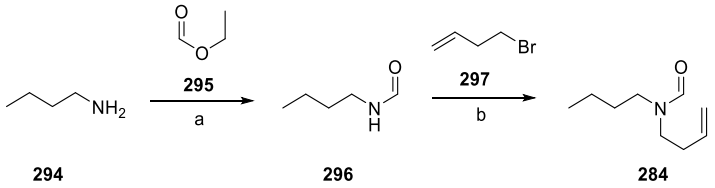
2. Investigation of the formation of DMF radical

The formamide bearing an alkene moiety **284** (see Scheme 70) was tested since if the carbamoyl anion **1**, formed after deprotonation by KO*t*Bu, donates an electron to a generic substrate, then the radical **285** (analogous to the radical **233**) ought to react with the alkene moiety to afford cyclised product **287**.



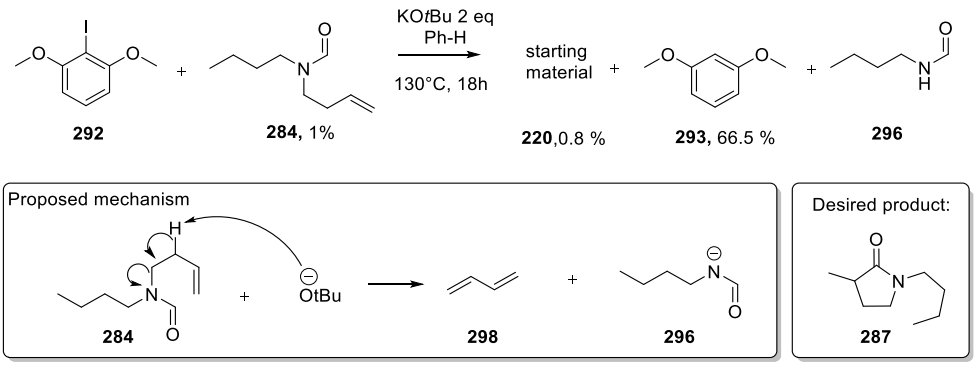
Scheme 70. Idea to probe Taillefer's mechanism.

A two-step route was applied to synthesise *N*-but-3-enyl-*N*-butylformamide **284**. At first, *N*-butylformamide **296** was obtained by reacting butylamine **294** with ethyl formate **295**. In the second step, **296** was reacted with 4-bromobut-1-ene **226** (Scheme 71).



Scheme 71. A. argon, 110 °C, 4 h, 89 % yield. B. NaH, toluene, argon, reflux, 16 h, 45 % yield.

The 2,6-dimethoxyiodobenzene **292** was chosen as a substrate for the test with **284**, whose concentration was kept at 1%. A similar deiodination was observed, but the formation of a secondary amide **296** was seen instead of the expected cyclised amide **287**. The blank reaction in the absence of the iodo-substrate **292** also showed formation of secondary amide **296**. The explanation for this result could be an E_2 elimination to form amide **296** and the volatile butadiene **298** as shown in Scheme 72.

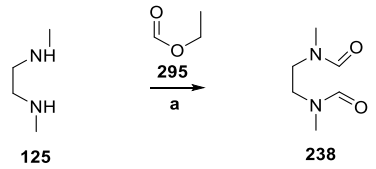


Scheme 72. Test reaction using the formamide **284** instead of DMF. Proposed mechanism for the formation of secondary amide **296** formation.

Despite the first non-positive results, the study went further and two different diformamides **238** and **239** were prepared.

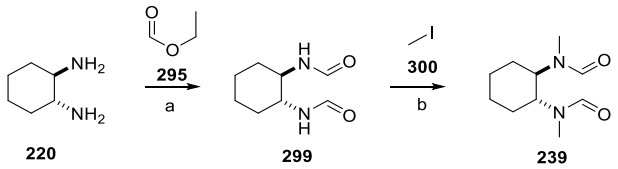
3. Investigation with diformamides

For the synthesis of the linear diformamide *N*,*N*′-(ethane-1,2-diyl)bis(*N*-methylformamide) **238**, *N*,*N*′-dimethylethylenediamine **125** was simply reacted with ethyl formate **295** as both solvent and reactant of the reaction (Scheme 73).



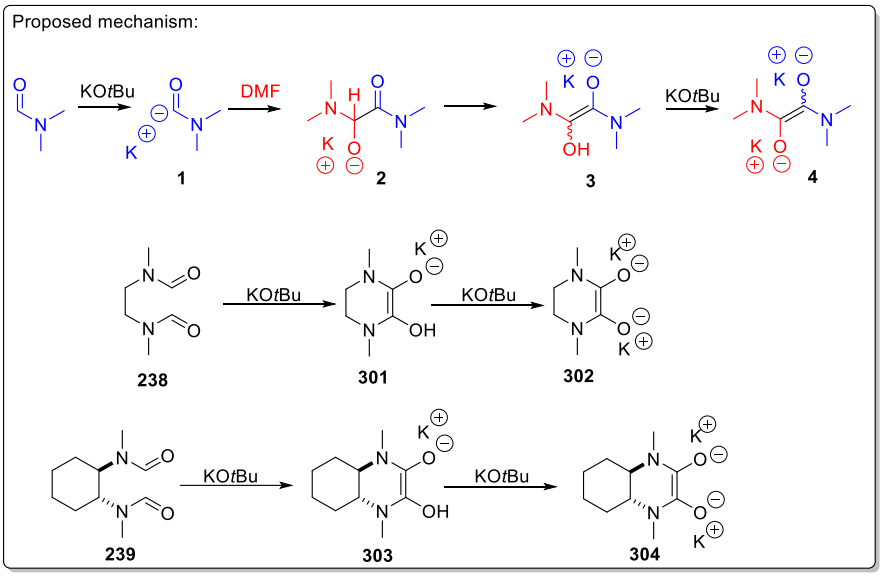
Scheme 73. a. argon, 50 °C, 16 h, 91% yield.

The cyclic diformamide *N*,*N*′-[(±)-*trans*-cyclohexane-1,2-diyl]diformamide **191** was synthesised in a similar way, by reacting (±)-*trans*-1,2-diaminocyclohexane **228** with ethyl formate **295**, and then **299** was methylated by using methyl iodide **300** in the presence of sodium hydride (Scheme 7).



Scheme 74. A. argon, 50 °C, 16 h, 84 % yield. B. NaH, toluene, argon, reflux, 16 h, 83 % yield.

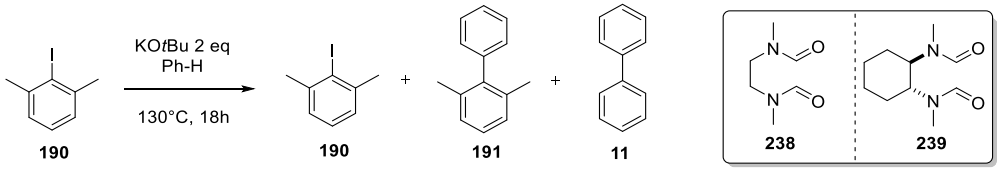
The idea, as mentioned before, was to evaluate whether dimerisation of DMF occurs, in a similar vein to the proposed dimerisation of 1,10-phenanthroline and pyridine,[72] which then could trigger BHAS reactions.[87] The mechanism proposed for the formation of the electron donor starts with the deprotonation of DMF by KO*t*Bu, as suggested also by Knochel,[91] Yan,[82–86] Taillefer,[87] and Reeves.[89,90] The DMF-derived anion is known to be a nucleophile,[97,99] therefore it adds to a neutral DMF to form the anion **2**, as shown in Scheme 75. Proton transfer affords the enolate **3**, which is a candidate electron donor; alternatively, further deprotonation affords the dianion **4**, likely to be an excellent electron donor. The diformamides **238** and **239** will follow the same fate, leading to anionic electron donors **301** and **303**, or to the even more powerful dianionic electron donors **302** and **304**.



Scheme 75. Formation of organic electron donors from DMF, **238** and **239** mediated by KO*t*Bu.[1]

Once again, iodo-*m*-xylene **190** was chosen as substrate. The strategy adopted for these new tests consisted in the comparison reactions between a fixed concentration of diformamide **238** or **239** and twice this concentration of DMF. When the amount of DMF was 0.1 mmol (Table 6, entry 3) a trace amount of biaryls **191** and **11** was formed (0.6%). However, under the same reaction conditions using linear diformamide (0.05 mmol, 0.1 equiv., entry 4), a very clear increase in the yield of biaryls was seen (8.0%), whereas the more

conformationally restricted diformamide provided 16.1% of biaryl products (entry 5). At 110 °C for 4 h and using an increased amount of additive (1% DMF, 0.5% for the two formamides), a similar trend of an increased quantity of biaryls was observed when switching from DMF to linear diformamide **238** (entries 6 and 7). A further increase in biaryl yield was observed when cyclic diformamide **239** was used (entry 8).

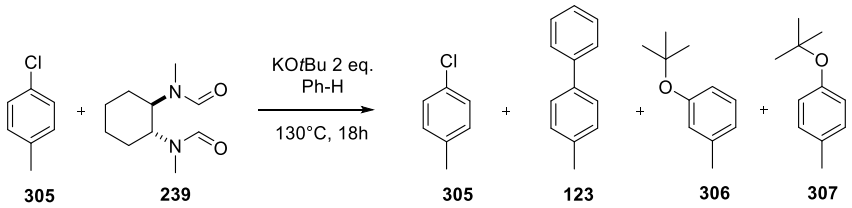


Entry	Additive	190 (%)	191+11 (%)[d]
1[a]	none	65	0.5
2[a]	DMF (1%[c])	84	2.8
3[a]	DMF (0.1 mmol)	95.5	0.6
4[a]	**238** (0.05 mmol)	59.4	8.0
5[a]	**239** (0.05 mmol)	55.4	16.1
6[b]	DMF (1%[c])	85	0.4
7[b]	**238** (0.5%[c])	trace	19.6
8[b]	**239** (0.5%[c])	trace	31.6

Table 6.[a] Iodo-*m*-xylene (0. 5 mmol), 1 mmol KO*t*Bu, benzene as solvent, 130 °C, 18 h. [b] reaction at 110 °C, 4 h. [c] Relative to benzene (v/v) as solvent. d The yields have been calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard. The sum of the yields of both coupled products is reported.[1]

Afterwards, the reducing power of the diformamide **239** in the presence of KO*t*Bu was investigated, as well as the importance of the base used. When *p*-chlorotoluene **305** was tested with the same conditions mentioned above with 0.2 eq. of additive **239** (Table 7, Entry

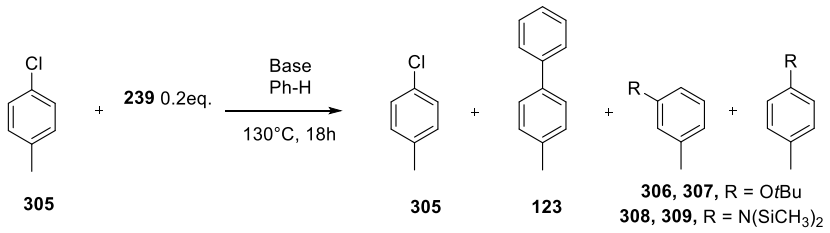
1), only 6.8% of 4-methylbiphenyl **123** was obtained; however, this result mirrored the expectation since the chloroarenes **305** are much more difficult to reduce, compared to the iodoarenes. Furthermore, small amounts of butoxide anion addition products (**306** and **307**) were found, which suggests that a benzyne-type reaction was occurring. The reaction in the absence of additive (Entry 2) showed no coupled product, but a larger amount of butoxide anion-derived products (**306** and **307**).



Entry	Additive 239	305 (%)	123 (%)	306+307 (%)
1[a]	0.2 eq.	7.8	10.0	1.2
2[b]	no	25	no	16.8

Table 7. [a]The reactions were performed using substrate 0.5 mmol, base (1 mmol) diformamide as additive (0.1 mmol), benzene 5 mL.[b] reaction in absence of additive. The yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

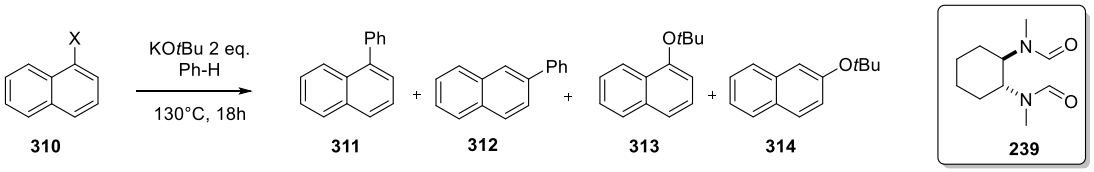
When different bases were tested in the presence of diformamide **239** and 4-chlorotoluene **305**, the first result that stood out was that the coupled product **123** was afforded only in the reaction with KO*t*Bu, whereas a great amount of benzyne by-products **308** and **309** were found when KHMDS was used and only starting material **305** was returned when NaH was employed. The addition of hexamethylsilazide anion to haloarenes *via* a benzyne reaction was previously demonstrated by Rakhlin.[105]



Entry	Base	R=	305 (%)	123 (%)	Benzyne byproducts (%)
1[a]	KO*t*Bu	-O*t*Bu	7.8	10.0	1.2
2[a]	KHDMS	-N(SiCH$_3$)$_2$	n.d.	n.d.	50.4
3[a]	NaH	H	34.5	n.d.	n.d.

Table 8. [a]The reactions were performed using substrate 0.5 mmol, base (1 mmol) diformamide as additive (0.1 mmol), benzene 5 mL. The yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

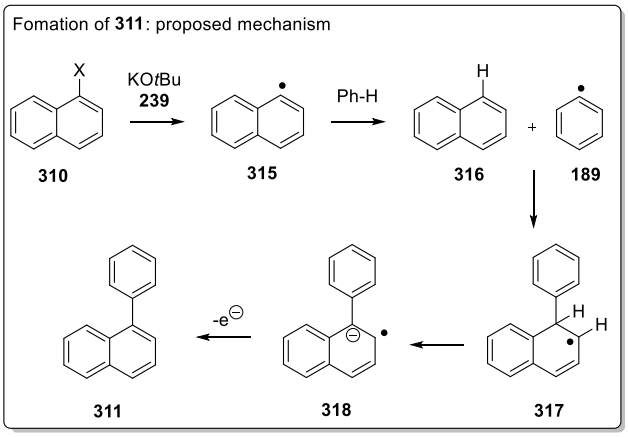
The halonaphthalenes **310** were also tested under the same conditions. These results were consistent with the observation that iodonaphthalenes are much easier to reduce, compared to the chloro derivatives. Moreover, the presence of the additive **239** promoted the arylation reaction (entry 1 and 3, Table 9); otherwise the main products were found to be butoxide anion addition products **313** and **314** to the corresponding naphthalyne (Entries 2 and 4) in the absence of additive **239**.



Entry	X	Additive	310 (%)	311 (%)	312 (%)	313+314 (%)[d]
1[a]	I	**239**	n.d.	61	trace	trace
2[b]	I	none	n.d.	24.4	n.d.	16.6
3[a]	Cl	**239**	trace	41[c]	3[c]	trace
4[b]	Cl	none	35.5	n.d.	n.d.	42.9

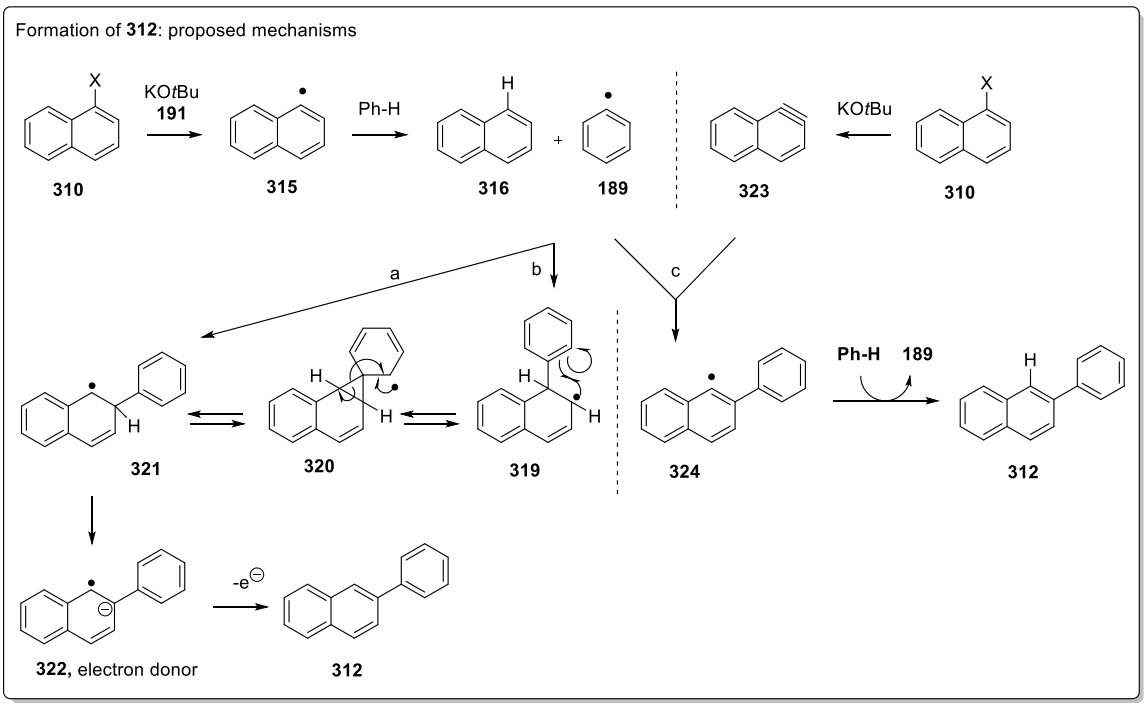
Table 9. [a]The reactions were performed using substrate 1.0 mmol, diformamide as additive 0.1 mmol, benzene 5 mL.[b] The reaction have been performed in absence of additive.[c] Yields calculated by isolation. [d] Yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

A possible explanation for the formation of the coupled product **311** is shown in Scheme 76. The halonaphthalene **310** receives firstly an electron from the donor formed by KO*t*Bu and **239** to afford naphthyl radical **315**. This abstracts a hydrogen from benzene to afford naphthalene **316** (a C-C bond formation would be more difficult to happen due to the *peri*-hydrogen) and radical **189** which couples with naphthalene to afford radical **317**. Species **317** then undergoes deprotonation to afford the new electron donor **318**, giving rise to 1-phenylnaphthalene **311**, after electron loss.



Scheme 76. Proposed mechanism of the formation of **311**.

Product **312** can form *via* 3 different pathways (Scheme 77). Radical **189** could attack the 2-position of naphthalene leading to radical **321** directly (pathway a); alternatively, it could attack the 1- position of naphthalene and form radical **319** (pathway b). The new C-centered radical **319** could add to the *ipso*-carbon of the phenyl ring to form the spiropolycycle **320**. This then rearranges to the new radical species **321**, driven by the aromatisation of the phenyl. The new radical species **321** undergoes further deprotonation to afford the new electron donor **322**, giving rise to 2-phenylnaphthalene **312**. Alternatively, α-naphthalyne **323** could form via deprotonation on the 2 position. Phenyl radical **189** would then attack **323** and form radical **324** (pathway c) which would abstract an hydrogen from benzene and form the product **312**. Previous studies on α-naphthalyne by Bunnett revealed that the nucleophilic additions on the 2-position is 2 times more favoured than the 1-position.[106]



Scheme 77. Proposed mechanisms a, b and c that could explain the formation of **312**.

After this first exploration with formamides, a new study with different aldehydes was carried out.

KO*t*Bu promotes the *in situ* formation of a strong organic electron donor from the hitherto unlikely precursor, DMF.[1] A mechanism is proposed that is consistent with other mechanisms recently used to explain the formation of organic electron donors triggered by reactions of KO*t*Bu.

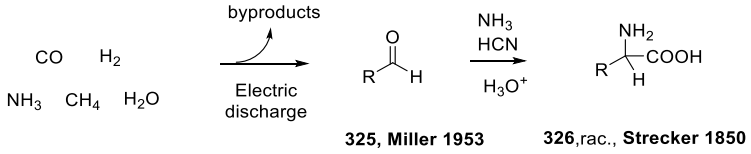
3.A2 Exploring the Deprotonation of Non-Enolisable Aldehydes

A very fascinating but unsolved puzzle is the origin of life. The origin of life has been well studied and many interesting views have been proposed. Many scientists believe that the entire biomolecular system comes from simpler "building blocks", which represent the "key monad" of the entire complex apparatus.[107] Moreover, it has been reported that both

formaldehyde and glycolaldehyde are among the *circa* 150 compounds that have been identified in interstellar space,[108] and this evidence could strengthen the hypothesis whereby formaldehyde could represent the "key monad" of the biomolecular system as mentioned above.[107]

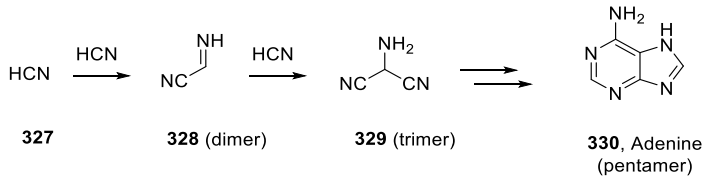
3.A2.1 Background

The primordial setting for an experiment to probe chemical evolution from simple starting material was firstly put in place by Miller in 1953,[109] who achieved the production of amino acids simply using CH_4, NH_3, H_2O and H_2, compounds which would represent the earth's atmosphere in the primitive earth conditions. Electrical discharge was used to form free radicals. The possibility of production of bioorganic compounds by reacting simple compounds was hypothesised by Oparin in 1923. The production of amino acids **326** was postulated to occur *via* Strecker synthesis[110] starting from the formation of aldehydes **325** and hydrogen cyanide.



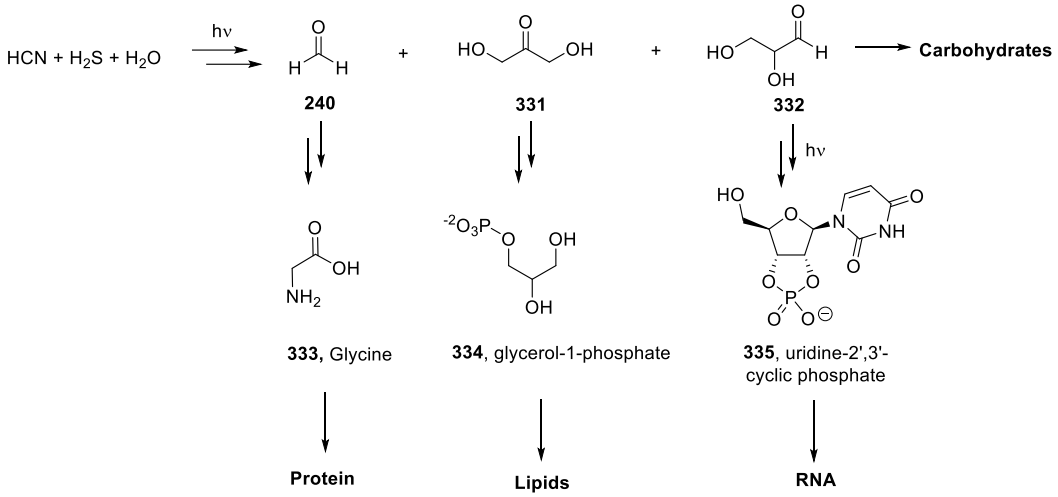
Scheme 78. Miller's experiment.[109]

Moreover, another experimental chemical investigation was Orò's synthesis of purines from ammonium cyanide.[111] An interesting mechanism where adenine **330** could easily form from a multistep "pentamerisation" of HCN **327** in liquid ammonia (Scheme 79) was recently proposed by Schleyer *et al.*[112]



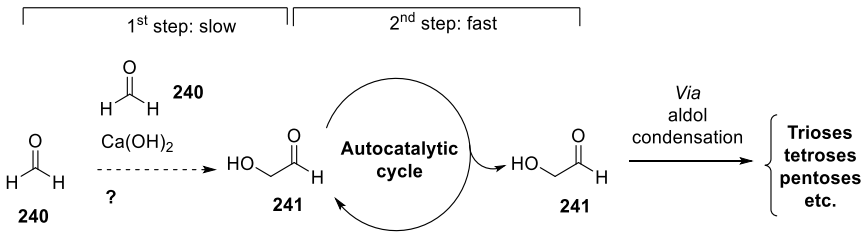
Scheme 79. Formation of adenine in aqueous ammonium cyanide solution proposed by Schleyer *et al.*[112]

In 2015, Sutherland proposed that RNA, protein and lipid precursors have common origins in a cyanosulfidic protometabolism. From photoexcitation of hydrogen cyanide and hydrogen sulfide, formaldehyde **240**, dihydroxyacetone **33** and glyceraldehyde **332**, precursors of carbohydrates, occur. These simple molecules then create an intertwined series of reactions which lead to the formation of glycine **333** and other amino acids, glycerol-1-phosphate **334**, precursor of lipids, and cyclic uridine 2′,3′-phosphate **335**, a precursor of RNA.[113]



Scheme 80. Reaction network that leads to RNA, protein and lipid precursor proposed by Sutherland.[113]

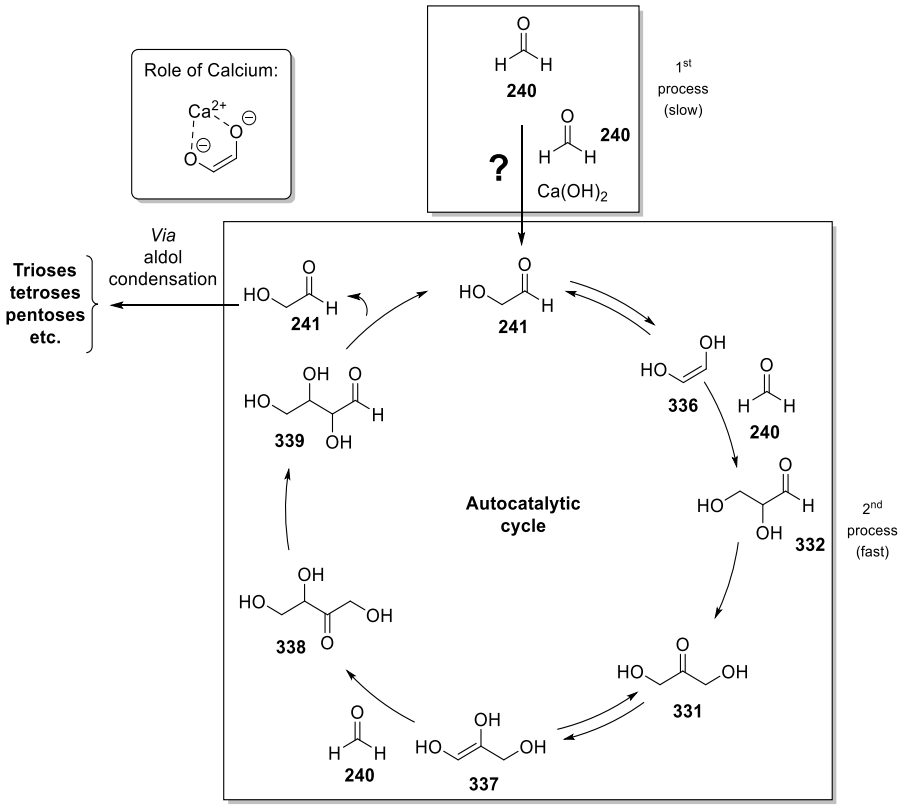
Another very interesting experiment was performed by Butlerov in 1861. He treated formaldehyde **240** with calcium hydroxide affording a complex carbohydrate mixture (Scheme 81). Many years later, Breslow proposed the first mechanism, in which glycolaldehdye **241** was proposed to play a key role.



Scheme 81. The formose reaction proposed by Breslow.[100]

The previous examples have been the starting point for many later theories and experiments. Nevertheless it's not the aim of this report to speculate on every case. One important element is the widely accepted theory that the formation of ribose from formaldehyde would be the key element for the formation of RNA and then the biotic world.[114] Nevertheless, the formation of ribose from formaldehyde is a process that is still not well defined.

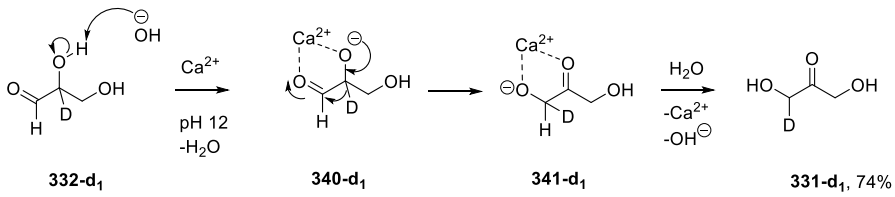
In regard to the "formose reaction", discovered by Butlerov in 1861, an interesting study was carried out by Breslow in 1959, who proposed his first mechanism. The 1st crucial step is represented by a slow formaldehyde dimerisation to afford glycolaldehyde **241**. Then the autocatalytic cycle shown in Scheme 82 runs faster and faster to produce more glycolaldehyde, which can also further react to form the various carbohydrates.[100]



Scheme 82. The formose reaction mechanism proposed by Breslow in 1959.[100]

The autocatalytic cycle starts when a tiny amount of glycolaldehyde **241** is produced. Breslow did not propose any mechanism for the dimerisation of formaldehyde **240**; he only reported that it might involve γ radiation; nonetheless other theories have been advanced (see later). The rapid second process starts with an aldol condensation *via* 1,2-dihydroxyethene **336**, an enediol intermediate, which gives rise to glyceraldehyde **332**. This species then isomerises to give dihydroxyacetone **331**, which then condenses with formaldehyde *via* 1,2,3-trihydroxypropene **337**, another enediol intermediate, to form the ketotetrose **338**. The ketotetrose tautomerises to the aldotetrose **339**, which then regenerates the original glycolaldehyde **241** and liberates a new molecule, by a simple retroaldol reaction.[115]

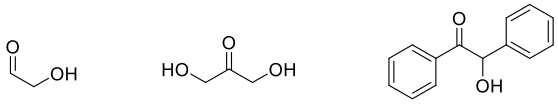
This first proposed mechanism was debated by Benner in 2006, who examined the reaction in D_2O as solvent. Since he did not detect any deuterium incorporation in the dihydroxyacetone **331**, he proposed a new mechanism, in which **331** was not involved in the mechanism, instead introducing new species detected *via* Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR).[116] More recently, Breslow in light of the new results shown by Benner, speculated further on the mechanism initially proposed. He elegantly demonstrated that the isomerisation of 2-deuteroglyceraldehyde **332-d$_1$** occurs by deuteride shift to afford 1-deuterodihydroxyacetone **331-d$_1$** with 74% of deuterium still retained (Scheme 83).[115] Therefore, in the Benner experiment, the incorporation of deuterium from D_2O was not observed because the species **332** and **341** are formed by isomerisation *via* hydride shift and not by enolisation.[115]



Scheme 83. Isomerisation of 2-deuteroglyceraldehyde **332-d$_1$** to 1-deuterodihydroxyacetone **331-d$_1$** through 1,2-deuteride shift.[115]

The glycolaldehyde **241** produced from the cycle represents the simplest carbohydrate which subsequently enolises and reacts further with formaldehyde *via* classical aldol condensation to yield more complex carbohydrates (trioses, tetroses. pentoses, hexoses etc.).[117]

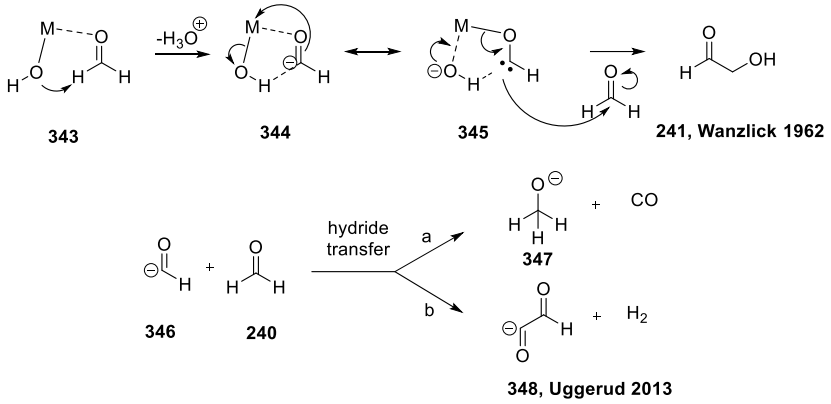
The undetermined point of the proposed mechanism is the formation of the first catalytic amount of glycolaldehyde **241**. The period when this formation takes place is called "induction time" or "lag period" and varies as a function of the presence of "co-catalysts" such as glycolaldehyde **241**, dihydroxyacetone **331** and benzoin **342** (Figure 5). All these species are able, with a different efficiency, to shorten the induction period, without affecting the fast autocatalytic process.[100] Many theories about what could be going on during the induction time have been advanced.



241 **331** **342**

Figure 5. Glycolaldehyde **241**, dihydroxyacetone **331** and benzoin **342**.

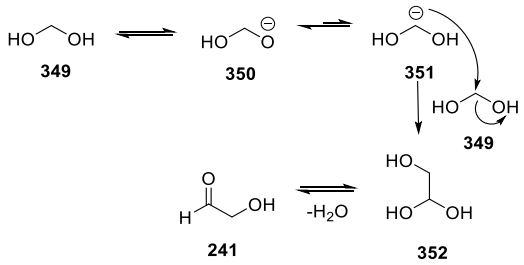
Wanzlick, in 1962, suggested that the mechanism could involve the formation of carbenoid species. The formyl anion **344**, resulting from deprotonation of **343** in basic pH, would form a nucleophilic carbene **345** which then attacks a neutral formaldehyde to afford glycolaldehyde **241** (see Scheme 84).[118] Nevertheless, more recently the idea that the formyl anion was involved in first step of the process was considered unlikely by Uggerud *et al.* in 2013. With a retrosynthetic perspective, they investigated the fragmentation of deprotonated glycolaldehyde in the gas phase. From the analysis they detected the loss of formaldehyde, carbon monoxide and molecular hydrogen. To explain the formation of the last two species, Uggerud suggested two plausible hydride transfers (Scheme 84): a) to the carbon of formaldehyde and b) to one of the slightly acidic formaldehyde hydrogens, forming methoxide **347** and glyoxal anion **348** respectively.[119]



Scheme 84. Nucleophilic carbenoid formation from formaldehyde.[118]

Only a small amount of unhydrated formaldehyde is present in water solution, while the primary constituent is represented by methylene glycol, or hydrated formaldehyde **278**.[120]

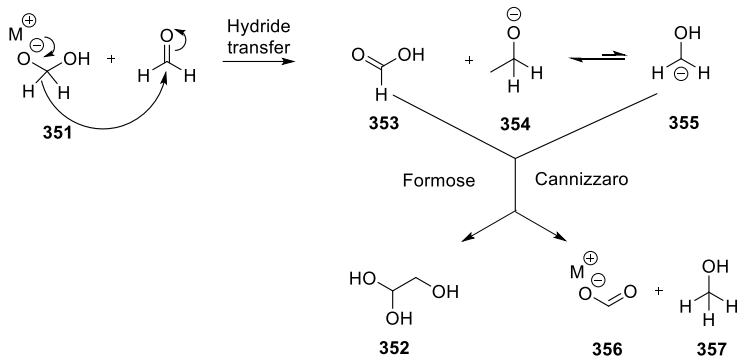
Mayer, in 1967, proposed a nucleophilic attack on a methylene glycol **349** by the carbanion **351**, formed from deprotonation of methyleneglycol **349**.[121]



Scheme 85. The nucleophile is represented by the methylene glycol carbanion.[121]

It is a common point of view that the Cannizzaro reaction[122] takes place simultaneously with the formose reaction, a reaction that is also famous as disproportionation of aldehyde lacking hydrogens in the α-position. Another hypothesis was proposed by John in 1974 who showed that the two reactions, formose and Cannizzaro, should compete along the reaction time; in particular they gave rise to the common intermediate complexed species **353** and **355**, for the two reactions, which derive from hydride transfer from **351** to formaldehyde as shown in the Scheme 86. The two reactions then would be intertwined; therefore a nucleophilic attack would give rise to the formose product **352** whereas the proton transfer would afford the

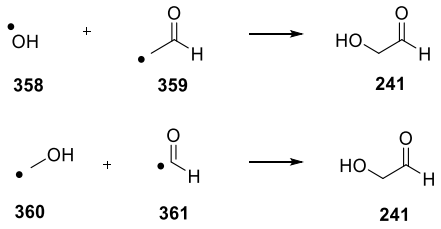
Cannizzaro products **356** and **357**. The reaction progress, explained by John, depends on the nature of the metal used.[123]



Scheme 86. Formose and Cannizzaro reactions intertwined by common intermediates.[123]

Also, the possible photocatalysis by UV light could explain formaldehyde autocondensation, since many theories say that formaldehyde itself would be formed by the action of UV light on carbon dioxide and water in presence of certain inorganic catalysts.[124]

A radical approach was also suggested by Bowie *et al.* in 2010. Within the *circa* 150 compounds identified in the interstellar clouds, some radical species also feature such as **358**, **359**, **360** and **361**. Some measurements *via* mass spectrometer (neutralisation/reionisation in the dual collision cells of VG ZAB 2HF) showed that these radical species can be produced. In light of this evidence, two theoretical radical combinations were suggested (all the species shown have been detected in interstellar space) to afford glycolaldehyde **241**, as shown in the Scheme 87.[125]



Scheme 87. Radical species detected in the interstellar space could probably explain the glycolaldehyde formation.[125]

3.A2.2 Project strategy

After the investigation on the dimerisation of DMF in presence of KO*t*Bu, the next step of the project was to determine whether similar reactions occur on aldehydes lacking a hydrogen atom in α-position such as **7**, **5** and **362** (Figure 6). If a deprotonation occurs to form formyl anion, then the eventual dimerisation of the formaldehyde could be an important element for understanding the first mysterious step of the formose reaction.

Formyl anion equivalents as synthons for C-C bond formation could find various applications, as reviewed by Kirchning *et al.*,[126] despite the proposal advanced by Uggerud,[119] who proposed that formyl anion should not be involved in the process.

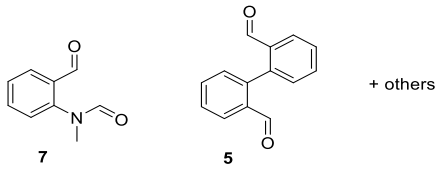
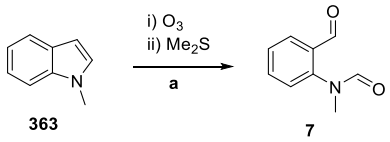


Figure 6. Substrates bearing formamide and formyl groups.

3.A2.3 Results and discussion

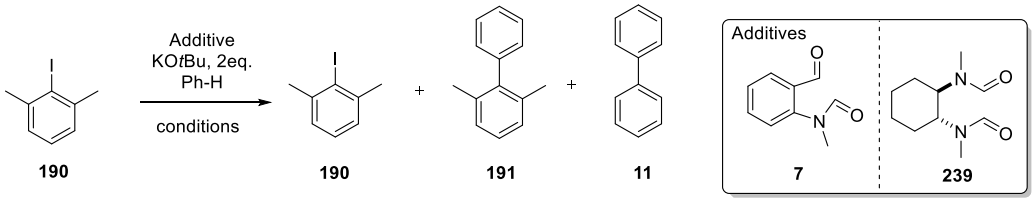
N-(2-Formylphenyl)-*N*-methylformamide **7** was prepared *via* ozonolysis. *N*-methylindole **363** was treated with a stream of ozone and then dimethyl sulfide was added as a reducing agent.



Scheme 88. a. i) MeOH, -78 °C, 6 h; ii) -78°C to RT, overnight, 35% yield.

Compound **7** was tested in a coupling reaction using iodo-*m*-xylene **190** as substrate and benzene as solvent under the same conditions as previously. The designed additive was found to be less effective than the diformamide **239** (Entry 4, Table 10): when 0.1 eq. of additive **7**

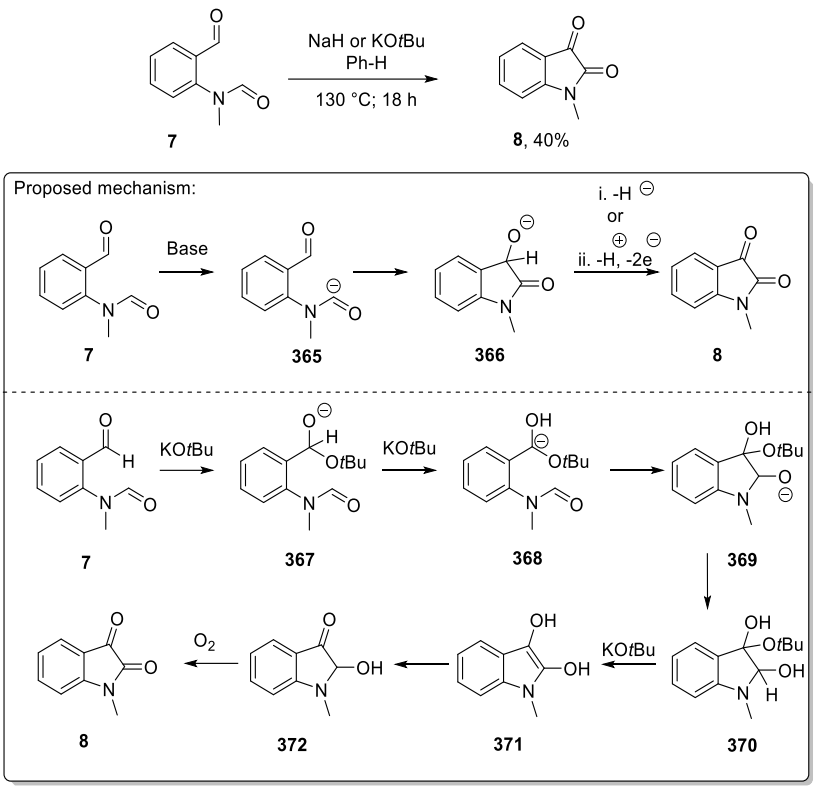
was used, only 5.8% of coupled products **191** and **11** were detected in the typical ratio 3.5:1 (Entry 1), whereas when the concentration was increased to 0.65 eq., the yield of coupled products did not increase significantly (Entry 3). Nevertheless, this test underscores the ability of the substrate to form an organic electron donor. Interestingly, when compound **7** was allowed to react with KO*t*Bu in the absence of any iodo-substrates, only isatin **8** was isolated in 40% yield. A very similar result was found when NaH was deployed, the reaction with a weaker base such as Na_2CO_3 gave only starting material **7** back.



Entry	Additive	191 + 11 (%)[b]
1[a]	-	0.5
2[a]	**7**, 0.1 eq.	5.8
3[a]	**7**, 0.65 eq.	10
4[c]	**239**, 0.65 eq.	31.6

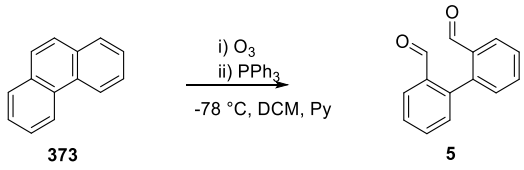
Table 10. [a] Iodo-*m*-xylene (0. 5 mmol), 1 mmol KO*t*Bu, benzene as solvent, 130 °C, 18 h. [b] Yields calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard. [c] reaction at 110 °C, 4 h.

The possible mechanisms which could explain the C-C bond formation are proposed in Scheme 89. i. If deprotonation occurs on the formamide, then anion **365** would undergo cyclisation to form anion **366**, which then forms *N*-methylisatin **8** after KH expulsion. ii. Alternatively, we could have deprotonation on the aldehyde, either directly or possibly *via* benzoin-type reaction to form anion **368**, which then cyclises to form anion **369**. After reprotonation, elimination can occur to form intermediate **371**. This tautomerises to form acyloin **372** which undergoes air oxidation to the dicarbonyl **8**.



Scheme 89. Different proposed mechanisms for the formation of *N*-methylisatin **8** from **7** mediated by a strong base**.**

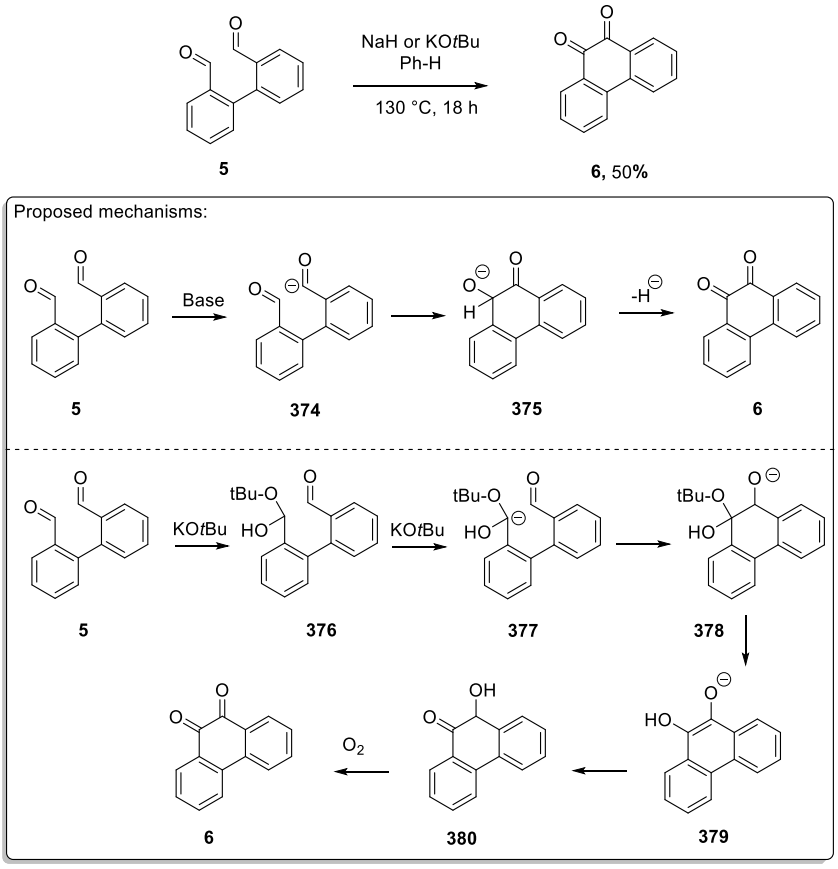
In the wake of these results, [1,1'-biphenyl]-2,2'-dicarbaldehyde **5** was prepared and tested using KO*t*Bu as base. The ozonolysis method was also applied to synthesise substrate **5** starting from phenanthrene **373** and triphenylphosphine was used as a reducing agent.[127]



Scheme 90. i) DCM, Py, -78 °C, 8 h; ii) Ph_3P, -78 °C to rt, overnight, 53 % yield.

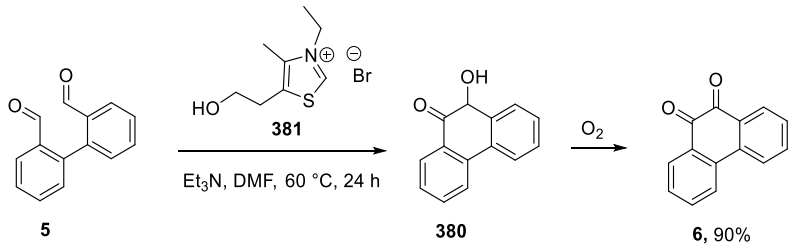
A similar result was obtained (Scheme 91), whereby a C-C bond formation was seen among the two aldehyde moieties, forming 9,10-phenanthrenequinone **6** in moderate yield. Two mechanisms are proposed for this reaction, both comparable with the mechanisms proposed for the previous substrate. In particular the dialdehyde **5** undergoes deprotonation by the

strong base, whereby the resulting anion **374** nucleophilically attacks the other aldehyde forming anion **375,** which then after hydride loss, gives rise to diketone **6** with a significant yield. ii. Alternatively, anion **377** could form via benzoin-type reaction and form anion **378**, then acyloin **380** which, after air exposure, oxidises to product **6**.



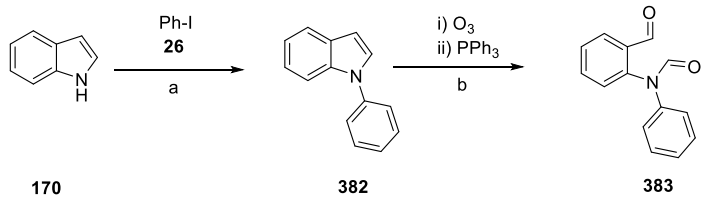
Scheme 91. Proposed mechanisms for the diketone **6** formation from dialdehyde **5**.

The substrate **5** has been previously studied by Enders in 2004, who reported the intramolecular crossed aldehyde-ketone and aldehyde-aldehyde benzoin-type reactions catalysed by nucleophilic carbenes such as the thiazolium salt **381**,[128] as shown in Scheme 92.



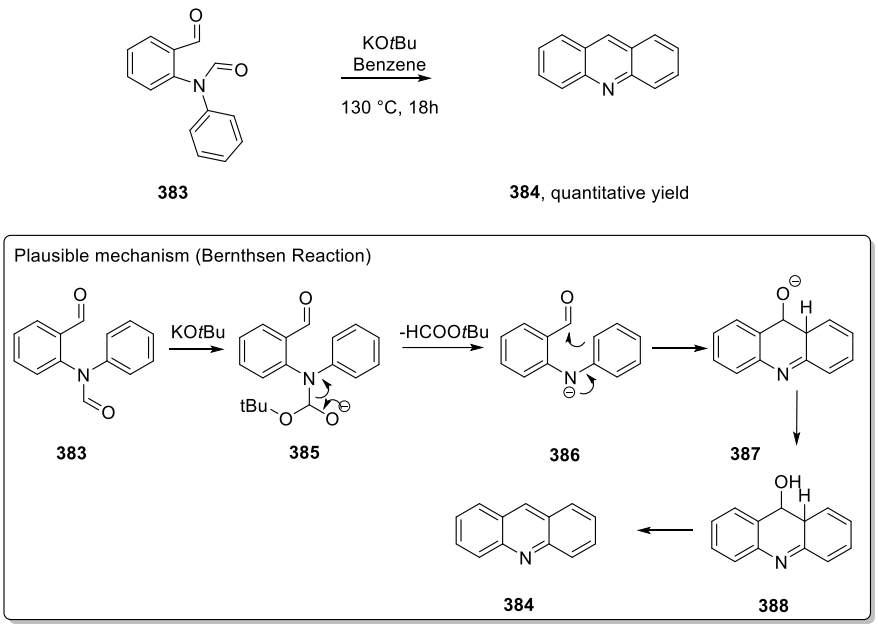
Scheme 92. Benzoin-type reactions catalysed by thiazolium salt **381** on dialdehydes.[128]

Substrate **383** was prepared *via* a two-step synthesis, i) Ullmann type coupling followed by ii) a stream of ozone.[129] The coupling in this case would be between an aldehyde and a formamide moieties.



Scheme 93. Preparation of substrate **383**. a) CuBr, *N*-methyl-pyrrolidone, Na_2CO_3, 170 °C, 6 h, 67%. b) DCM, -78 °C, 5h, 32%.

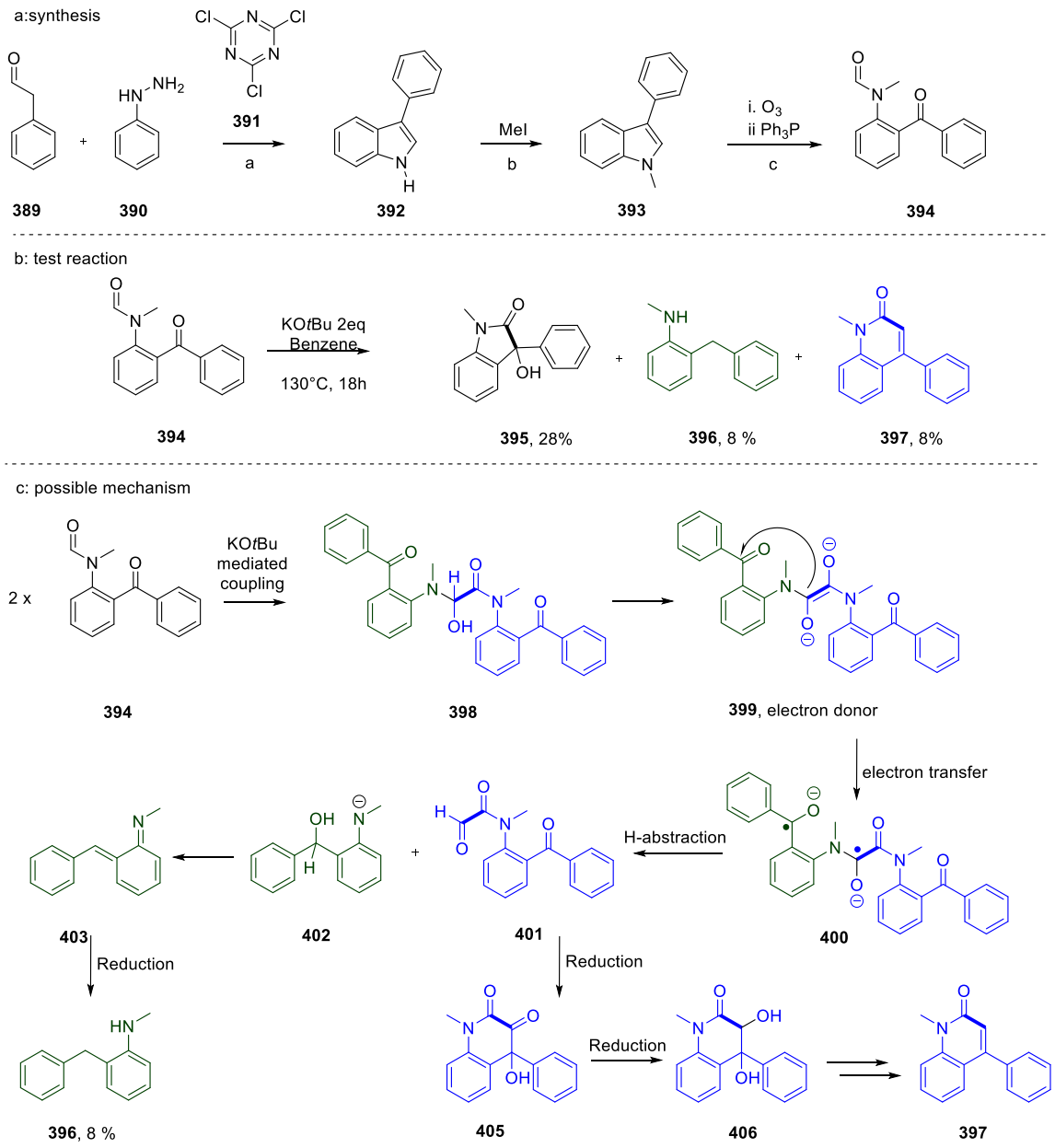
When compound **383** was subjected to KO*t*Bu, a quantitative yield of acridine **384** was isolated. The latter gave rise, likely, *via* Bernthsen reaction after butoxide attack on the formamide **383** to form anion **385**, anion **386** arises after ester expulsion and intramolecular rearrangement takes place.[130]



Scheme 94. KO*t*Bu-mediated acrydine formation *via* possible Bernthsen reaction.

Substrate **394** would allow a formamide to couple with a ketone. 2,4,6-Trichloro-1,3,5-triazine-catalysed Fischer-Indole synthesis led to indole **392**.[131] This was first methylated and then treated with a stream of O_3 followed by reductive work-up. When tested with KO*t*Bu, substrate **394** gave rise to a complex mixture from which three different products were isolated, **395**-**397** (Scheme 95). Product **395** derives from a similar coupling to that observed with the previous substrates *via* formamide deprotonation. For the structures **396**-**397**, a hypothetical mechanism is given. Since **396** and **397** gave the same yields, the two products could derive from the same process. Initally, a KO*t*Bu mediated coupling between two molecules of starting material **394** could form a dimeric intermediate, from which an organic electron donor **399** could arise, following the same process described previousely (Chapter 3.A1). Once the organic electron donor has formed, one electron can be shuttled to the benzophenone moiety (in green) to form a diradical intermediate **400**. The latter then undergoes H-abstraction and cleavage of the C-N bond to form the two intermediates **401** and **402**. The two intermediates can now follow two different pathways. **401** can undergo another KO*t*Bu-mediated aldehyde-ketone coupling, from which product **397** could arise, possible through the formation of diol **406**. This mechanism is only an hyphothesis, more

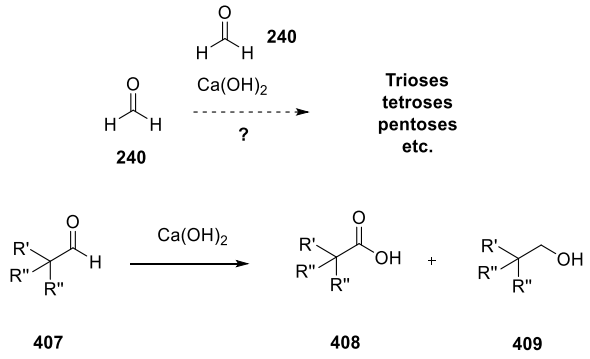
studies will aim to find evidence for this. Product **404** could arise from a rearrangement of amide **402**, *via* de-aromatisation and re-aromatisation process.



Scheme 95. a)Synthesis of **394** and reaction with KO*t*Bu. a) EtOH, 85°C, 2 h, 48%; b) NaH, DMF, 4 h, 0 °C to RT, 93%; c) DCM, -78 °C, overnight, 35%. b) Test reaction with substrate **394**. c) possible outline mechanism for the formation of products **396** and **397**.

3.A2.4 Conclusion and future work

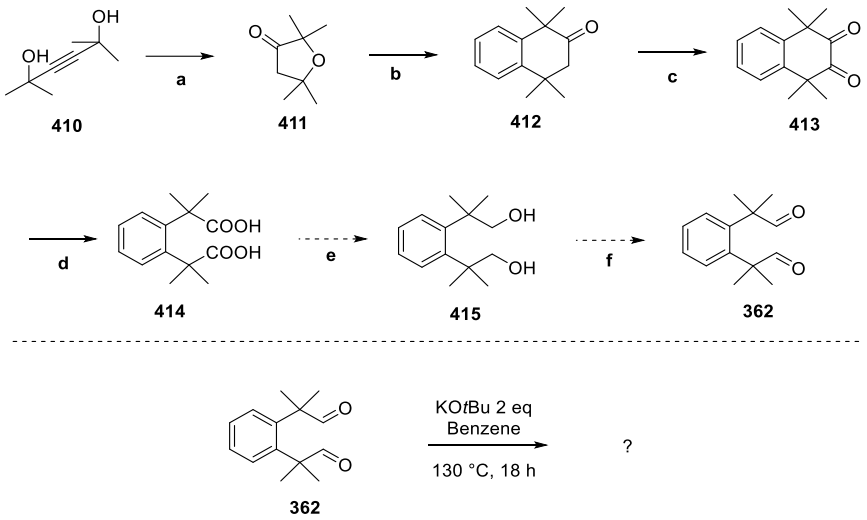
After the preliminary investigation on the intermolecular and intramolecular C-C coupling between formamides, the intramolecular coupling with aromatic aldehydes was achieved. The next step would be to test non-enolisable aliphatic aldehydes such as **407** (Scheme 96) and try to probe the mechanism which underpins these base-promoted-cross couplings. For this preliminary study, a strong base such as KO*t*Bu was used. A screening of different bases, would also lead to a better comprehension of these transformations. Bases such as $Ca(OH)_2$ are known to be important for the Breslow mechanism for the sugar formation from formaldehyde **240**[100,115,123] and also for the Cannizzaro reaction of non-enolisable aldehydes **407**.[122,123] Whereas, stronger bases such as KO*t*Bu and NaH are less commonly used for these type of transformations.



Scheme 96. Fomation of sugars from formaldehyde and Cannizzaro mechanism of a generic non-enolisable aldehyde.

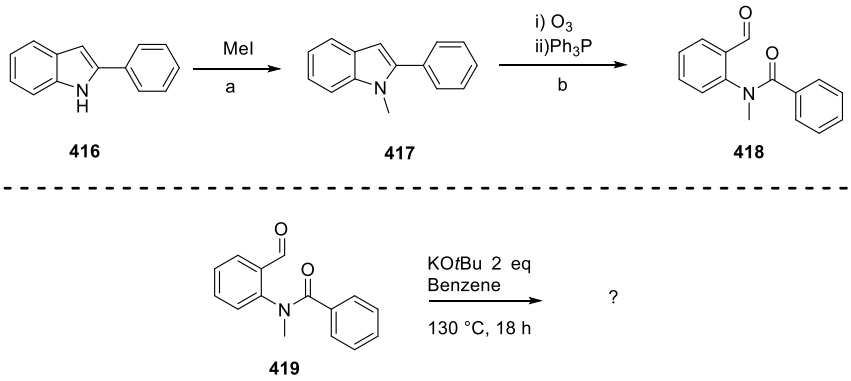
Aldehyde **362** was selected as a plausible tester as no enol can be formed and the product would be easily isolable thanks to the aromatic ring (Scheme 97). For the synthesis of 2,2'-(1,2-phenylene)bis(2-methylpropanal) **362** a six-step route was found in the literature and applied.[132] The diol **410** was first reacted with mercuric acetate and then the resulting tetrahydrofuranone **411** was treated with aluminium chloride in benzene. The purification of the ketone **412** was found to be a quite critical process; various attempts such as chromatographic columns or distillation were performed but they were ineffective. Only a crystallisation gave rise to the product but with a very limited yield (13%); moreover this process required several weeks. The resulting ketone **412** was oxidised with selenium dioxide

to diketone **413** and further oxidised using periodic acid to get the resulting diacid **414**. An direct oxidation from **412** to **414** was attempted using $KMnO_4$ but the yield achieved was much less than the 2-step route c-d. The last two steps e-f still need to be performed due to the complexity and length of the scheme.



Scheme 97. a. $Hg(OAc)_2$, H_2SO_4, water, 80 °C, 4 h, 84 % yield, b. $AlCl_3$, benzene, argon, RT, 16 h, 13 % yield, c. SeO_2, dioxane, reflux, 44 h, 80 % yield; d. H_5IO_6, dioxane/water, 70 °C, 40 h, 39 % yield.

Substrate **419** represents the coupling of a formamide and an aldehyde. It was made after methylation of 2-phenylindole **416**, followed by ozonolysis. This compound will also be tested under the same conditions and added to the series of experiments performed for this project.



Scheme 98. Preparation and test of substrate **419**. a) NaH, DMF, 4h, 0°C to RT, 93%; b) DCM, -78 °C, overnight, 95%.

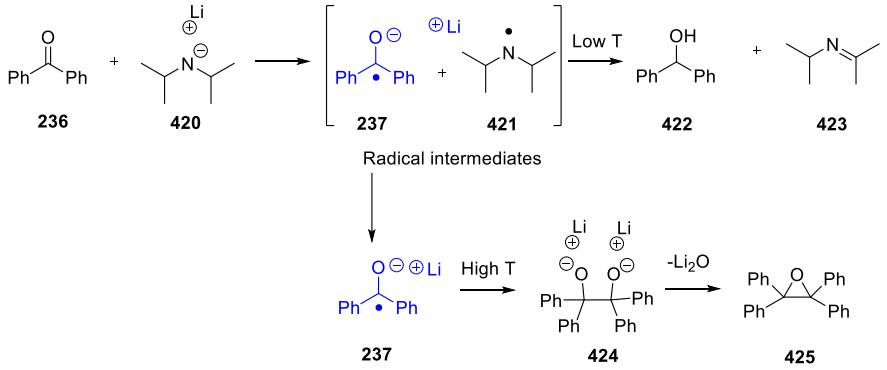
3.A3 KO*t*Bu (but not NaO*t*Bu) Photoreduces Benzophenone under Activation by Visible Light

Some academics believe that a direct electron transfer from alkoxide can occur,[92,95,133] after Prof Ashby with his studies on benzophenone [93,94,102,134] triggered this unconventional idea. The Murphy group, supported by many different studies, proposed the *in situ* formation of organic electron donors starting from KO*t*Bu and organic precursors (ligands, solvent), as previously mentioned.[66,72,76] The following pages detail an unprecedented study of the direct electron transfer from alkoxides of alkali metals and reveal a new, experimentally and computationally supported, mechanism that finally unmasks the "urban legend" after some 37 years.[2] The computational work was entirely performed by Allan Young, a member of the Murphy group, under the supervision of Prof. Tuttle.

3.A3.1 Background

Discussion of electron transfer in reactions of KO*t*Bu with benzophenone goes back to Russell *et al*. in 1962,[135] who showed that radicals were generated when benzophenone and its dihydro derivative, benzhydrol **422** (Scheme 99), were mixed in the presence of KO*t*Bu in DMSO, although the paper did not discuss mechanism. In 1978, Screttas and Cazianis proposed electron transfer from lithium *s*-butoxide to fluorenones as a result of detection of ketyl radicals, as possible intermediates in a Meerwein-Pondorf-Verley radical type reduction.[136] The story was taken up in 1981 by Ashby *et al.* who observed the blue colour of the potassium ketyl of benzophenone upon reaction of benzophenone with KO*t*Bu.[93,102] Ashby attributed the reaction to direct electron transfer from KO*t*Bu to benzophenone. Although not considered then, the reduction potential for benzophenone to its ketyl radical anion (cited values vary from −1.33 V [137] to −2.2 V, [138] -1.72 V in DMF vs SCE, [139] -1.77 V in DMF vs SCE [96]) and oxidation potential of KO*t*Bu (+0.1 V in DMF, vs SCE)[95] indicate that this is not possible as a direct bimolecular outer sphere electron transfer, whereas no investigation of an inner sphere electron transfer has been pursued so far, to the best of my knolewdge.

Ashby reported the generation of the ketyl radical anion **237** (Scheme 99) by reacting benzophenone **236** and strong bases such as lithium amides[102,134] and alkoxides of alkali metals.[93,94] The radical species were detected by EPR and visible spectroscopy: moreover the formation of the ketyl is always accompanied by a blue colouration of the solution. In his first paper, he reported that benzophenone in the presence of lithium amides such as LDA **420** in THF forms ketyl radical anion **237** up to 35%. The benzyhydrol **422** was slowly formed throughout the reaction by hydrogen abstraction from the base, therefore the more reduced product **422** was produced, the less EPR signal was observed. Moreover, a minor product observed at higher temperature was the 2,2′,3,3′-tetraphenyloxirane **425,** which comes from the radical combination of two radicals **237** followed by dehydration.

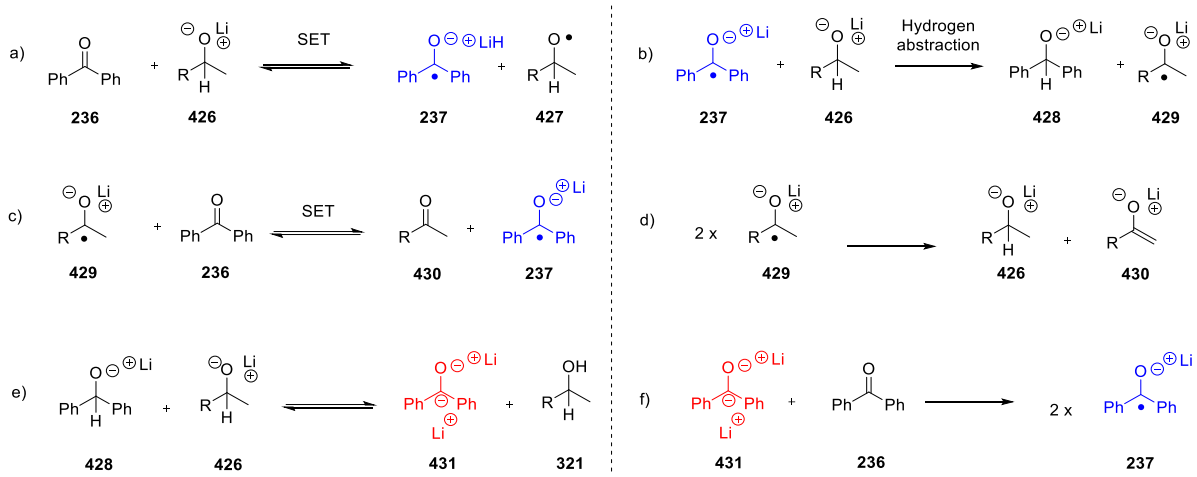


Scheme 99. Reduction of benzophenone by LDA proposed by Ashby.[102]

In Scheme 100 the Ashby proposal is shown for the single electron transfer from the lithium alkoxide **426** to benzophenone **236** (step a), which generates the ketyl radical anion species **237**. This latter is transformed to lithium benzhydrolate **428** by abstracting a hydrogen from the alkoxide **426** (step b). The resulting radical anion **429** would be also able to donate an electron to benzophenone **236** (step c); otherwise it could disproportionate with itself **429** abstracting a hydrogen from the $–CH_3$ (step d).

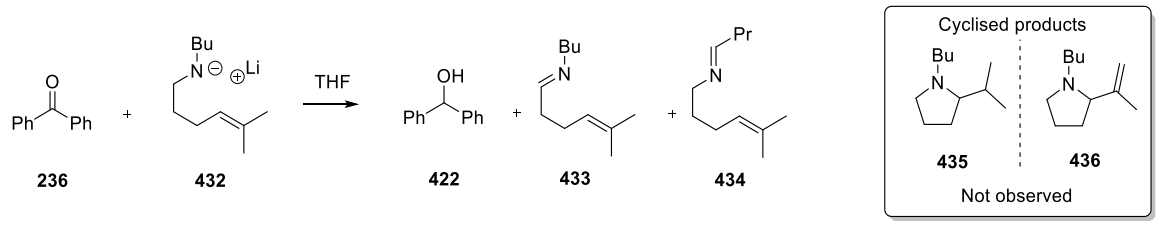
Ashby also underlined that the formation of benzhydrolate is only noticed when an alkoxide presenting an hydrogen in its α-position is used. In fact, when Ashby used KO*t*Bu, benzhydrol **422** was not detected, (step b does not occur). Moreover, Ashby proposed that the benzhydrolate **428** can be deprotonated by the alkoxide to form the dianion **431**, which

gives a red coloration of the solution instead (step e). The dianion finally undergoes disproportionation with the ketone **236** to afford the ketyl radical anion **237** (step f).[94]



Scheme 100. Single electron transfer from lithium alkoxide **426** to benzophenone **236**, as suggested by Ashby.[94]

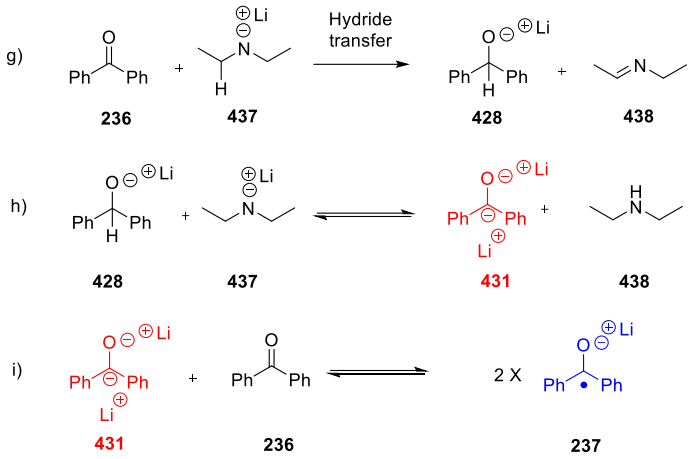
In 1984, Newcomb reported that the reduction of benzophenone by a lithium dialkylamide containing β-hydrogen atoms does not proceed *via* electron transfer. This new view was elegantly reported by testing trapping probes such as **432**.[140]



Scheme 101. Reduction of benzophenone *via* hydride shift proposed by Newcomb in 1984.[140]

The reaction gave a good yield of benzyhydrol **422**, but no cyclised products **435** or **436** were observed; the imines **433** and **434** were observed instead (Scheme 101). With a different point of view, Newcomb proposed an alternative mechanism involving a concerted hydride transfer from lithium dialkylamides **437** to benzophenone to give lithium benzydrolate **428**. (step g, Scheme 102). This latter undergoes deprotonation to afford the dianion **431** (step h) which can donate an electron to benzophenone **236** to afford the ketyl radical anion species

237 (step i).[140] Summarily, Newcomb shows the generation of the dianion **431**, and suggests that this species is able to donate an electron to neutral benzophenone **236** and finally form the ketyl radical species **237**. This reversed disproportionation was previously shown by Wooster in 1927 and Garst in 1976.[141,142]



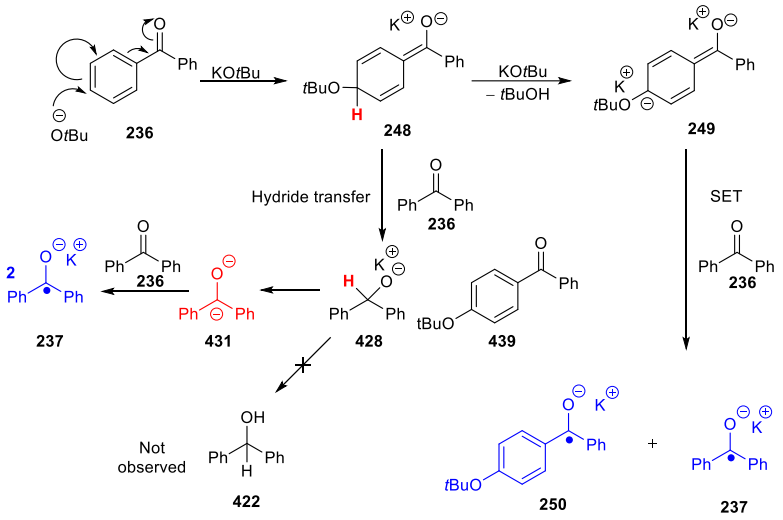
Scheme 102. The electron donor is the dianion species **431**, as suggested by Newcomb.[140]

With our background in the *in situ* formation of organic electron donors, we therefore explored whether formation of organic electron donors could explain the Ashby reactions.

3.A3.2 Project strategy

The strategy for this project was to re-examine the role of KO*t*Bu with aromatic ketones. The first part was to examine how this base was able to reduce aromatic ketones. A number of ways in which organic electron donors might arise in these reactions were proposed and investigated. Attack by KO*t*Bu in the *para*-position of benzophenone **236** (Scheme 105) would afford anionic intermediate **248** (attack in the *ortho*-position should be a comparable alternative, and was considered as well). Two fates might await **248**: (a) hydride transfer to a molecule of benzophenone would afford **428** and **439** (a previous paper from the Murphy group disclosed the hydride transfer from an alkoxide under BHAS conditions).[76] As already stated, no benzhydrol **422** is formed in this reaction, so if **428** were formed, it would need to

evolve in a different way; deprotonation would afford dianion **431** (formation of dianions by KO*t*Bu has already been showed in a previous paper in the Murphy group)[79] which would be a strong electron donor and could reduce benzophenone **236** to form two ketyl radicals **237**. (b) a second possible fate of molecule **248** would involve deprotonation to afford dianion **249**, another candidate for donating an electron to benzophenone **236**. The result of the electron transfer would be two potassium ketyl species, **237** and **250** (Scheme 103).



Scheme 103. Proposed mechanism for the enolate-type donors **248** and/or **249** generation.

Although there might be at least 2 fates awaiting anion **248**, its formation (the first step of the process shown) ought to be the keystone of the process. *Tert*-butoxides of alkali metals are known to be very powerful bases but not good nucleophiles if compared with the less bulky methoxide and ethoxide analogues.[143,144]

To test the validity of the proposed mechanism, differently substituted benzophenones were prepared and a qualitative evaluation (based on the colour switch to blue of the reaction mixture) of the ketyl radical formation from substrates **236**, **440**, **441**, **251** and **253** (Figure 7) was firstly performed.

If butoxide anion is capable of donating an electron to benzophenone, then it likely ought to be able to donate an electron to the substrates **440**, **441**, **251** and **253**. If addition of KO*t*Bu to the aryl rings of these substrates is valid, then at least for steric reason some of these

substrates, substituted in *ortho* and/or *para* positions, are likely to afford significantly diminished amounts of the potassium ketyl in comparison to **236**.

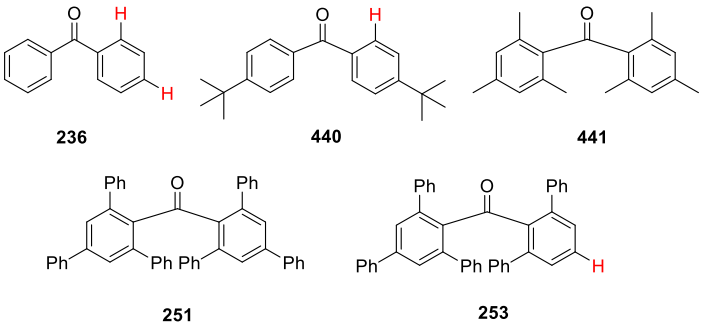


Figure 7. Evaluating the reduction of benzophenone and benzophenone derivatives **236**, **440**, **441**, **251**, **253**.

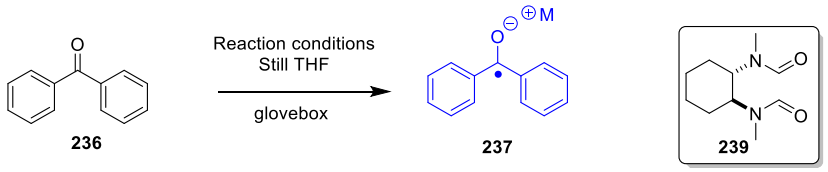
The outcome from the qualitative tests was unclear, due to the extended chromophors in some of the structures. Therefore, after this preliminary qualitative test, a quantitative test was performed. The compounds in Figure 7 were now used as additives for the Base-Promoted Homolytic Aromatic Substitution reaction, already discussed in the Chapter 1.2.3. The idea behind this test is analogous to the qualitative tests: if addition of KO*t*Bu to the aryl rings of these substrates is valid, then at least some of these substrates, substituted in *ortho* and/or *para* positions, are likely to afford significantly diminished amounts initiator for the BHAS mechanism which will reflect the diminished amounts of coupled products at the end of the reactions.

If the outcome of the qualitative and quantitative tests were reflected our idea, this could corroborate the enolate-type generation, shown in the new proposal (Scheme 103). If not, then something else might be happening and it would need further investigation.

3.A3.3 Results and discussion

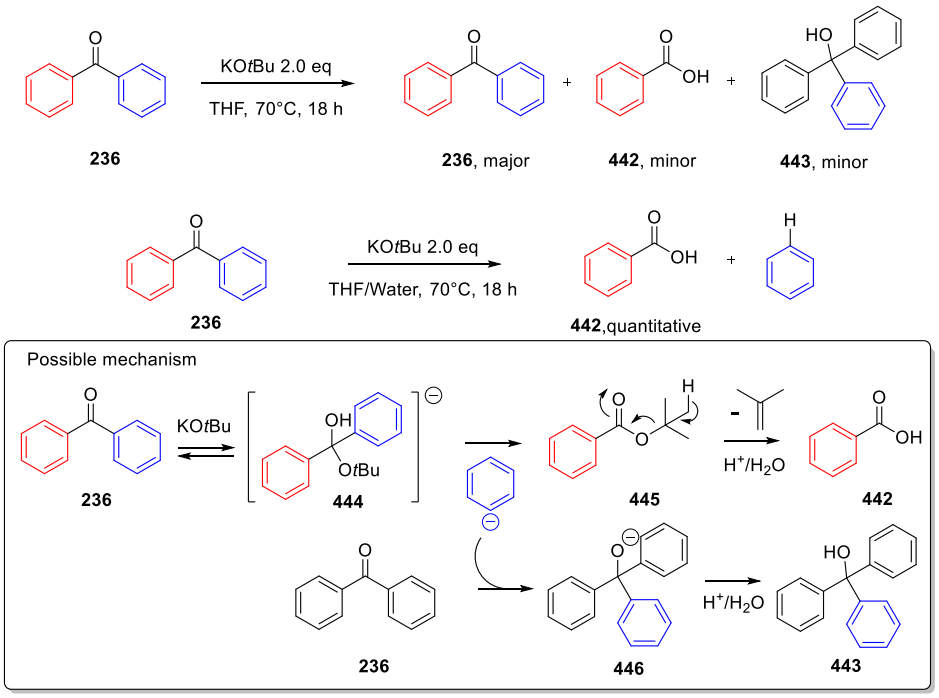
3.A3.3.1 Qualitative tests

Ashby described the evidence of formation of ketyl radical anion from benzophenone simply by reacting the substrate with alkoxides of alkali metals. The formation of the ketyl radical is always indicated by a characteristic blue coloration of the solution, using distilled THF as solvent. The first experiment was to reproduce the evidence of the blue coloration using the Ashby conditions.[94] Thus, a series of experiments using benzophenone as substrate was performed. When this was reacted with Na or K (1 eq), the characteristic blue coloration was observed gradually from the first minute (Entries 1 and 2, Table 11). When KO*t*Bu was employed, the blue colour was only detected when the mixture was heated at 70°C (Entry 3). Moreover benzoic acid **442** and triphenylcarbinol **443** were detected *via* GC-MS at the end of this reaction as products of the fission of the benzophenone (Scheme 104); this phenomenon was proposed to happen in the presence of water in the literature.[145,146] The formation of small amounts of side-products would be due to traces of water or *tert*-butanol in the reaction mixture. When water was added to the reaction, a quantitative yield of benzoic acid was found at the end of the reaction.



Entry	Reactants	T (°C) and time	Ketyl radical 237
1	Na (1 eq)	RT, few min	Yes
2	K (1 eq)	RT, few min	Yes
3	KO*t*Bu	70 °C, 3 h	Yes
4	KO*t*Bu	RT, 3 h	No
5	KO*t*Bu, **239** (0.2eq)	70 °C, 10 min	Yes
6	KO*t*Bu	RT, 48h	No

Table 11. Visual tests with benzophenone with alkali metals and alkali metals alkoxides.

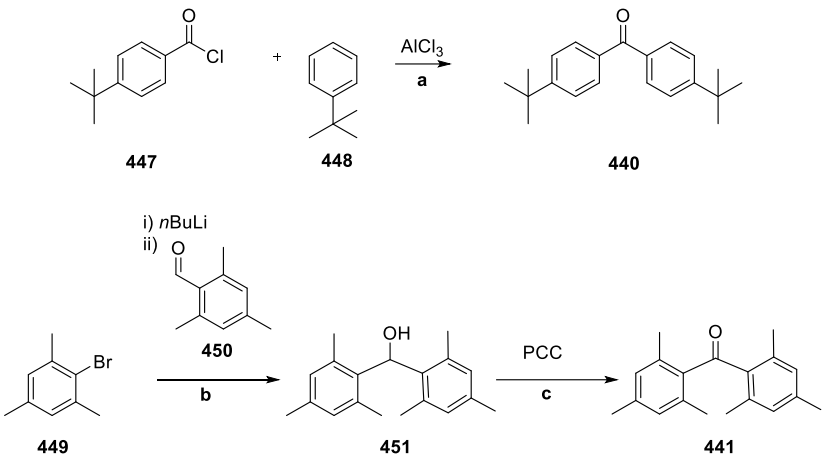


Scheme 104. Formation of traces amount of byproducts **442** and **443** and possible mechanism.

At room temperature, no change of colour was observed (Entry 4, Table 11). Afterwards, KO*t*Bu was added in the presence of additive **239** and the blue coloration was detected after 10 min by heating the reaction up to 70 °C (Entry 5). This latter case represents further evidence that **239** acts as a precursor for an organic electron donor.

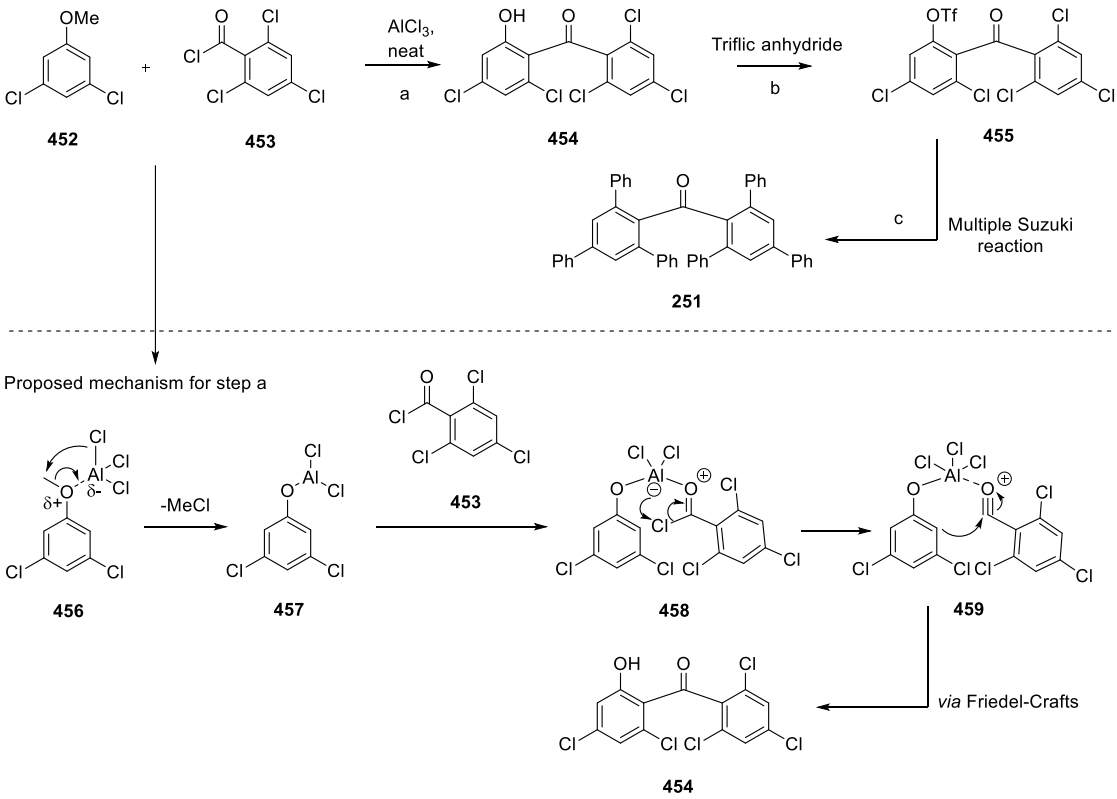
After this first set of results, differently substituted benzophenones were prepared.

4,4'-Di-*t*butylbenzophenone **440** was prepared by reacting *tert*-butylbenzene **448** with the pertinent benzoyl chloride **447** *via* Friedel-Crafts reaction triggered by aluminium chloride,[147] whereas dimesitylmethanone **441** was synthesised by a two-step route. During the first step the mesityllithium, prepared by addition of *n*-buthyllithium to a solution of mesityl bromide **449**, was reacted with mesitylaldehyde **450**. The resulting alcohol **451** was then oxidised using pyridinium chlorochromate to afford the resulting dimesitylmethanone **441**.[148]



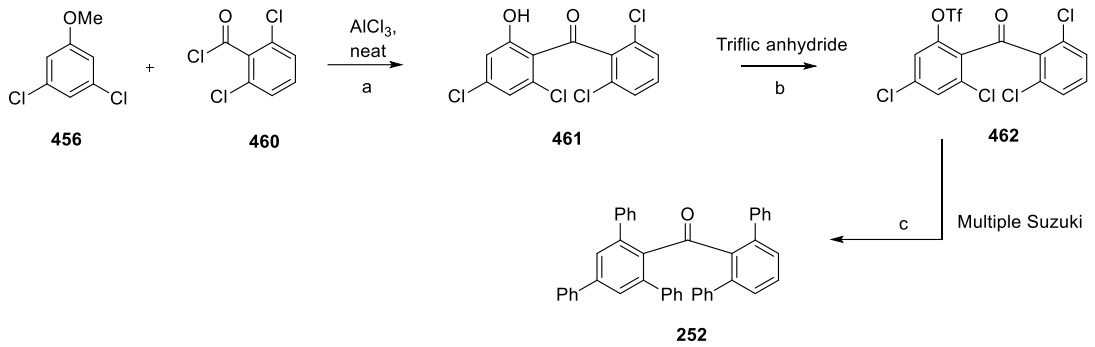
Scheme 105. a. 80 °C, 2.5 h, 34% yield. b.i) THF, -78 °C, 1 h; ii) THF, -78 °C, 30 min, 59% yield. c. DCM, RT, 3 h, 67% yield.

The hindered ketone **251** was prepared using a 3-step synthesis. In the first step $AlCl_3$ induces the demethylation of **452** followed by a Friedel-Crafts coupling with acyl chloride **453**. Anisole type compounds form with aluminium chloride an oxonium complex **456**, which decomposes above 40 °C with the evolution of methyl chloride, giving rise to the demethylated intermediate **457.** This then undergoes a regioselective Friedel-Crafts coupling.[149] Ketone **454** was then treated with triflic anhydride to form triflate **455** which was then used as a core moiety. A multiple Suzuki reaction on all the six activated carbons gave rise to the final product **251**. This last step was inspired by the literature,[150] but the conditions were optimised. In particular, it was observed that dividing the reaction among many smaller pressure vessels, afforded a higher yield than where the big batch reaction was deployed.



Scheme 106. a. $AlCl_3$, neat, argon, 110 °C, 15 h, 58.6 % yield. b. Triflic anhydride, pyridine, anhydrous DCM, argon, from 0 °C to rt, 4 h, 56.4% yield. c. $PdCl_2(CH_3CN)$ (5.0 %), Sphos (10 %), phenylboronic acid, K_3PO_4, microwave vial, nitrogen, 110°C, 4 days, 59.3 % yield. Below, the proposed mechanism for step a is reported.

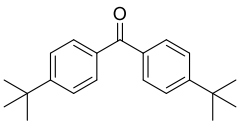
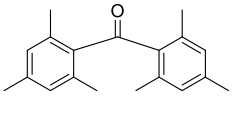
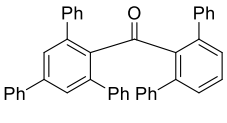
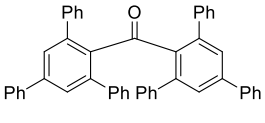
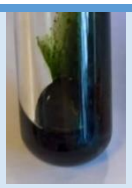
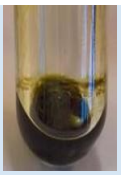
Following a similar approach but using the acyl chloride **460** as starting reagent led to the ketone **252**, bearing a free *para* positon. This substrate differs from the analogous compound **251** because a possible nucleophilic attack (perhaps by butoxide anion) on the ring would be compatible with **252** and not with **251**.



Scheme 107. a. $AlCl_3$, neat, argon, 110 °C, 15 h, 72 % yield. b. Triflic anhydride, pyridine, anhydrous DCM, argon, from 0 °C to rt, 4 h, 92 % yield. c. $PdCl_2(CH_3CN)$ (5.0 %), Sphos (10 %), phenylboronic acid, K_3PO_4, microwave vial, nitrogen, 110°C, 4 days, 62 % yield.

The differently substituted ketones were tested using the same approach as for benzophenone. We recognised that the simple colour test for the ketyl formation could be complicated with some of these substrates due to the extended chromophores and also to the likely variation in kinetics, compared to benzophenone. Picture 1 shows the complex outcomes for these experiments. If with compounds **440** and **441** the difference between the reaction with Na and KO*t*Bu is pretty evident, the same cannot be said for the **251** and **252** cases, as the reaction with Na with these substrates did not lead to the diagnostic blue ketyl colour, and consequently, also the test with KO*t*Bu cannot be considered reliable (Picture 1).

Whilst performing some tests with D_2O, deuterium incorporation for substrate **441** up to 7 deuterium atoms was observed at the end of the reaction (see mass spectra in the experimental data), indicating that subsrate **441** might have additional avenues of reactivity open to it, compared to the other substrates.

Conditions \ Ketone	 440	 441	 252	 251
Na, rt				
Time	10 min	1h	1h	5h
KO*t*Bu, 70°C				
Time	36 h	36 h	36 h	36 h

Picture 1. All the reactions were performed in a glovebox in THF as solvent. A picture was taken at the mentioned time.

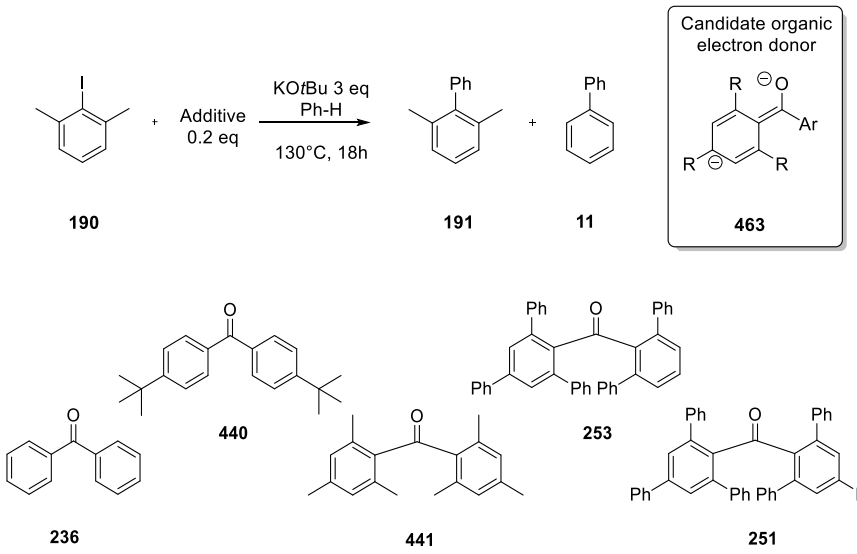
After this preliminary evaluation, some quantitative test were then performed.

3.A3.3.2 Quantitative tests

The idea behind this study was similar to the qualitative test. If KO*t*Bu acts as nucleophile towards benzophenone, a diminished amount of organic electron donor would occur with the substituted benzophenones. This would reflect in a more sluggish Base-promoted Homolytic Aromatic Substitution (BHAS),[51] and therefore lead to a range of yields among the different benzophenones.

With this idea, iodo-*m*-xylene **190** was deployed for this test, as this substrate is incapable of forming any benzyne intermediate which could interfere with our quantification.

As usual with substrate **190**, the yield of the coupled products, **191** and **11**, was not very high, but they were at least three times higher than the non-zero yield of the blank reaction. This indicated a small activity of the different additives via the formation of a plausible electron donor. Nonetheless, the outcome from this test did not lead us to a comprehensive understanding of the case.



Yield (%)	No additive	236	440	441	253	251
191 + 11	0.6	4.7	4.2	2.5	3.2	1.6

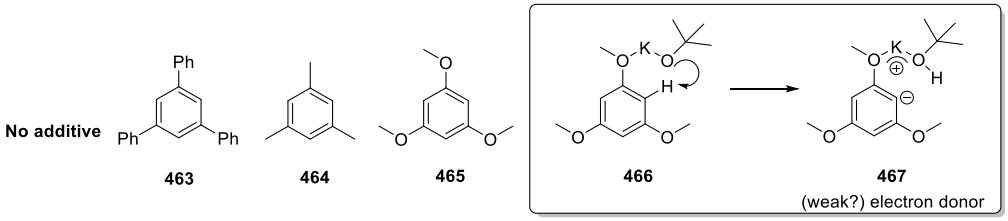
Table 12. Testing the series of benzophenones in BHAS with iodo-*m*-xylene **190**. Trimethoxybenzene was used as internal standard for the NMR spectrum.

Independently from the additive used, the yields of the two inseparable coupled products **191** + **11** were similar in every case (Table 12). The predicted higher amount of products with the additives **236**, **253** and perhaps **440** (as resulting of an *ortho*- attack from butoxide) needed to be reconsidered.

We were keen to understand what these small amounts of coupled products meant and whether the presence of an aromatic compound other than benzene would have influenced the formation of the coupled products in the reaction mixture somehow. For this reason triphenylbenzene **463**, trimethyl **464** and trimethoxybenzene **465** were tested. Electron rich

465 gave 2.8 % combined yield of **191** + **11**, a comparable yield to the previous tests with the benzophenones, whereas additives **463** and **464** did not affect the reaction at all.

Can a weak organic electron donor, such as **467**, form *via* O-assisted deprotonation of **466** and, therefore, be capable of triggering the BHAS mechanism? No evidence for this has been reported, therefore a better investigation would be needed.

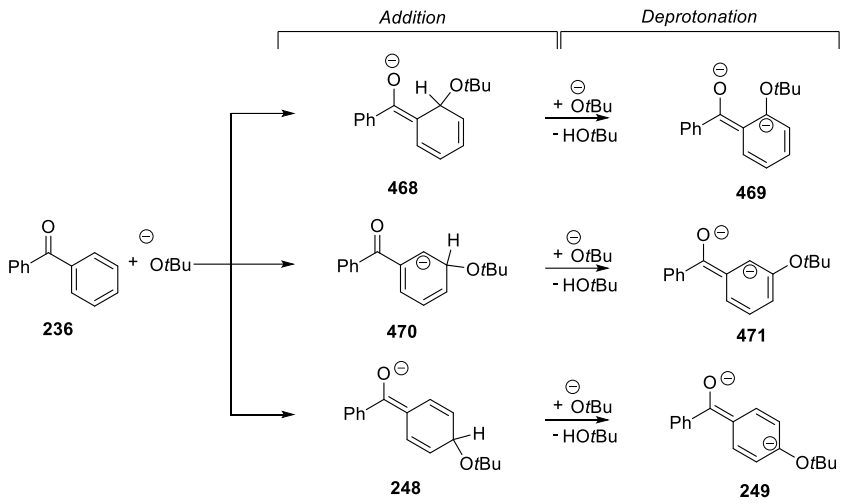


Yield %				
191 + **11**	0.8	0.9	1.1	2.8[a]

Table 13. Combined yields (**191** + **11**) in the BHAS test with iodo-m-xylene **190**.[a] CH_2Br_2 was used as internal standard for ^{1}H-NMR

The reaction was now examined computationally by DFT calculations.

As shown in Table 14, addition in the *meta* position has an accessible free energy barrier (21.1 kcal/mol) but is highly endergonic (18.6 kcal/mol) thus disfavouring the addition reaction and we therefore disregarded any further reactivity through a *meta*-adduct. Addition in the *ortho* and *para* positions exhibits accessible free energy barriers at the reported experimental conditions (room temperature), whilst being endergonic by 5.8 and 5.0 kcal/mol, respectively. Subsequent deprotonation of *ortho* (**468**) and *para* (**248**) adducts to form dianions **469** and **249** respectively, occurs with accessible free energy barriers, with both reactions being endergonic (9.7 and 7.0 kcal/mol, calculated relative to reactant complex of **468** or **248** with *tert*-butoxide anion). This computational part was carried out and evaluated by Allan Young.



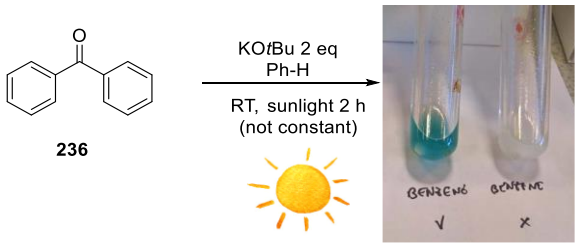
Entry	Event	*ortho* (kcal/mol)		*meta* (kcal/mol)		*para* (kcal/mol)	
		ΔG*	***ΔG*rel**	***ΔG****	***ΔG*rel**	***ΔG****	***ΔG*rel**
1	Butoxide addition	15.6	5.8	21.1	18.6	15.1	5.0
2	Deprotonation	25.9	9.7	-	-	20.7	7.0

Table 14. Calculated Gibbs free changes for addition and deprotonation.

Overall, these qualitative and quantitative tests, coupled with computational studies which indicated unfavourable energy profiles for the proposal, made us think afresh about these reactions.

3.A3.3.3 The effect of light

While performing repeat experiments on the formation of the potassium salt of benzophenone ketyl through reaction with KO*t*Bu on many different days, it was noticed that the time required for the development of the blue colour varied by day. During a (rare) sunny day, the switch to the blue colour was much faster than usual. Parallel experiments with vessel (v) directly exposed to the sunlight and (x) covered in foil, showed the result to be strongly dependent on the irradiation (Picture 2).



Picture 2. Reaction under sunlight: the tube on the left was exposed to the light, the tube on the right was foil-covered.

After this observation, some study of the UV absorption of **236** and of the mixture of **236** with KO*t*Bu in distilled THF was performed (Figure 8). Benzophenone does not absorb radiation at >400 nm (black trace). When KO*t*Bu was added, a tail in the absorption in the visible region (400-600 nm) was detected (violet trace). With time, the appearance of a new maximum around 400 nm revealed new insights into the mixture's UV absorption. A plausible explanation for this time-dependent process is that KO*t*Bu interacts with benzophenone affecting the absorption diagram when it is in its monomeric form. Since KO*t*Bu is known to have a tetrameric structure,[151,152] it takes some time for the solvent to disrupt its structure and create the monomeric form.

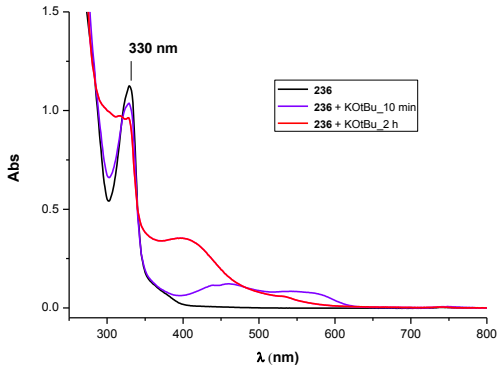


Figure 8. UV absorption of benzophenone (10^{-2} M, black trace) and of benzophenone after addition of the KO*t*Bu (violet trace after 10 min from the addition and red trace after 2 h from the addition) in the absence of any preliminary irradiation.

The samples of mixture of benzophenone and KO*t*Bu in distilled THF were, therefore, separately irradiated with (i.) UV light (λ= 365 nm, 200 W) and (ii.) Vis light (λ= 400 nm,

14.4 W) at room temperature under inert atmosphere. The characteristic blue ketyl gradually developed from the first minute (the photo in Figure 9 shows the characteristic blue ketyl colour developing from the reaction exposed to Vis light 400 nm). The UV light was found to be more effective than Vis light: the development of the colour was much faster when UV light was employed. The confirmation of the formation of the ketyl radical anion of benzophenone **236** was given by UV-Vis spectrometry analysis; after irradiation with UV light for 30 min at rt, the solution was placed in the spectrometer, revealing the appearance of a broad band around $\lambda = 685 \pm 30$ nm, diagnostic of the formation of the ketyl anion **237** as reported in the literature.[153] After air exposure, the band disappeared completely as well as the blue colour, turning the solution colourless. Some NMR measurements were performed and they confirm the formation of radical species (see experimental chapter).

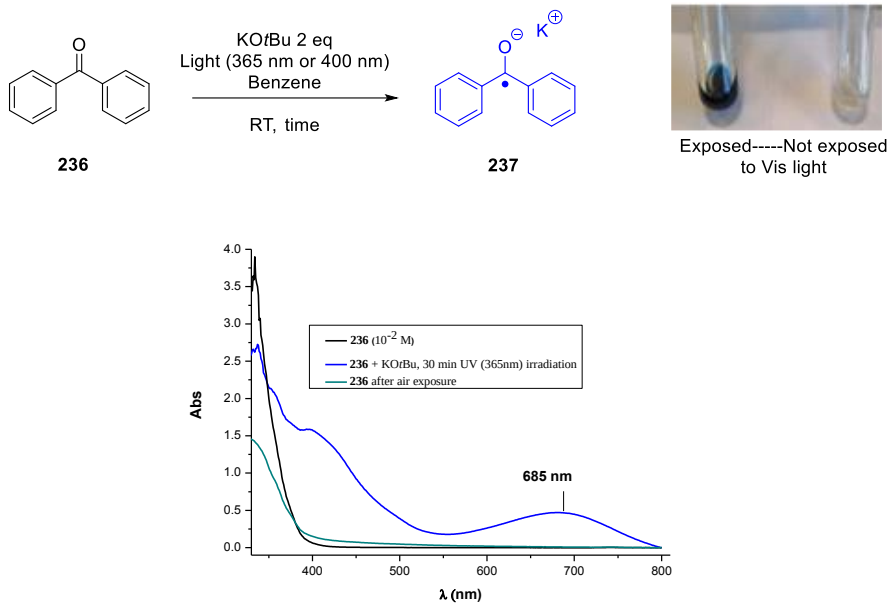


Figure 9. UV absorption of benzophenone (10^{-2} M, black trace) and after addition of the KO*t*Bu + irradiation with UV source (365 nm, 200 W for 30 min, blue trace) in THF. After air exposure, the band disappeared as well as the blue colour giving rise to the green trace.

Interestingly, when NaO*t*Bu was employed instead of KO*t*Bu, the solution remained colourless. Moreover, from the UV-Vis analysis of benzophenone before and after adding NaO*t*Bu, the absorption spectrum did not show any interference as shown in Figure 10.

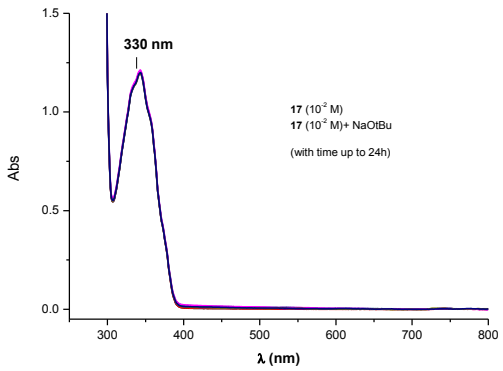
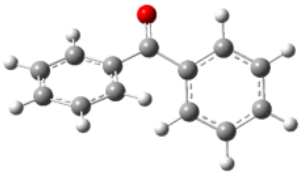
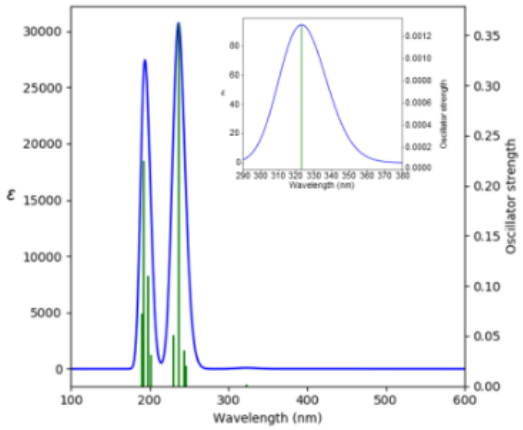


Figure 10. UV-Vis spectrum of benzophenone before and after adding NaO*t*Bu.

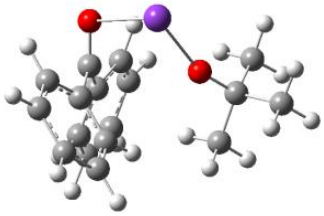
The most intriguing parts of these new observations were that (i) Vis light could cause the formation of the ketyl radical of benzophenone and that (ii) NaO*t*Bu was completely ineffective, even under UV irradiation. To understand these experimental observations, time-dependent density functional theory (TD-DFT) calculations were conducted (Fgure 6, these calculations were performed by Allan Young, member of the Murphy-Tuttle group). Initially, the first singlet excited state of benzophenone was calculated, which corresponds to an n-π^* excitation occurring at 332 nm. It was therefore clear that Vis light could not be responsible for the excitation of benzophenone alone. A study of the complex between a monomer of KO*t*Bu and benzophenone was undertaken. This exhibits excitations at 406 nm and 404 nm which correspond to the charge transfer (CT) from the [HOMO] and [HOMO^{-1}], both residing on KO*t*Bu, to the LUMO, residing on benzophenone. This indicates that it is indeed possible to photo-excite a complex of KO*t*Bu and benzophenone using visible light. The complex between NaO*t*Bu monomer and benzophenone however, does not exhibit any excitation in the visible region, with excitations occurring at 322 nm and 318 nm corresponding to CT from the [HOMO] and [HOMO^{-1}], both residing on NaO*t*Bu, to the LUMO, residing on benzophenone. This lack of excitation in the visible region can explain why no ketyl radical anion is observed in reactions with NaO*t*Bu (Figure 11).

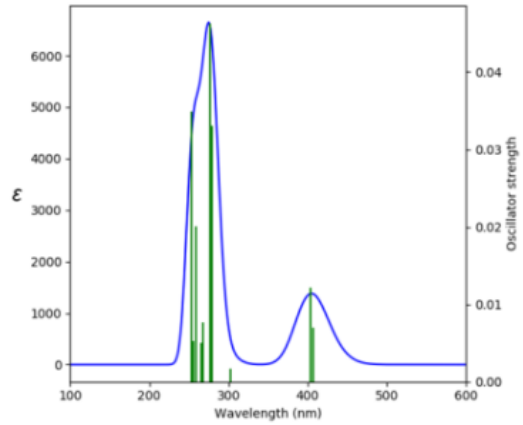
(a)



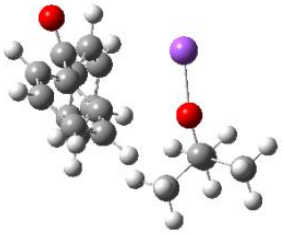


(b)





(c)



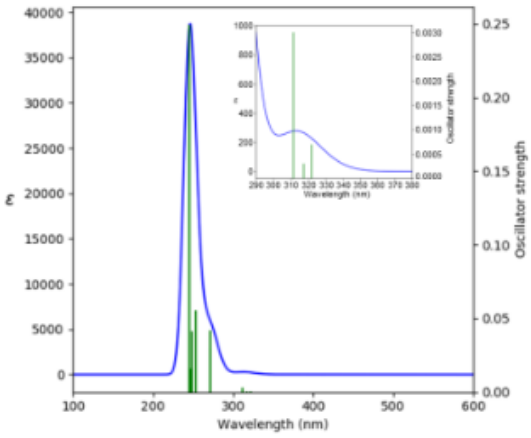


Figure 11. (a)Benzophenone **236** (left) and its computed absorption spectrum (right) with expansion of weak n- π* at 332 nm inset. (b) complex of **236** with KO*t*Bu (left) and predicted spectrum showing the n-π* > 404 and 406 nm (right) (c) complex of **236** with NaO*t*Bu (left) and predicted spectrum (right).

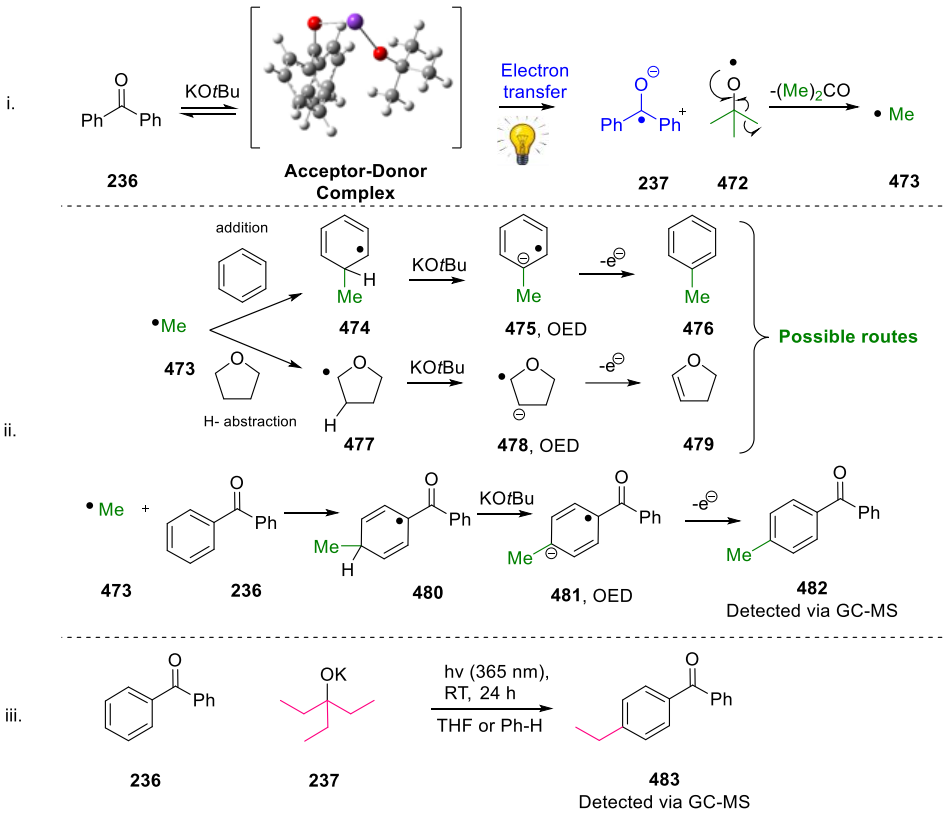
Both experimental observations and computational calculations agreed with the evidence that light plays a key role in the reduction of benzophenone by KO*t*Bu. Moreover, the change of the UV-Vis absorption in the spectrometer as well as in the predicted spectrum (TD-DFT calculations) shows that a complex is formed between benzophenone and KO*t*Bu prior to excitation.

Nevertheless, if direct electron transfer from butoxide anion to benzophenone occurs under light excitation, evidence to support the formation of the corresponding *tert*-butoxyl radical **457** ought to be available (Scheme 108). *Tert*-butoxyl radicals undergo fragmentation instantaneously to form acetone and methyl radicals, as reported in the literature.[154,155] If methyl radical forms, this ought to react with the solvent as it is a very reactive species.[156] In benzene, methyl radical would likely add to form radical **474**, which after further deprotonation by the base would form radical anion **475,** a plausible organic electron donor. In THF, methyl radical would preferably abstract a hydrogen to form radical **477**, which then would form an organic electron donor after deprotonation. The formation of these organic electron donors could lead to the reduction of more benzophenone as well as to the formation of toluene **476** and dihydrofuran **479**. A smaller portion of methyl radical can also add to benzophenone to form radical **480**; this leads to the formation of the organic electron donor **481** after deprotonation. The loss of one electron from **481** determines the formation of methylated benzophenone **482**, detected and characterised via GC-MS. Polymethylated benzophenone was also detected via GC-MS (see Experimental part).

To confirm this result, KO*t*Bu was replaced by the similar base $KOCEt_3$, and this led to the formation of the monoethylated product **483**, also detected via GC-MS.

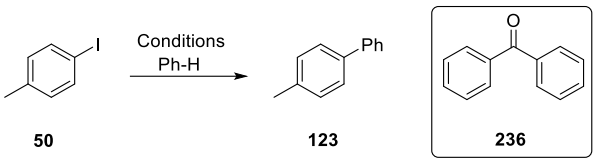
The complexation of KO*t*Bu with benzophenone is an unknown phenomenon (to the best of my knowledge), but similar cases where organic donor and acceptor molecules form a complex have been observed in the past few years (the next chapter will disclose a few examples of this new emerging topic).[157–161]

The formation of the methylated and ethylated benzophenones **482** and **483** represents the first piece of evidence of a direct electron transfer from KO*t*Bu to benzophenone.



Scheme 108. Proposed mechanism. (i) direct electron transfer from KO*t*Bu to benzophenone under UV-Vis light, (ii) fate of methyl radical and formation of methylated benzophenone **482**; (iii) test to prove the origin of methyl radical.

In order to find further evidence of electron transfers in benzene, benzophenone was used as photoactivated initiator of the BHAS with *p*-iodotoluene **50**. The reaction mixture included **50**, benzophenone and KO*t*Bu in benzene (coupling partner and solvent for the reaction). The reaction tube was irradiated at 365 nm for 15 min and then, after switching off the irradiation, the reaction was heated for 18 h at 130 °C. This afforded 74% of 4-methylbiphenyl **123**; the blank reaction with benzophenone omitted gave 12% of product **123** in comparison.



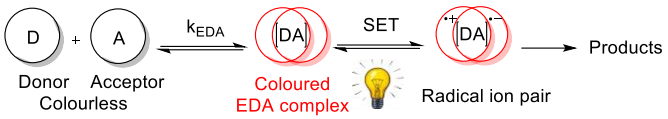
50 123 236

Entry	Conditions	Light (λ) 200W	123 (%)
1a	**236**, 1 eq KO*t*Bu 2 eq	365 nm	74
2a	KO*t*Bu 2 eq	365 nm	12

Table 15. The reactions were firstly placed at RT under UV irradiation for 15 min and then placed in absence of irradiation at 130 °C for 18 h in an oil bath.

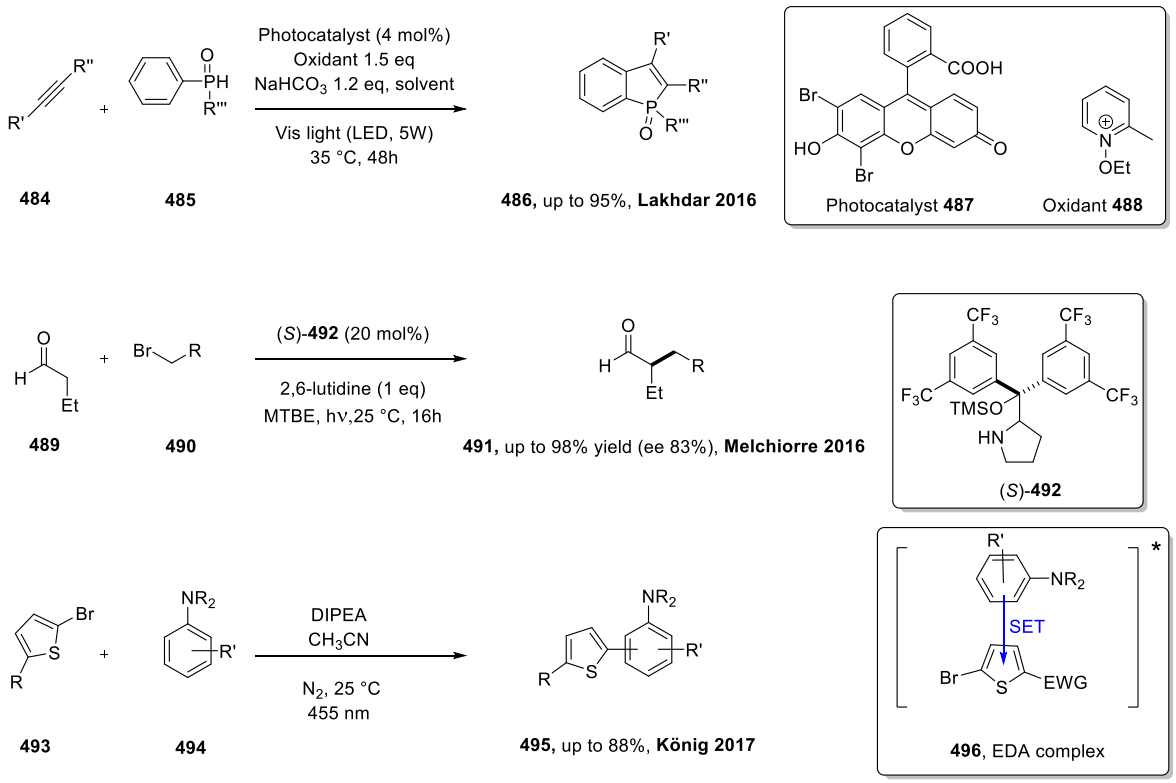
3.A3.3.4 Where photochemistry meets organocatalysis

In 1952 Robert Mulliken formulated the charge-transfer theory to rationalise the formation of a strong colour by reacting two colourless species, under photochemical conditions.[162] This theory discloses how an electron-rich species (the donor D) and an electron-accepting species (the acceptor A) can form a molecular aggregate in their ground state. The association of suitable D and A forms a new entity, (an intermediate) termed an electron donor-acceptor (EDA) complex. This latter has different chemical and physical properties from the two precursors. For example, it might show a new UV absorption band, called a charge-transfer band (hνCT). This new absorption is associated with the single electron transfer (SET) from the donor to the acceptor (Scheme 109).



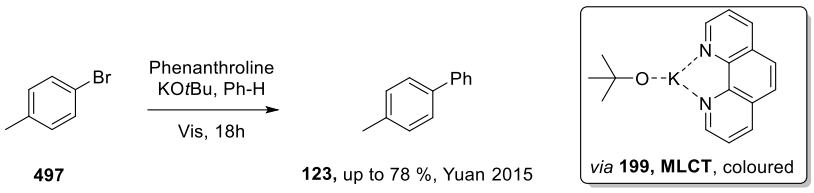
Scheme 109. Intermolecular EDA complex formation between two substrates and SET, after complexation, triggered by light.

A very interesting point of this process is that the charge-transfer band can lie at a wavelength far away from the absorption of the precursors, often in the visible region.[159,163] New chemical reactions are then accessible under activation by Vis light. Some recent publications show the potential of this new methodology. Lakhdar performed a mechanistic investigation on the EDA complex between eosin (the photocatalyst **487**) and a pyridinium salt (oxidant **488**). Highly functionalised benzophosphole oxides **486** were synthesised from reactions of arylphosphine oxide **485** with alkynes using the aforementioned EDA complex.[161] Melchiorre recently reported an enantioselective photochemical α-alkylation of aldehydes **489** with electron-poor organic halides **490**, by using chiral amines, such as (*S*)-**492**. This latter forms an enamine with aldehyde **489** and this latter forms a photoactive EDA complex with halide **490**. Moreover, it determines the asymmetric process leading to enantioselective products **491**.[157] Other similar methodology of enantioselective organocatalysis with light activation have been reviewed by Melchiorre. [159] Recently, König achieved a catalyst-free, direct (hetero)arylation of anilines under blue LED irradiation. The aniline **494** is suggested to be the donor species, whereas the bromoarene **493** is the electron-acceptor species. The complexation of the two species (**496**, EDA complex) creates a charge-transfer band (hνCT) which allows a photoexcitation in the blue region.[164]



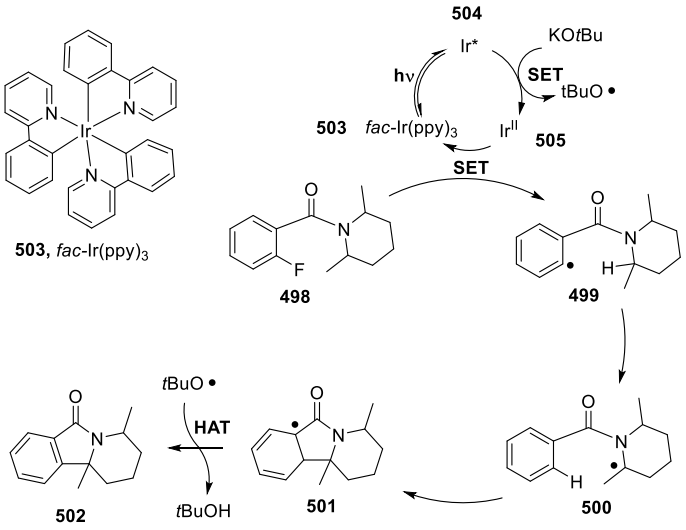
Scheme 110. Recent works on the EDA complexes.[157,161,164]

The involvement of KO*t*Bu in the formation of EDA complexes is somewhat new. Yuan in 2015 reported a biaryl synthesis under visible light photoredox using phenanthroline and KO*t*Bu as promoters.[165] In his case, KO*t*Bu was proposed to create a metal ligand charge transfer (MLCT) complex **199** (Scheme 111) with phenanthroline which was coloured under inert atmosphere. The mixture of KO*t*Bu with phenanthroline gave rise to a new absorption in the Vis region, which does not occur when both reagents are analysed singularly *via* UV-Vis spectrometry. This complex can then donate an electron to *p*-bromotoluene **497** and promote the formation of the coupled product **123**. The reaction does not occur in the dark, unless the temperature is raised at 100 °C where then organic electron donors take hold, as previously shown (Chapter 1.2.3).[72]



Scheme 111. Arylation chemistry promoted by the photoactive complex **199,** reported by Yuan.[165]

More recently, Tan and coworkers reported a single electron transfer from KO*t*Bu to photoactivated Ir complex **504**.[166] Ir^{II} then donates an electron to fluoroarene **498** leading to radical **499.** This then evolves to the more stable radical **500**, and finally after HAT to *t*-butoxyl radical, product **502** forms.[166]



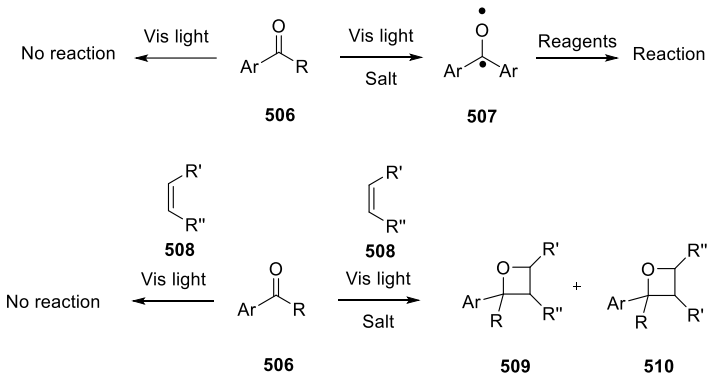
Scheme 112. Direct electron transfer to photoactivated Ir* complex **504** proposed by Tan *et al.*.[162]

3.A3.4 Conclusion and future work

Thanks to this investigation, the mysterious formation of radicals in the reaction with benzophenone and KO*t*Bu was finally solved. Although benzophenone absorbs strictly in the UV region, the presence of KO*t*Bu determines the formation of a discrete complex between

the two reagents, which absorbs Vis light. This event makes possible the electron transfer from butoxide to benzophenone.[2]

Further studies will aim to find whether other salts can modify the UV absorption of aromatic ketones. Starting from this, an evaluation of new types of reactions can be undertaken under conditions otherwise not optimal in absence of the additive salt (Scheme 113). An example of reaction that could be promoted by the presence of a salt would be the Paterno-Büchi reaction.[167,168] With this perspective, different oxetanes **509** and **510** would originate from different aromatic ketones **506** with different alkenes **508**. After benzophenone, other substrates can be tested as well.[169]



Scheme 113. Evaluation of new type of reactivity triggered only with the presence of additive salts.

3.B K^+ TRIUMPHS OVER Na^+ IN ELECTRON TRANSFER REACTIONS

An intriguing point of the transition metal-free cross coupling reactions and, more generally, electron transfer reactions, is that K^+ cation prevails in the literature over Na^+ cation. Albeit that a few examples in the literature engage NaO*t*Bu as base in the BHAS process,[50,101] overall, KO*t*Bu is the undisputed ruler in electron transfer reactions. This project aims to find alternatives to KO*t*Bu and/or perhaps give more evidence that K^+ plays a key role in electron transfer reaction.

3.B4 Role of KH in benzene in electron transfer reactions

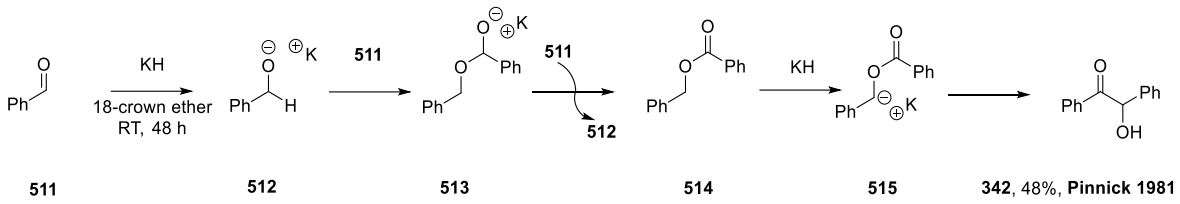
Potassium hydride, KH is widely used in organic synthesis, especially as powerful base. Due to its extremely basicity, it is a very reactive reagent and not easy to handle. It is commercially available as a dispersion in mineral oil. The oil-free powder is only compatible with aprotic solvents under inert atmosphere.

3.B4.1 Background

KH is used to deprotonate many different substrates such as enolisable carbonyl compounds, alcohols, amines, phenols and sulfoxides and it is normally used when NaH and LiH (weaker bases) are not effective enough.[170]

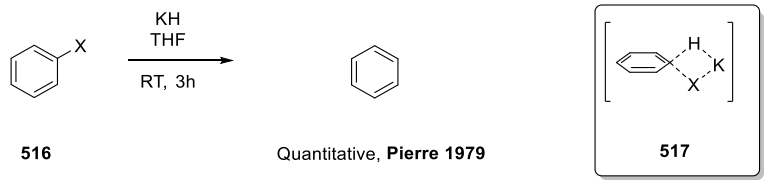
KH can also act as a nucleophile. One of the first examples was reported by Pinnick in 1981, where KH, and not NaH, was responsible of the reduction of benzaldehyde **511** (Scheme 114).[171] The reaction is proposed to proceed *via* intermediate **513** after hydride delivery from KH to **498** and attack of the resulting anion **512** on the starting material. Intermediate **513** then delivers a hydride to starting material and intermediate **514** can undergo deprotonation to form anion **515** which finally rearrages analogously to the Wittig rearrangement of ether anions.[172] This mechanism was supported by the fact that adding methyl iodide to the reaction, methylated **512** was obtained. A first hypothetical

deprotonation of **511** by KH was ruled out as no acetophenone was observed at the end of the reaction in presence of MeI.



Scheme 114. Report by Pinnick where KH acts as a nucleophile with benzaldehyde leading to benzoin **342**.[171]

KH behaves uniquely and differently than sodium hydride, NaH, towards haloarenes as well. Pierre *et al.* observed quantitative dehalogenation of halobenzene with KH in THF. [173] He found the order of reactivity ArI > ArBr >> ArCl, opposite to the normal order of reactivity for S_NAr reactions. Moreover, benzyne formation was ruled out in THF due to the absence of hydrogen gas evolution. Pierre suggested the possibility of a concerted dehalogenation through a 4-membered transition state **517**. Many other examples of this type of transformation, now named CS_NAr, were reported thereafter. [174,175]

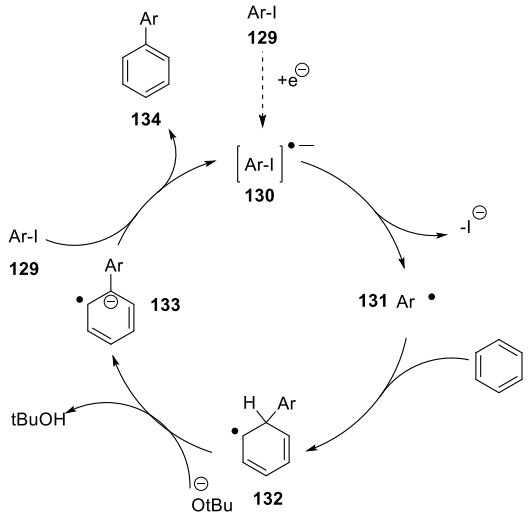


Scheme 115. Concerted dehalogenation through a 4-membered transition state reported by Pierre.[173]

Intrigued by the extremely strong basicity of KH, as well as its unique properties in THF, we aimed to study the role of KH in electron transfer reactions.

3.B4.2 Project Strategy

The transition metal-free cross coupling of haloarenes (BHAS), mediated by the base (often KO*t*Bu) and an organic additive now has a lot of evidence that supports the proposed mechanism in the literature.[47–50,55,56,92,95,101] The BHAS process (Scheme 116) which lies at this type of transformation, firstly proposed by Studer and Curran[51] has been already described in this thesis (Chapter 1.2.3). In this radical process, the base is proposed to play an important role for both initiation and propagation steps and it seems that in most of the reports, KO*t*Bu is preferred to NaO*t*Bu, although in some studies this latter was effective as well.[50,101]

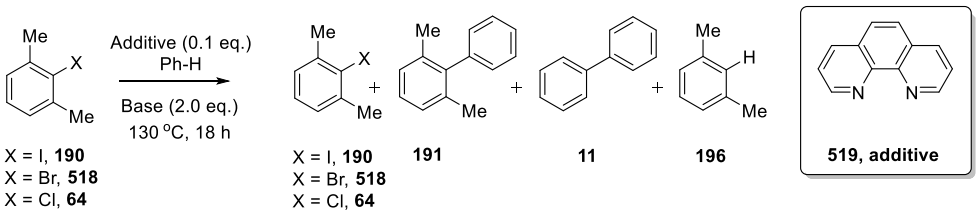


Scheme 116. Base-promoted Homolytic Aromatic Substitution (BHAS) proposed by Studer and Curran.[51]

KH is not a commonly used base in transition metal-free cross coupling reactions. The aim of this project is to study the behaviour of KH in electron transfer reactions, in particular in the arylation chemistry where benzene is the solvent and the coupling partner.

3.B4.3 Results and discussion: role of KH in benzene in electron transfer reactions

In chapter 1.2.3 the roles of organic electron donor and the base were explained in the BHAS mechanism. A key element of the BHAS mechanism is that it can be triggered by either an organic electron donor or by a benzyne intermediate. This latter cannot be formed with *ortho*-blocked substrates such as **190** and the BHAS mechanism can only be triggered by an organic electron donor formed with the additive **519**; therefore the reaction with only KO*t*Bu gives almost no conversion as usual (Entry 1, Table 16). Moreover, after many tests with different organic electron donors, the ratio of the mixture of the coupled products (**11** and **191**) was always found to be similar (~3.5:1, respectively).[1,66,76] In fact when a mixture of KO*t*Bu and phenanthroline was added in the reaction, the BHAS mechanism was triggered leading to a 18.2% yield with ratio 3.7:1 of coupled products (Entry 2). A very similar yield and ratio of products was found switching from KO*t*Bu to KH, with the only difference that less starting material was recovered at the end of the reaction (Entry 3). This latter result further challenges KO*t*Bu's privileged status and suggests that any base (that is powerful enough) could promote the formation of an organic electron donor.[1] In the absence of any additive, KH causes the formation of a modest amount of coupling products and dehalogenation of most of **190** (Entry 4), differently from what was observed with KO*t*Bu. Moreover, the ratio of the coupled products was somewhat changed in favour of a greater amount of biphenyl **11** (7.7:1) This suggests that KH, under these conditions, can trigger the BHAS and an additional route for the formation of biphenyl could occur alongside the normal BHAS pathway.

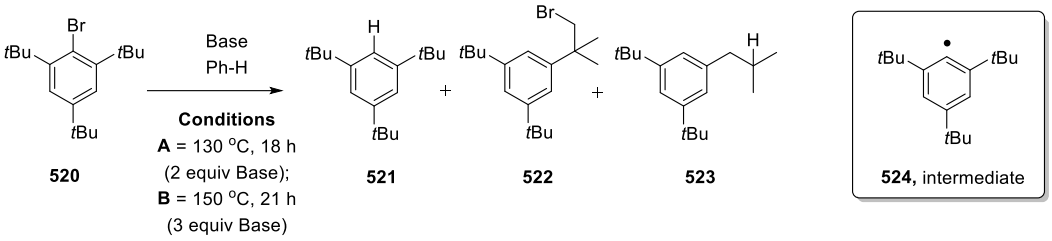


Entry	Additive /Base	Ratio[a] 11:191	11 + 191 yield[b] (%)	Recovered 190, 518 or 64 (%)[b]
1	-/KOtBu	-	<0.5	72
2	**519**/KO*t*Bu	3.7:1	18.2	33
3	**519**/KH	3.9:1	16.3	<1
4[c]	-/KH	7.7:1	5.5	14
5	-/NaH	No reaction detected		
6[d]	-/KH	7.4:1	3.9	3
7[e]	-/KH	7.0:1	1.5	9

Table 16. [a]2,6-Dimethyliodobenzene **190** was used as a substrate unless otherwise stated. Ratios are determined by ^{1}H NMR of the crude reaction mixture (see Supporting Information). [b]Yield (%) of combined biaryls (**11** and **191**), or yield (%) of returned haloarene determined by ^{1}H NMR. [c]Average of two runs. [d] **518** was used as a substrate. [e] **64** was used as a substrate.

The corresponding bromide **518** (Entry 6) and chloride **64** (Entry 7) showed similar results and almost identical ratio. On the other hand, NaH was ineffective under these conditions (Entry 5). The reactions in entries 5-7 were performed by Dr Samuel Dalton and Dr Joshua Barham and are added here for completeness.

Intrigued by the low recovery of starting material when haloarenes **190**, **518** and **64** were treated with KH, 2,4,6-tri-*tert*-butylbromobenzene **520** was deployed thereafter. This probe bears two hindered groups in the *ortho*-position, which would make difficult both coupling and H-abstraction from the solvent. Under conditions A (130 °C, 18h) the blank reactions in the absence of base, or using KO*t*Bu, gave no reaction (Entries 1-2, Table 17). When KH was employed as base, dehalogenated product **508** (28%) as well as recovered starting material (56%) were found; in addition, two other products were characterised, bromide **509** and rearranged product **510** (Entry 3). No deuterium incorporation was observed after quenching the reaction with D_2O (Entry 3, Footnote d).

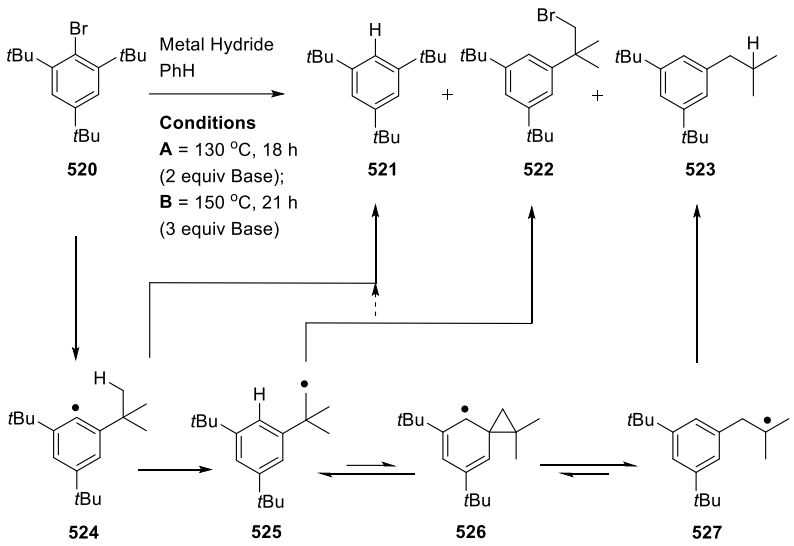


Entry	Base	Solvent/ Quench	Yields (%)[a]				D-incorporation
			521	522	523	520	
1[b]	-	C_6H_6/H_2O	No reaction				-
2[b]	KO*t*Bu	C_6H_6/H_2O	No reaction				-
3[c]	KH	C_6H_6/H_2O	28	5	6	56	No[d]
4	KH	C_6D_6/D_2O	18	11	3	66	Yes[e,f]
5[g]	KH	C_6H_6/H_2O	31	1	13	29	-

Table 17. D-incorp. = Deuterium incorporation. Unless otherwise stated, conditions **A** were used. [a]Yields determined by ^{1}H NMR of the crude reaction mixture. [b]No products were observed, **520** was recovered in quantitative (ca. 100%) yield. [c]Average of eight replicates. [d]After quenching with D_2O, D-incorporation was not detected. [e]D-incorporated was detected by ^{2}H NMR of the reaction mixture (see Experimental section). [f]After quenching with H_2O, D-incorporation was still detected. [g]Reaction conducted under conditions **B**.

In C_6D_6 as medium, **521** was detected (18%), a lower yield than in C_6H_6, but only traces of **521-d$_1$** were present, as well as the two side-products **522** + **523** (Entry 4). This is a clear indication that the proton that replaces the Br derives from KH, although solvent partially affects the reaction progress. Under harsher conditions B (150°C, 21h) an increased yield of products was observed, but with poorer mass balance (Entry 5).

The mechanism can be rationalised as described in Scheme 117. Bromide **522** and rearranged product **523** are clear reporters of a radical process. KH somehow causes the formation of radical **524** and this then undergoes 1,4-HAT to form radical **525** from which bromide **522** must arise. Alternatively, radical **525** can undergo a neophyl rearrangement from the less stable primary alkyl radical to the more stable tertiary radical **527** as a thermodynamic sink. Radical **527** would lead to arene **523**. Ingold reported that the radical intermediate **524** partakes in a very rapid 1,4-HAT with one of the *ortho*-*tert*-butyl groups via quantum mechanical tunnelling (QMT) leading to a new radical species **525**.[155]

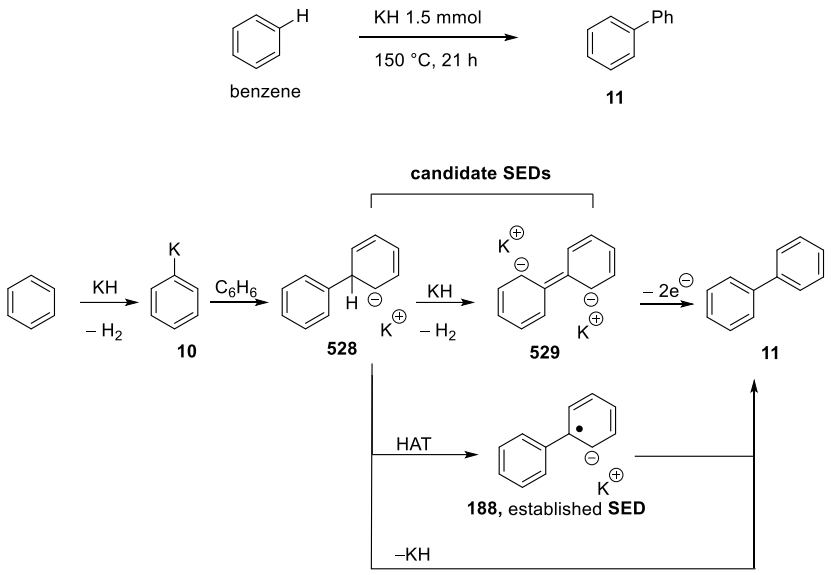


Scheme 117. KH-mediated reactions of 2,4,6-tri-*tert*-butyl-bromobenzene **520**.

Apart from the clear evidence that KH in benzene promotes radical reactions, two pieces of evidence raise the importance of benzene in the reaction: (i) the deuterium incorporation in the product could arise from deuterium abstraction by radical **525**; (ii) the deuterium must come from benzene-d_6 (Entry 4, Table 17) and not from the quencher D_2O, inasmuch as no deuterium incorporation was observed in entry 3 after D_2O quench (see footnote d).

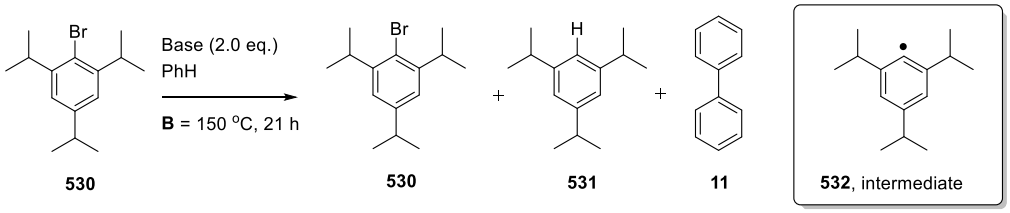
Intrigued by the role of benzene in such reactions, a blank reaction in the absence of haloarene was performed. When benzene was reacted with KH under 150 °C for 21h, a small amount of biphenyl was formed (Scheme 118). The formation of biphenyl is a key element of this process because it could explain: (i) the formation of a candidate organic electron donor; (ii) HAT from the solvent; (iii) the increased amount of biphenyl with substrate **190**. If deprotonation of benzene occurs to form phenylpotassium **10**, this then would attack benzene to form phenylcyclohexadienyl potassium **528**, as previusely observed by Morton *et al*.[176] Anion **528** can undergo deprotonation by a second equivalent of KH to form dianion **529**; both these two latter molecules would be plausible electron donors capable of donating an electron to a haloarene.[177,178] Alternatively, anion **528** would undergo HAT with abstraction by a radical species such as intermediate **524** to form **525**, or **528** could undergo KH expulsion. All these pathways would lead to the formation of biphenyl and would explain the three points previously mentioned. Switching the base from KH to KO*t*Bu or NaH, no

biphenyl was observed, and this would explain why no reaction was observed with substrates **190, 518** and **64** previously tested (Table 16).



Scheme 118. Formation of biphenyl from benzene and KH and proposed pathways.

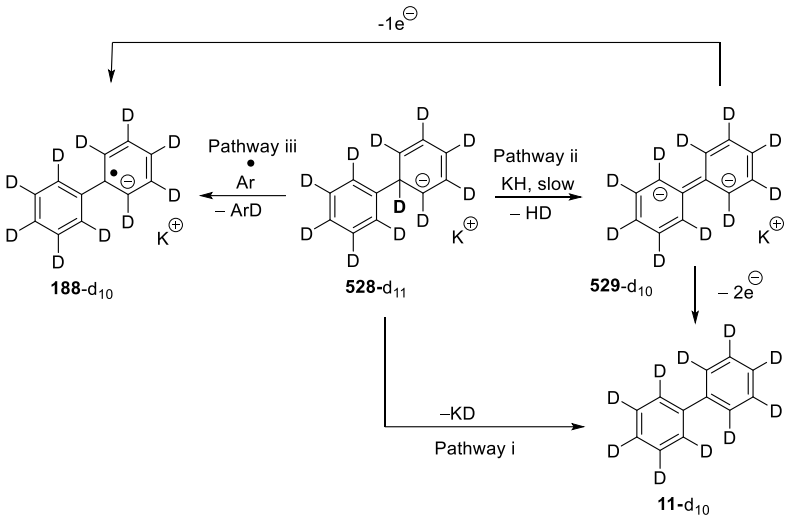
In light of the previous results, 2,4,6-tri-*iso*-propyl-bromobenzene **517** was tested. This substrate benefits from intermediate properties compared to the previous substrates, inasmuch as it is more hindered than iodo-*m*-xylene **190** (this would make any coupling with solvent much more difficult) and less than 2,4,6-tri-*tert*-butylbromobenzene **507** (this would allow an easier HAT from solvent). In fact the H-incorporation from KH vs HAT from solvent ratio was now clarified. Subjecting substrate **517** to KH under 150°C for 21h in C_6H_6, both dehalogenated product **518** and biphenyl **11** were detected as 25% and 10% respectively (Entry 1, Table 18), but conspicuously higher yields of **518** were obtained when deuterated solvent was employed under the same conditions (Entry 2, this reaction was performed in 3 replicates). In this case, dehalogenated product consists in the mixture of **518** and **518-d$_1$**, detected *via* ^{1}H-NMR and ^{2}H-NMR. Only traces of products were observed when NaH was used (Entry 3).



Entry	Base	Solvent/ Quench	Yields (%)[a]			D-incorporation
			531	11	530	
1	KH	C_6H_6/H_2O	25	10	62	-
2[b]	KH	C_6D_6/D_2O	55	0	14	Yes
3[c]	NaH	C_6H_6/H_2O	4	1	95	-

Table 18. Reactions were conducted using conditions **B**. [a]Yields determined by ^{1}H NMR of the crude reaction mixture. [b]Average of three replicates. [b]The yield of **531**+**531-d$_1$** is reported, see Supporting Information.

The higher yield of **531** when benzene-d_6 was employed could be rationalised taking into consideration the deuterated intermediates arising during the proposed process (Scheme 119). The formation of intermediate **528-d$_{11}$** is followed by 3 events as also previously mentioned: (i) expulsion of KD; (ii) de-deuteration to form disalt **529-d$_{10}$** with parallel liberation of HD; (iii) deuterium atom transfer (DAT) by **532** (Table 18) to get radical anion **188-d$_{10}$**. Only path (i) determines the termination of the reaction as this leads to the direct formation of biphenyl **11-d$_{10}$** with simultaneous electron donor disappearance. If isotope effects of paths (i) are significant, then the concentration of **528-d$_{11}$** may build up in the solution to a greater level than the non-deuterated counterpart that is present when benzene is used as solvent. This means that all electron donors may contribute in synergy to the progress of the radical process: for example, dianion **529-d$_{10}$** and radical anion **188-d$_{10}$** both contribute to the generation of aryl radical **532** by SET; on the other hand salt **528-d$_{11}$** acts as a deuterium source for the formation of product **531-d$_1$**.



Scheme 119. Consideration of deuterated intermediates arising from benzene-d_6 and KH.

3.B4.4 Conclusions

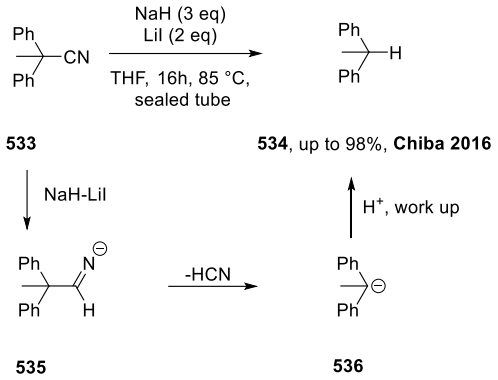
In summary, KH promotes CS_NAr in THF[173] and benzene. Additionally, in benzene, it promotes radical reactions and studies with deuterated vs. unlabelled benzene show a clear dependence on the solvents. Isolation of small amounts of biphenyl in the blank reaction (in the absence of substrate) justifies that deprotonation of benzene and formation of phenylpotassium occurs. Organic electron donors are generated subsequently, triggering radical processes that either initiate the BHAS process, when the radical is hindered, cause radical-mediated side reactions .[3] This study further supports that KO*t*Bu is not the only privileged base in electron transfer reactions. Morever, a competing electron donor formation can occur from other bases and, despite the small amount, this can trigger radical chains.

3.B5 Potassium Salts Facilitate Reductive Coupling of Arenes by Potassium Metal

With the previous investigations on the role of KO*t*Bu and KH in electron transfer reactions, a remarkable difference in reactivity with the respective counterparts NaO*t*Bu and NaH was found. Whilst performing some blank reactions trying to evaluate the reactivity of K metal, KH and KO*t*Bu in benzene, an interesting observation was made.

3.B5.1 Background

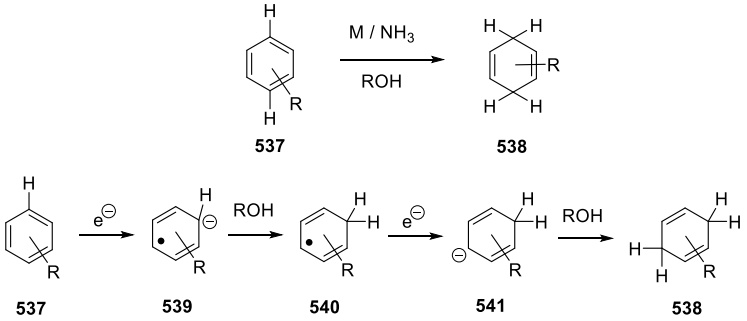
Arenes, such as benzene and toluene, are normally unreactive towards alkali metals. Routinely, they are dried by refluxing over potassium or other alkali metals.[179] Potassium, in particular, is the most convenient drying agent, since the melting point (mp: 63.5°C) is below the boiling point of the solvents and this allows a fresh liquid surface of the metal to be constantly exposed to the solvent. In a recent work from Murphy, K metal was found to be a much more effective drying agent for benzene than $LiAlH_4$ and sodium metal.[65] In the previous chapter (3.B4) the reactivity of benzene with i) KO*t*Bu and ii) KH was evaluated under harsh reaction conditions (150 °C, 21h) and a little biphenyl was formed when benzene was reacted with ii) KH. The reactivity of these powerful reagents can change, depending on the environment they are subjected to. For example, NaH can adapt its reactivity in the presence of selected salts: NaH normally acts as a powerful Brønsted base, but addition of lithium iodide or sodium iodide converts NaH in a hydridic reducing agent and this was elegantly illustrated by Chiba *et al*.[174,180–185] One example of this novel hydride reduction method is the decyanation of substrate **533** by using the NaH-LiI system (Scheme 120). This results from nucleophilic attack of hydride and fragmentation of the resulting iminyl anion **535**, followed by protonation during the work up.[180]



Scheme 120. Hydride reduction by a sodium hydride-iodide composite reported by Chiba.[180]

The reduction of benzene to benzene radical anion was firstly observed by Hackspill in 1912 by reacting benzene with caesium over two or three days in vacuum at 28°C.[186,187] At the end of the reaction, a black solid was formed which reacted with water and alcohol to form biphenyl and hydrogen gas.

When an arene **537** is subjected to an alkali metal in ammonia medium and in the presence of an alcohol, the Birch reduction takes place.[188] In particular, the metal donates an electron to the arene and forms the resulting radical anion **539**. This latter is protonated by an alcohol and the radical **540** can further receive another electron and form anion **541** which gives the 1,4-dihydrobenzene **538**.

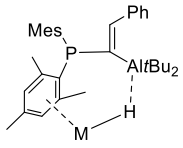


Scheme 121. Birch reduction of substituted benzene **537**.[188]

A change of reactivity of alkali metals was reported by Morton *et al.* over 60 years ago. He reported the metalation of fluorene by KOH with the assistance of Na metal to remove the

water formed simultaneously.[189] Moreover, he achieved the dimetalation of benzene, thiophene and other arenes by using a mixture of amylsodium and different alkoxides as additive. With benzene, *meta*- and *para*- di-metalation occurred according to the nature of the additive.[190] One year later, he reported the metalation of toluene by K metal in the presence of sodium oxide Na_2O. The reaction did not work if K metal was replaced by Na metal.[191] In all these studies, the presence of the additive was essential for the reaction success. The additive was suggested to influence the reactivity by cation interactions. Although, the cation does not participate directly in the reaction, the immediate proximity to electron-rich structures such as anions or arenes (*via* electrostatic force) was proposed to create a disturbance of the reactivity.[192]

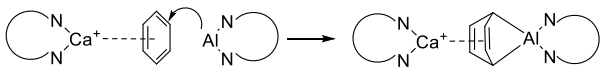
Another example of cation-arene interaction was reported by Uhl *et al.*[193] They used a phosphorus/aluminium-based frustrated Lewis pair (FLP) as an ion pair receptor capable of solubilising and activating metal hydrides LiH, NaH and KH (**542**). Crystal structure determination revealed a direct interaction Li-P but Na and K display no interactions with the phosphorus atom, but instead have short contacts with the aromatic ring.[193]



542, M = K or Na

Figure 12. FLP complexed with metal hydride reported by Uhl.

Another recent work published by Harder discloses the dearomatisation of benzene *via* complexation with Ca^{2+} (Lewis acid) **543** and Al(I) (Lewis base) organic complexes **544** to achieve a boat-shaped $C_6H_6^{2-}$ **545**. The crystal structure of the complexed boat-shaped $C_6H_6^{2-}$ was obtained by X-ray diffraction studies.[194]

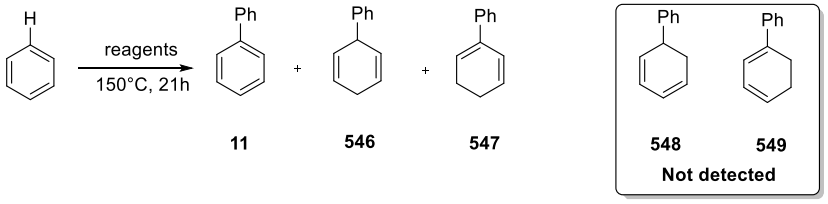


543 **544** **545**, **Harder** 2018

Scheme 122. Reduction of benzene facilitated by Lewis acid/base combination reported by Harder.[194]

3.B5.2 Project strategy

As previously mentioned, whilst performing some blank reactions trying to evaluate the reactivity of K metal, KH and KO*t*Bu in benzene, a change of reactivity of K in benzene was found in the presence of either KO*t*Bu or KH. During the reaction potassium became molten and spherical. When new products were observed, the potassium was found to be still present at the end of the reaction as a molten silver-coloured ball. The formation of the products was always accomplished by consumption of the the molten K metal and by the change of the colouration from colourless to black.



Entry	Reagents (1.5 mmol)	Conditions	Yields (mg)		
			11	**546**	**547**
1	K	150 °C, 21h	-	-	-
2	KH	150 °C, 21h	traces	-	-
3	KO*t*Bu	150 °C, 21h	-	-	-
4[a]	K + KO*t*Bu	150 °C, 21h	122 mg	12 mg	3 mg
5	K + KH	150 °C, 21h	51 mg	12 mg	16 mg

Table 19. Reactions performed in pressure tubes under inert atmosphere at 150°C for 21h, 1.5 mmol of each reagent were used with a large excess of benzene (5 mL).[a] Average of 4 replicates.

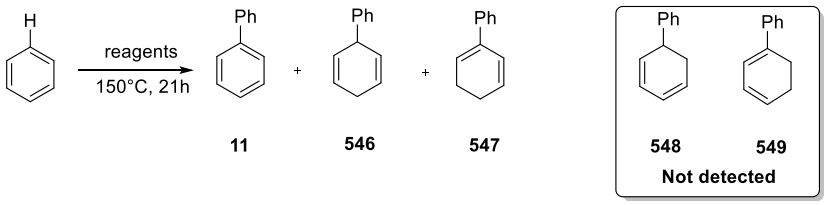
When K metal was allowed to react with benzene at 150 °C, no reactivity was observed (Entry 1, Table 19). When benzene was treated with KH a small amount (less than 1 mg) of biphenyl was found (Entry 2), whereas when KO*t*Bu was employed no product at all was observed (Entry 3). When benzene was allowed to react with a 1:1 mixture of K metal and KO*t*Bu, biphenyl (122 mg) was found at the end of the reaction, as well as small amounts of regioisomers **546** and **547** of dihydrobiphenyl **(**Entry 3, average of 4 replicates, see

Experimental chapter). When KH was added to K and benzene in a 1:1 ratio, biphenyl (51 mg) was found as well as **546** (12 mg) and **547** (16 mg). With this preliminary screening, the importance of a synergic effect was underlined for this reaction. In the literature, no precedent for such new observation was found. It was not clear whether the reaction originated in a change to the potassium metal or to the benzene or to the K^+ source, so a series of experiments was performed to probe this.

3.B5.3 Results and discussion

3.B5.3.1 Reactions with K metal

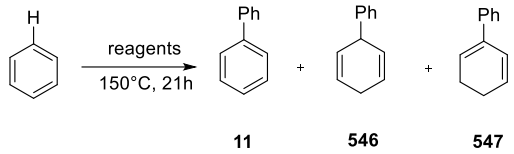
A first investigation on how varying the quantities of K metal and KO*t*Bu altered the outcome of the reaction was performed. When 1.5 mmol of K metal and KO*t*Bu were used, 115 mg of biphenyl was obtained (yield by isolation this time, Entry 1, Table 20). Three experiments (Entries 2-4) explored the reaction on a smaller scale, using benzene (2 mL, previously 5 mL of benzene were used) with equimolar K and KO*t*Bu (0.5 mmol) a proportional amount of biphenyl was obtained. Comparison of entry 3 with entry 4 shows that the effect of the stoichiometry of the K metal is much more significant than the stoichiometry of KO*t*Bu. This emphasises the fact that a reductive process is happening with potassium as the source of electrons, and with the salt supporting the process. If electrons in K metal are available, then the reductive coupling can occur with much less than stoichiometric salt, but if the amount of K is curtailed, then the progress of the reaction is limited, regardless of the presence of the stoichiometric amount of the salt. No reaction occurs at room temperature (Entry 5).



Entry	Reagents	Yields (mg)		
		11	**546**	**547**
1[a]	K (1.5 mmol), KO*t*Bu (1.5 mmol)	122 mg	12 mg	3 mg
2	K (0.5 mmol), KO*t*Bu (0.5 mmol)	32 mg	-	-
3	K (0.1 mmol), KO*t*Bu (1.5 mmol)	1.0 mg	-	-
4	K (0.5 mmol), KO*t*Bu (0.1 mmol)	30 mg	-	-
5[b]	K (0.5 mmol), KO*t*Bu (0.5 mmol)	-	-	-

Table 20. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via NMR using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents. [a] Isolated yield.[b] Reaction performed at RT.

The next step was the evaluation of the nature of the cation, keeping the anionic counterpart constant. Interestingly, adding LiI to an equimolar amount of K metal led to no reaction (Entry, 1 Table 21). NaI, KI, RbI and CsI were all effective, although the reaction with NaI gave a much lower yield (Entries 2-5). This series of experiments underscores the unimportance of a base in the reductive coupling process. Nonetheless, higher amounts of regioisomers **546** and **547** of dihydrobiphenyl were produced in absence of base, underlining that the base might play an important only in the biphenyl formation. Due to the commercial paucity of Rb and Cs salts, attention was focused on the difference between Na and K cations. Interestingly, when K metal was reacted with NaO*t*Bu in benzene, no coupling was observed (Entry 7) and a similar outcome was found between KBF_4 and $NaBF_4$: only the presence of K salt resulted in effective formation of coupled product, whereas Na salt only gave a small amount of dihydrobiphenyl **546** (Entries 8-9).



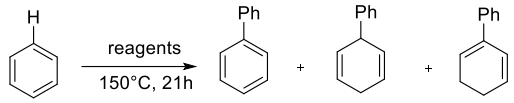
Entry	Reagents	Yields (mg)		
		11	**546**	**547**
1	K (1.5 mmol), LiI (1.5 mmol)	-	-	-
2	K (1.5 mmol), NaI (1.5 mmol)	15 mg	6 mg	-
3	K (1.5 mmol), KI (1.5 mmol)	54 mg	traces	traces
4	K (1.5 mmol), RbI (1.5 mmol)	42 mg	41 mg	-
5	K (1.5 mmol), CsI (1.5 mmol)	18 mg	43 mg	25 mg
6	K (1.5 mmol), KO*t*Bu (1.5 mmol)	122 mg	12 mg	3 mg
7	K (1.5 mmol), NaO*t*Bu (1.5 mmol)	-	-	-
8	K (1.5 mmol), KBF_4 (1.5 mmol)	96 mg	11 mg	5 mg
9	K (1.5 mmol), $NaBF_4$ (1.5 mmol)	-	5 mg	-
10	K (1.5 mmol), KBr (1.5 mmol)	47 mg	17 mg	5 mg
11	K (1.5 mmol), KF (1.5 mmol)	14 mg	11 mg	traces
12	K (1.5 mmol), Me_4NCl (1.5 mmol)	-	-	-

Table 21. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents.

The investigation now progressed to vary the nature of the anionic counterpart of the salt. KI and KBr (Entries 3 and 10) both afforded similar quantities of biphenyl, but about half of the amount that had resulted from KO*t*Bu. Another question that arose was: does the yield of this reaction depend on the extent of the freedom of the potassium salt to coordinate to the arene that is being reduced? Looking firstly at KF (Entry 11), where we imagine the potassium to be strongly held by the fluoride, the reaction yield drops down. On the other extreme, when KBF_4 was deployed (Entry 8), featuring a potassium cation that is much more available for coordination, a massive increase in the amount of product was obtained.

When Me_4NCl was added to the reaction (Entry 12) no conversion was observed, supporting the hypothesis that the cation is much more important than the anions in the reaction process.

A small screening of the group II metals was carried out (Table 22). Mg^{2+} cation was found to be ineffective in the reaction as neither MgI_2 (Entry 1; Table 23) nor $MgBr_2$ (Entry 2) led to any products. Ca^{2+} cation was found to be fairly effective, whereas Sr^{2+} cation was much less so (Entries 3-4). Switching from K to Na metal and utilising the most powerful additive for the K counterpart, no reaction occurred (Entry 5), suggesting that the electron transfer requires a stronger reducing agent (E°_{K/K^+} = 2.998 V, E°_{Na/Na^+} = 2.787 V, measured in glycol).[195]

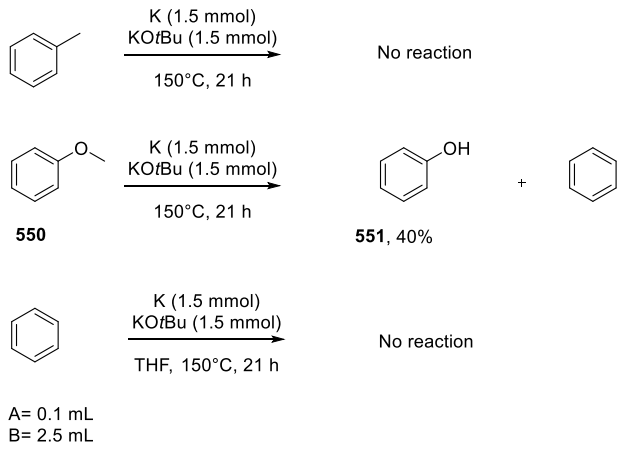


11 546 547

Entry	Reagents	Yields (mg)		
		11	**546**	**547**
1	K (1.5 mmol), MgI_2 (1.5 mmol)	-	-	-
2	K (1.5 mmol), $MgBr_2$ (1.5 mmol)	-	-	-
3	K (1.5 mmol), CaI_2 (1.5 mmol)	44 mg	traces	traces
4	K (0.5 mmol), SrI_2 (0.5 mmol)	5 mg	-	-
5	Na (0.5 mmol), KO*t*Bu (0.5 mmol)	-	-	-

Table 22. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents.

An extension of the scope was explored (Scheme 123). Toluene was completely ineffective as a substrate, and, with anisole, only demethylation and demethoxylation was afforded but no coupling, as previously reported in the literature.[196] THF was then employed as solvent under two conditions : A) large excess of THF (4.9 mL) was used compared to benzene (0.1 mL); and B) a solvent ratio of 1:1 of THF (2.5 mL) and benzene (2.5 mL) was also used. No biphenyl was formed in either cases, suggesting that the choice of the solvent influences the reactivity of the system.

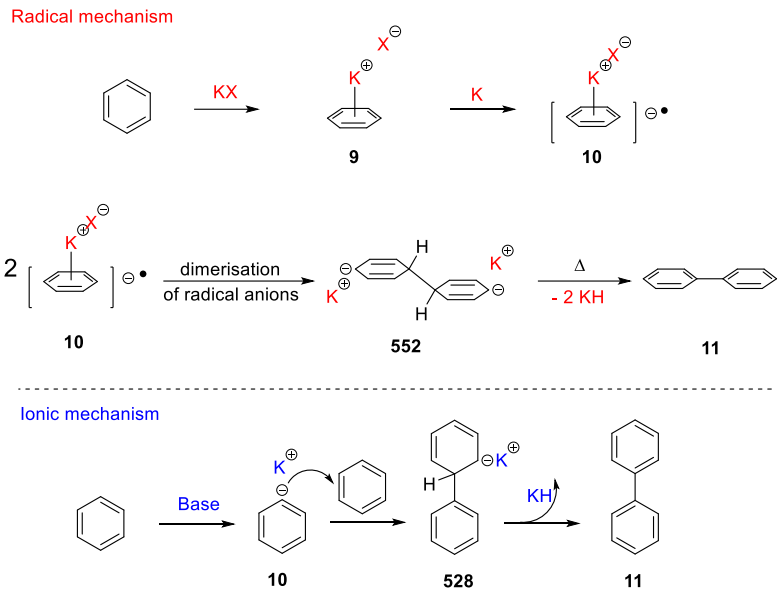


Scheme 123. Substrate scope exploration.

3.B5.3.2 Plausible mechanisms

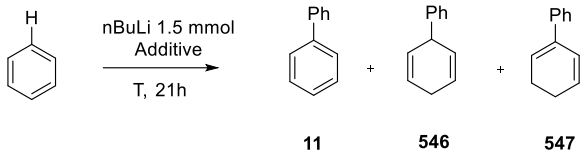
A plausible mechanism to rationalise the results in hand, speaks to the role of K metal as an electron donor, and K^+ cation as a facilitator of the process (Scheme 124). In particular, the coordination of K^+ cation to a benzene ring activates the ring by withdrawing electron density (**9)** and bringing it within range for electron transfer by K metal. Dimerisation of the coordinated radical anion product **10** leads to dianion **552**; this gives rise to biphenyl after elimination of KH (a plausible event at high T).

Alternatively, an ionic mechanism could take place if the formation of a superbase is involved in the process. This hypothesis is not supported by the previous experiments, as neither KO*t*Bu nor KH is needed for the reaction. The simple mix of K metal and pH-neutral K^+ salt (such as KI) can afford benzene dimerisation. In the previous chapter KH was found to be capable of deprotonating a very small amount of benzene at high T.[3] The resulting anion **10** could attack neutral benzene giving rise to the formation of anion **528**. After KH expulsion, biphenyl is formed.



Scheme 124. Possible mechanisms for the formation of biphenyl.

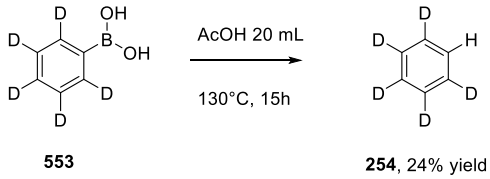
KO*t*Bu was reported in the literature to form a special reagent when mixed together with organolithium compounds. Schlosser *et al.* reported the formation of the eponymous "super base" coming from a 1:1 ratio of KO*t*Bu and *n*BuLi. This superbase is capable of deprotonating many different hydrocarbons in the low acidity range of p*K*a (35-50), including benzene.[197,198] When a 1:1 mixture of *n*BuLi and KO*t*Bu was allowed to react with benzene, biphenyl was formed in high amounts (Entry 6, Table 23). The blank reaction, in the absence of any additive leads to only a small amount of biphenyl (Entry 5). A critical point of this investigation is that, at temperatures below 130°C, the reaction struggled to happen even in the presence of a superbase (Entries 1-4). Using NaO*t*Bu instead of KO*t*Bu causes a drop of the yield, but the additive is still effective for the reaction, whereas KI does not help the reaction at all, showing that K^+ cation does not help the deprotonation to occur under the conditions. This strengthened the likelihood of a possible radical mechanism.



Entry	Additive (1.5 mmol)	Temperature (°C)	Yields (mg)		
			11	**546**	**547**
1	-	RT	-	-	-
2	KO*t*Bu	RT	-	-	-
3	-	110 °C	traces	-	-
4	KO*t*Bu	110 °C	traces	-	-
5	-	130 °C	6 mg	-	-
6	KO*t*Bu	130 °C	100 mg	-	-
7	KI	130 °C	5 mg	-	-
8	NaO*t*Bu	130 °C	39 mg	-	-

Table 23. Reaction of benzene + *n*BuLi in the absence or presence of additives.

To investigate whether the radical process was occurring or not, fresh benzene-d_5 **254** was prepared via acid-promoted protodeborylation of deuteroboronic acid **553.**[199]



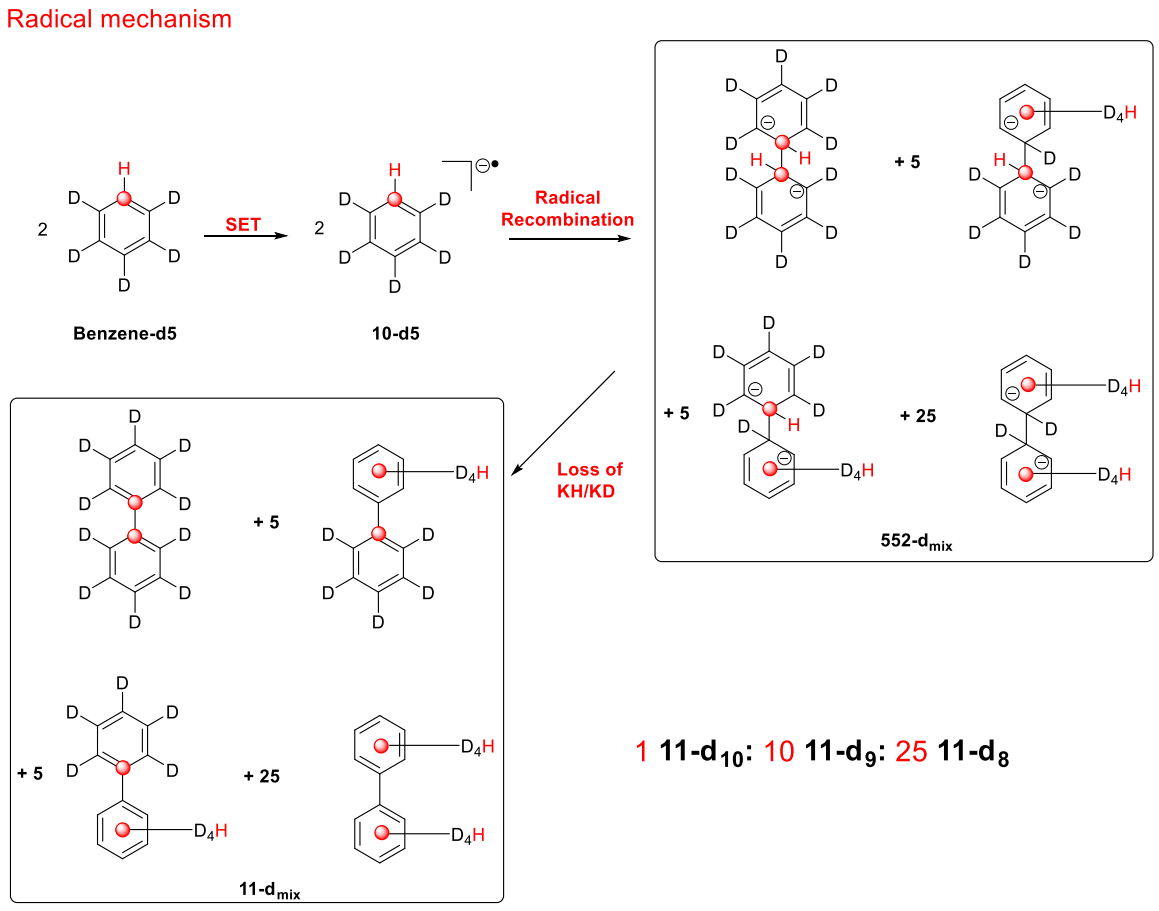
553 **254**, 24% yield

Scheme 125. Acid-catalysed deborylation of arylboronic acid.[199]

Below, an analysis of what might happen in an idealised and simplified outcome was undertaken. From the outset, it was recognised that reality could be much more complex, therefore, this work was undertaken as an optimistic exploration.

The reaction of benzene-d_5 with K metal and KO*t*Bu would lead to different outcomes, depending on the mechanism underpinning the transformation. If KO*t*Bu works as a facilitator with K metal directing the SET to benzene then radical anion **10-d_5** would form.

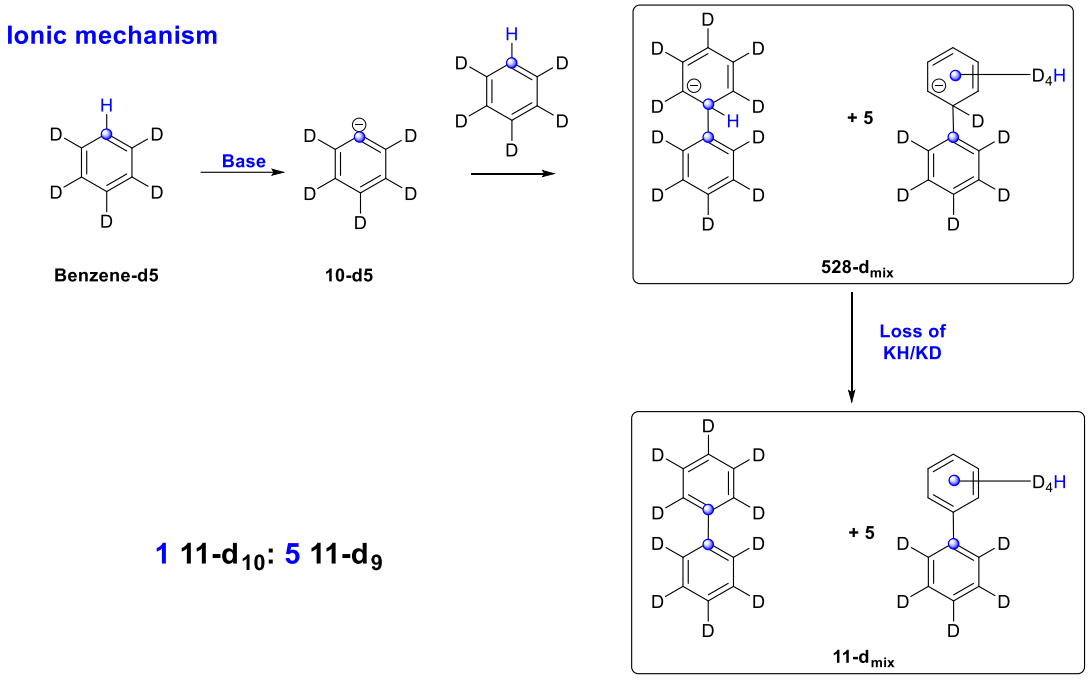
Recombination of two radical anions would lead to a mixture of different dianions **552-d$_{mix}$** bearing from 0 up to 2 hydrogens in the structure as shown in Scheme 126. The ratio would only be determined by probability since the presence of D and H should not significantly interfere with the SET. Therefore a 1 : 10 : 25 mixture of dianions **552-d$_{mix}$** would form, and from this, a proportional mixture of biphenyl **11-d$_{mix}$** would follow. At the end of the reaction a ratio 1:10:25 for **11-d$_{10}$** : **11-d$_9$** : **11-d$_8$** respectively would occur, if (i) no [1,5]-sigmatropic shifts complicate matters and if (ii) a significant KIE is not associated with the final loss of hydride/deuteride.



Scheme 126. Outcome from the reaction with benzene-d$_5$ if radical mechanism occurs.

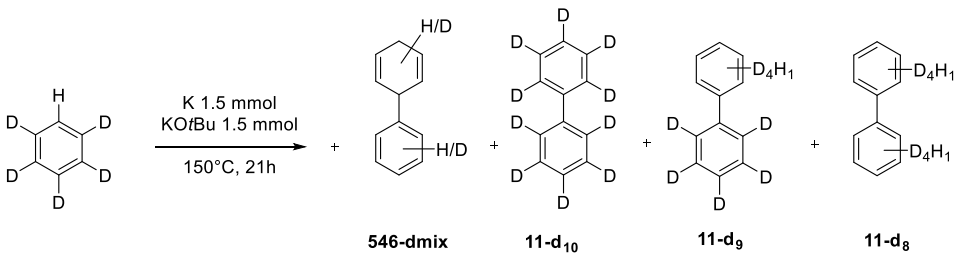
If an ionic mechanism takes place, then the presence of a hydrogen would determine a different outcome for the reaction (Scheme 127). If the KIE for the deprotonation is good

and if no [1,5]-sigmatropic shifts complicate matters in the **528-d$_{mix}$** intermediates, then the outcoming ratio between **11-d$_{10}$** and **11-d$_9$** ought to be 1:5.



Scheme 127. Outcome from the reaction with benzene-d$_5$ if ionic mechanism occurs.

When benzene-d$_5$ was finally tested the outcome was quite difficult to interpret. A few interesting points need to be underlined: (i) the reaction led to only few mg of product mixture, mirrored by the fact that most of the molten K sphere was still present at the end of the reaction; (ii) looking at the ^{1}HNMR spectrum, most of the product was represented by dihydrobiphenyl **11-d$_{mix}$** and not biphenyl. We knew this would have compromised our ratio calculations as, potentially, dihydrobiphenyl could convert to biphenyl during the GC-MS analysis. After working-up the reaction the ratio calculated *via* HRMS was 1 : 2.5 : 2.5 for the products **11-d$_{10}$** : **11-d$_9$** : **11-d$_8$**, respectively.



Compound	Mass		Mass (%)	Calculated ratio	Predicted ratio	
	Theoretical	**Found**			Radical	Ionic
11-d$_{10}$	164.1410	164.1409	40	1	1	1
11-d$_9$	163.1347	163.1345	97	2.5	10	5
11-d$_8$	162.1285	162.1278	100	2.5	25	-

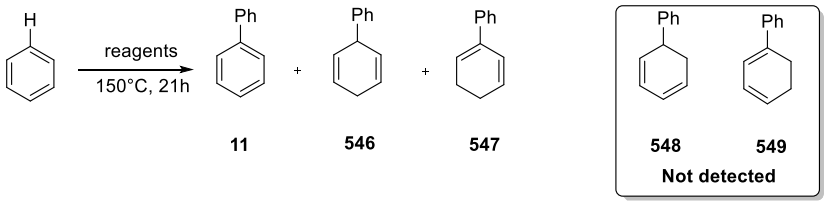
Table 24. Outcome of the reaction with benzene-d$_5$.

The outcome of this study does not say much about a possible mechanism since only a small consumption of K metal was observed. The presence of mostly deuterium in the substrate determines a disturbance of the mechanism, confirmed by the fact the reaction struggled to progress also when benzene-d$_6$ was deployed as substrate and solvent for the reaction. The ratio calculated *via* HRMS was 3.3 : 1 : 1.7 for the products **11-d$_{10}$** : **11-d$_9$** : **11-d$_8$**, respectively.

3.B5.3.3 Reactions with KH

In the previous chapter, the role of KH in benzene in electron transfer reactions was explored. When KH was mixed with benzene, a small amount of biphenyl was observed at 150 °C (Entry 1; Table 25). The equimolar mixture of KH and K metal led to a notable amount of biphenyl and dihydrobiphenyl (Entry 2), and lowering the amount of K metal, a lower amount of products was obtained (Entry 3) suggesting that K metal does not work as an additive in the reaction, but actively participates in the process. The mixture KH/KO*t*Bu was also found to be effective for the reaction, giving rise to 47 mg of biphenyl (Entry 4) and by lowering the reaction temperature to 130 °C, about half of the amount of product was found (Entry

5). Interestingly, NaO*t*Bu was also effective but 3 times lower yielding than KO*t*Bu (Entry 6), but when NaH was deployed with NaO*t*Bu, no products were observed (Entry 7). The mixture of NaH and KO*t*Bu was somehow effective, suggesting that the activity might arise from K/Na exchange between the bases. Although Me_4NCl was found to be an ineffective additive (Entry 9), other salts (Entries 10-13) were all likewise effective suggesting that also in this case the presence of the salts helps the reaction.

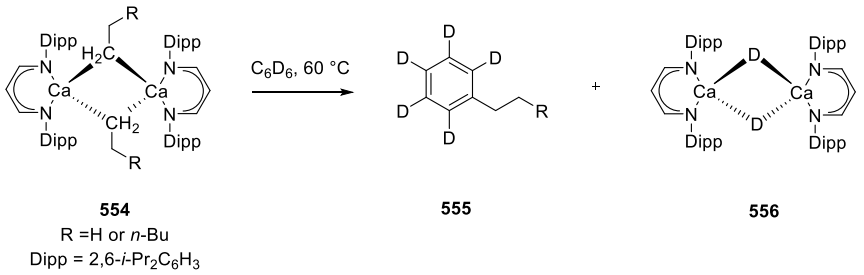


Entry	Reagents	Yields (mg)		
		11	**534**	**535**
1	KH (1.5 mmol)	traces	-	-
2	KH (1.5 mmol), K (1.5 mmol)	51 mg	12 mg	16 mg
3	KH (1.5 mmol), K (0.5 mmol)	35 mg	3 mg	traces
4	KH (0.5 mmol), KO*t*Bu (0.5 mmol)	47 mg	-	-
5[a]	KH (0.5 mmol), KO*t*Bu (0.5 mmol)	17 mg	-	-
6	KH (0.5 mmol), NaO*t*Bu (0.5 mmol)	11 mg	-	-
7	NaH (0.5 mmol), NaO*t*Bu (0.5 mmol)	-	-	-
8	NaH (0.5 mmol), KO*t*Bu (0.5 mmol)	21 mg	-	-
9	KH (1.5 mmol), Me_4NCl (1.5 mmol)	traces	-	-
10	KH (1.5 mmol), $NaBF_4$ (1.5 mmol)	27 mg	-	-
11	KH (1.5 mmol), KBF_4 (1.5 mmol)	36 mg	-	-
12	KH (1.5 mmol), KF (1.5 mmol)	27 mg	-	-
13	KH (1.5 mmol), LiI (1.5 mmol)	23 mg	traces	traces

Table 25. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents. [a] Reaction performed at 130 °C for 18h.

3.B5.4 Conclusions and further work

This study puts in evidence the importance of cation-arene interactions.[200] Electron transfer from K metal to benzene can be achieved in the presence of selected salts. No reaction occurred in the absence of these salts. A recent paper from Wilson *et al.*[201] discloses the alkylation of non-activated benzene by organocalcium nucleophiles **542**. The process is facilitated by the Ca-arene interaction and DFT calculations support this theory, as reported by Wilson.[201]

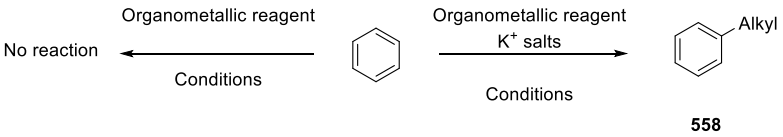


554
R =H or *n*-Bu
Dipp = 2,6-*i*-$Pr_2C_6H_3$

555 **556**

Scheme 128. Alkylation of benzene from organocalcium reagents reported by Wilson *et al*.[201]

The next step for the K^+ interaction would be to test whether it is possible to achieve similar cation-promoted benzene alkylation with organomagnesium and organolithium compounds as nucleophiles (Scheme 129). This new method to alkylate arenes would avoid the polyalkylation obtained with the Friedel-Crafts process, since the newly alkylated and more electron-rich product would be less susceptible to a new nucleophilic attack.



558

Scheme 129. Future work: alkylation of benzene in the presence of a K^+ source.

4 OVERALL CONCLUSIONS

As organic chemists, we often tend to focus on the organic parts of our ionic reactant molecules, and assume that the role of counterions of similar valency in these molecules is negligible, but the literature shows that certain particular salts are widely preferred for certain roles, while similar reagents are rarely used. For example, NaO*t*Bu is used routinely as a base in Buchwald-Hartwig reactions,[202–204] but not KO*t*Bu. On the other hand, KO*t*Bu has been favoured in many recent reactions of other types, for example in facilitating the formation of different organic electron donors from the corresponding precursors. This is very important for various branches of chemistry such as arylation reactions (BHAS),[1,47,75,76] C-X cleavages[66,68] and polymerisations.[205] In most of the cases KO*t*Bu is required, but in some others NaO*t*Bu is also effective,[50,101] suggesting that the role played by the cation is somewhat important, but not essential. In electron transfer reactions, KO*t*Bu was clearly demonstrated to act as a promoter of the *in situ* formation of organic electron donors. A few reports arose the topic wheter the base can directly act as electron donor, despite this lacks evidence.

This thesis adds further information and some insights into the roles of the salts KO*t*Bu and KH in electron transfer reactions.

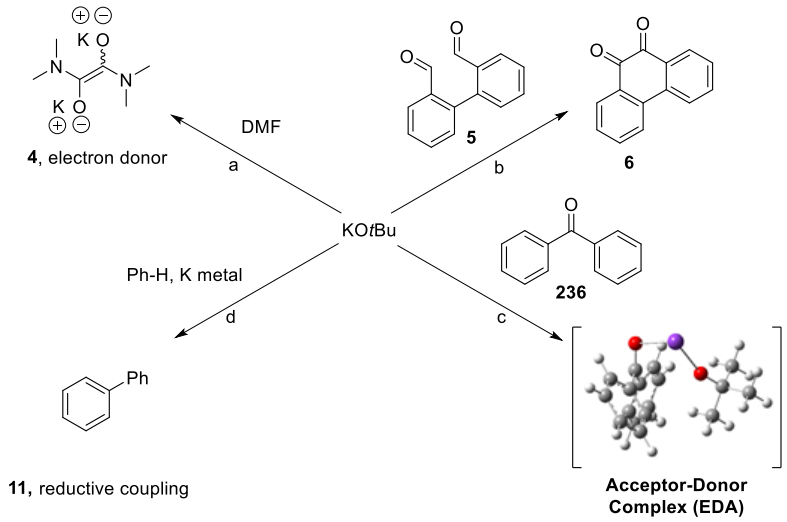
(a) KO*t*Bu promotes formation of a strong organic electron donor from the hitherto unlikely precursor, DMF.[1] A mechanism is proposed that is consistent with other mechanisms recently used to explain the formation of organic electron donors triggered by reactions of KO*t*Bu.

(b) A similar mechanism can be proposed to explain the intramolecular coupling of non-enolisable aldehydes by KO*t*Bu; this latter observation may be important in understanding the initial formation of sugars in the prebiotic era.

(c) For the first time, KO*t*Bu was found to form an EDA complex with benzophenone, capable of absorbing Vis light (even cold sunlight);[2] this finally explained the original observation by Ashby of direct electron transfer from KO*t*Bu to benzophenone.[102] In this study, NaO*t*Bu was ineffective, underlining that KO*t*Bu has unique properties in this

particular transformation. Computational studies within our group support help to illustrate the detailed subtle differences between KO*t*Bu and NaO*t*Bu in these cases.

(d) KO*t*Bu plays an important role in facilitating the electron transfer from K metal to benzene. NaO*t*Bu was found ineffective again, suggesting that the reactivity is intimately associated with the cation used, and that the K^+ has indeed a special efficacy here, although the detailed nature of its interactions remain to be determined. In some cases, Na^+ was found to act as a promoter as well, but was much less effective.



Scheme 130. Summary of the reactions with KO*t*Bu.

KH is used to deprotonate many different substrates such as enolisable carbonyl compounds, alcohols, amines, phenols and sulfoxides and it is normally used when NaH and LiH (weaker bases) are not effective enough.[170] In some cases, KH was found to act as a nucleophile, leading to the hydride reduction of benzaldehydes.[171] Pierre reported for the first time the KH-mediated dehalogenation of iodobenzene *via* CS_NAr.

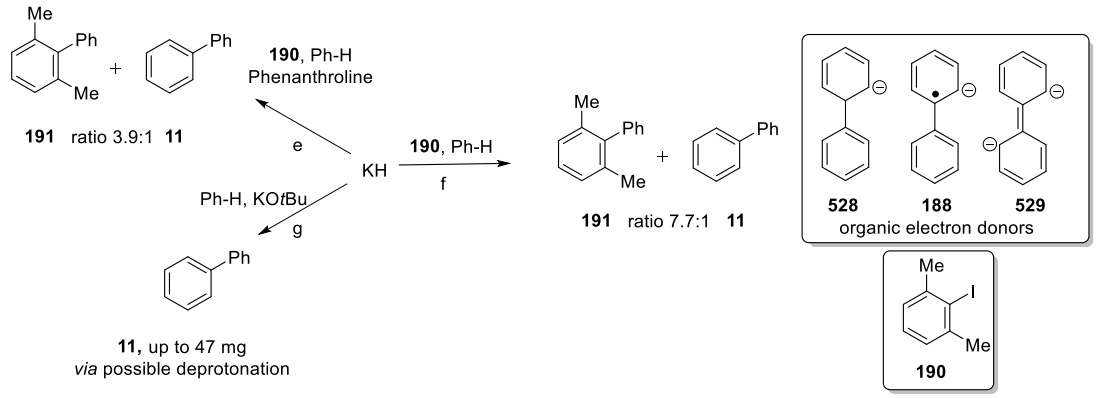
The role of KH in electron transfer reactions was also analysed.[3]

(e) The formation of the BHAS diagnostic ratio (3.9:1) of coupling products **191** + **11** in the reaction with iodo-*m*-xylene **190** and phenanthroline challenges the apparent unique properties of KO*t*Bu in electron transfer reaction. The different ratio of coupled products

(7.7:1) with KH in benzene in the apparent absence of any organic additive suggests that different chemistry takes place compared to the KO*t*Bu reactions.

(f) Possibly due to the strong basicity of KH, a modest amount of biphenyl can be obtained in the blank reaction with benzene alone; this suggests the formation of plausible organic electron donors **188**, **528**-**529** that could trigger radical chemistry with different haloarenes.

(g) Once again, the presence of salts (that are completely ineffective in the absence of KH) helps the deprotonation of benzene, leading to conspicuously higher amount of biphenyl.



Scheme 131. Summary of the reactions with KH.

We are at an interesting time in developing an understanding of subtle effects associated with the role of specific alkali metal ions in organic reactions, and can look forward to rapid developments in this area in the near future.

5 EXPERIMENTAL CHAPTER

As for the results and discussion, the experimental part is divided in five different sub-chapters, each one dedicated to the corresponding project (A1, A2, A3, B4, B5).

A first general information of the materials and instruments will be given. Where conditions are different from the general information, this will be stated each time.

General information

All reagents were purchased from commercial sources and used without further purification, except where stated. Anhydrous diethyl ether, tetrahydrofuran, dichloromethane and hexane were dried using a Pure-Solv 400 solvent purification system (Innovative Technology Inc., U.S.A.). Tetrahydrofuran was further distilled over sodium "wire" using benzophenone as indicator using a still. The distilled THF was used for all the ketyl radical development. Anhydrous benzene was purchased from Sigma Aldrich and dried over 3Å molecular sieves, previously activated by microwave heating. Thin layer chromatography analyses were carried out on silica gel pre-coated aluminum foil sheets and were visualised using UV light (254 nm). Flash column chromatography was carried out using slurry packed silica gel (SiO_2), 35-75 μm particle size, 60 Å pore size, under a light positive pressure, eluting with the specified solvent system.

Where reactions were carried out in a glovebox, the atmosphere used was nitrogen and the glovebox was supplied by Innovative Technology Inc., USA. ^{1}H-NMR, ^{2}H-NMR and ^{13}C-NMR spectra were recorded on Bruker spectrometers operating at 400 or 500 MHz, 61 MHz and 101 or 126 MHz, respectively. All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s (singlet), d (doublet), t

(triplet), q (quartet), qn (quintet), sextet (st), m (multiplet). Infrared (IR) spectra were recorded using an FTIR-ATR spectrometer. High resolution mass spectrometry was performed at the University of Swansea, in the EPSRC National Mass Spectrometry Centre. Accurate mass measurements were obtained using a LTQ Orbitrap XL using Atmospheric Pressure Chemical Ionisation (APCI) or High Resolution Nano-Electrospray (HNESP) using Electrospray Ionisation (ESI). Low resolution spectrometry was recorded by gas-phase chromatography (GCMS) using electron ionization (EI) in the University of Strathclyde. Data were recorded using an Agilent Technologies 7890A GC system coupled to a 5975C inert XL EI/CI MSD detector. Separation was performed using the DB5MS-UI column (30 m x 0.25 mm x 0.25 μm) at a temperature of 320 ^{o}C, using helium as the carrier gas.

All the UV reactions were carried out by using two focused UV lamps with filters (λ= 365 nm, each 100 watts) placed opposite to each other, around the reaction flask, at room temperature. All the Vis light reactions were carried out by using 60 LEDs in series (410 nm, 14.4 W total, SMD5050). The series internally lined a beaker and the reaction tubes were placed centrally in the beaker (2-3 cm of distance from the LEDs). When stated, the reactions were performed in direct sunlight. The 'dark' reactions were performed by covering the tube in foil to avoid any light exposure.

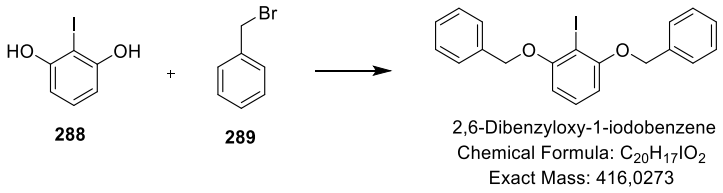
UV-visible absorption measurements were performed using a PerkinElmer Lambda 25 UV/VIS spectrophotometer.

Calculations of the yields of reactions using the internal standard 1,3,5-trimethoxybenzene (^{1}H-NMR internal standard) were performed as follows: 1,3,5-trimethoxybenzene (8.4 mg, 0.050 mmol, 10 mol%) was added as a solid to the reaction mixture. $CDCl_3$ (~1 mL) was added and the solution stirred for 5 min. A portion of the solution was taken and diluted for NMR analysis. The yields were therefore calculated using the integration of similar types of peaks: aromatic peaks of the compound were compared with the aromatic peak of the internal standard, aliphatic peaks of the compounds were compared with the aliphatic peaks of the internal standard.

5.A1 The Formation of Organic Electron Donors by Dimer Formation of Formamides in the Presence of KO*t*Bu

5.A1.1 Preparation of substrates

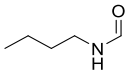
2,6-Dibenzyloxy-1-iodobenzene, **290**



2-Iodoresorcinol **288** (0.30 g, 1.27 mmol) and potassium carbonate (0.53 g, 3.81 mmol) were dissolved in DMF (15 mL). After stirring for 10 min, benzyl bromide **289** (0.65 g, 3.81 mmol) was added and the reaction mixture was stirred at 80 °C for 18 h. After cooling to RT the reaction mixture was partitioned between ethyl acetate and water (50 mL each). The separated organic phase was washed with two further portions (50 mL) of water and the combined water phases washed with ethyl acetate (50 mL). The combined organic phases were washed with brine (50 mL) dried over anhydrous sodium sulfate and concentrated in *vacuo* to afford the crude product, which then was purified by chromatography using ethyl acetate: petroleum ether as 9:1 to afford the title compound as a white solid (350 mg; 66% yield). Mp: 89-91 °C (lit: 90-92 °C).[206] ν_{max} (neat/cm^{-1}) 3026, 2961, 1587, 1445, 1252, 1090, 736, 692. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (4 H, d, *J* = 7.5, Ar*H*), 7.40 (4 H, t, *J* = 7.4, Ar*H*), 7.32 (2 H, t, *J* = 7.3, Ar*H*), 7.19 (1 H, t, *J* = 8.3, Ar*H*), 6.54 (2 H, d, *J* = 8.3, Ar*H*), 5.18 (4 H, s, C*H*$_2$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 158.3, 136.2, 129.2, 128.0, 127.3,

126.5, 105.5, 79.0, 70.5. GC-MS (EI, M^+) *m/z* 416.1. Data were consistent with the literature.[207]

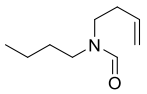
n-Butylformamide, **296**



n-Butylformamide
Chemical Formula: $C_5H_{11}NO$
Exact Mass: 101,0841

Formamide **296** was prepared by slowly adding ethyl formate (1.93 mL) to *n*-butylamine (3 mL, 2.22 g, 20 mmol) at 0°C, then heating to 100 °C for 1 h, and 110 °C for 3 h. The mixture was concentrated at 35 °C to remove most of the ethanol and unreacted ethyl formate, and left in *vacuo* whilst the title compound was obtained as a yellow oil (1.8 g, 17.8 mmol, 89% yield). The NMR spectra of this material clearly showed the presence of rotamers. For simplicity, only the data of the major rotamer will be given. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (1 H, s, C*H*O), 6.00 (1 H, s, N*H*), 3.25 (2 H, q, *J* = 7.2, CH_2NH), 1.48 (2 H, q, *J* = 7.2, CH_2CH$_2$), 1.33 (2 H, st, *J* = 7.2, CH_2CH$_3$), 0.89 (3 H, t, *J* = 7.3, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 160.8, 37.4, 31.0, 19.5, 13.1. GC-MS (EI) *m/z* 101.1. Data were consistent with the literature.[208]

N-But-3-enyl-*N*-butylformamide, **284**

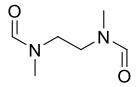


N-(but-3-en-1-yl)-*N*-butylformamide
Chemical Formula: $C_9H_{17}NO$
Exact Mass: 155,1310

A solution of *N*-butylformamide, **296** (1.01 g, 10 mmol) in toluene (5 mL) was added to a suspension of NaH (0.288 g, 12 mmol) and toluene (35 mL). The resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, 4-bromo-1-butene (2.01 g, 15 mmol) was added. The mixture was refluxed over 16 h. Afterwards the reaction mixture was cooled to 23 °C, poured into brine (10 mL), extracted with EtOAc (10 mL x 3), dried over sodium

sulfate and concentrated by rotary evaporator. The crude mixture was then purified by chromatography using petroleum ether : ethyl acetate as 8:2 as eluent. The title compound was obtained as a slightly orange oil (700 mg, 4.5 mmol, 45% yield). The NMR spectra of this material clearly showed the presence of rotamers with an almost 1:1 ratio: therefore it was difficult to distinguish the peaks of each rotamer. ν_{max} (neat/cm^{-1}) 2957, 2929, 1666, 1425, 1398, 1120, 912. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (1 H, s, C*H*O), 5.83 – 5.60 (1 H, m, C*H*CH_2), 5.11 – 4.97 (2 H, m, C*H*$_2$CH), 3.38 – 3.25 (2 H, m, C*H*$_2$), 3.26 – 3.11 (2 H, m, C*H*$_2$), 2.32 – 2.22 (2 H, m, C*H*$_2$), 1.55 – 1.43 (2 H, m, C*H*$_2$), 1.36 – 1.24 (2 H, m, C*H*$_2$), 0.90 (3 H, t, *J* = 7.3, C*H*$_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 162.7, 135.0, 134.0, 117.9, 116.8, 47.3, 46.9, 41.9, 41.5, 33.1, 31.7, 30.6, 29.3, 20.1, 19.5, 13.7, 13.5. GC-MS (EI) *m/z* 155.2. Data were consistent with the literature.[209]

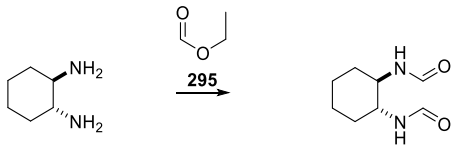
N,*N*'-Diformyl-*N*,*N*'-dimethylethylene-1,2-diamine, **238**



N,*N*'-Diformyl-*N*,*N*'-dimethylethylene-1,2-diamine
Chemical Formula: $C_6H_{12}N_2O_2$
Exact Mass: 144,0899

N,*N*'-Dimethylethylene-1,2-diamine **125** (1.00 g, 1.22 mL, 11.34 mmol) was dissolved in ethyl formate (10 mL) and the solution stirred at 50 °C for 16 h. The reaction was allowed to cool and then concentrated to give the title compound as an oil, which solidified (1.49 g, 91%) on standing. The NMR spectra of this material clearly showed the presence of rotamers. Due to the absence of a major rotamer, all the peaks will be mentioned. Mp 80–83 ° C [lit., 81–82 °C].[210] ν_{max} (neat/cm^{-1}) 2947, 1662, 1633, 1394, 1182, 1080, 964, 841, 636. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.02 (2 H, s, C*H*O), 3.54–3.40 (4 H, m, C*H*$_2$), 2.94 (6 H, s, C*H*$_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 163.2, 162.9, 162.6, 47.5, 46.4, 42.5, 40.5, 35.4, 34.6, 30.0, 29.9. GC-MS (EI) *m/z* 144.1. Data were consistent with the literature.[211]

N,*N*'-[(±)-*trans*-Cyclohexane-1,2-diyl]diformamide, **299**

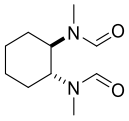


220

N,*N*'-[(±)-*trans*-Cyclohexane-1,2-diyl]diformamide
Chemical Formula: $C_8H_{14}N_2O_2$
Exact Mass: 170,1055

A solution of (±)-*trans*-1,2-diaminocyclohexane **220** (0.36 mL, 3 mmol) in ethyl formate (1.45 mL, 18 mmol) was heated at 50 °C overnight. The mixture was concentrated at 35 °C to remove most of the ethanol and unreacted ethyl formate, and left in *vacuo* for 30 min to afford a white solid. The solid was washed with ethyl acetate and filtered to give the title diformamide **299** (1.28 g, 84% yield) as a white solid. The NMR spectra of this material clearly showed the presence of rotamers. Mp 162–165 °C [lit., 187–188 °C (from ethanol)].[212] ν_{max} (neat)/cm^{-1} 3261, 3064, 2931, 2854, 1625, 1550,1386, 1251, 1231, 723. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (2 H, d, *J* = 1.6, C*H*O), 5.98 (2 H, s, N*H*), 3.86 – 3.79 (2 H, m, *H*CNH), 2.08 – 2.05 (2 H, m, CH_2), 1.79 – 1.77 (3 H, m, CH_2), 1.34 – 1.25 (3 H, m, CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 161.2, 51.8, 31.7, 24.0. GC-MS (EI) *m/z* 170.2. Data are consistent with the literature.[213]

N,*N*'-[(±)-*trans*-Cyclohexane-1,2-diyl]bis(*N*-methylformamide), **239**



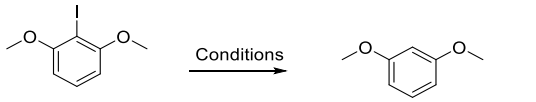
N,*N*'-[(±)-*trans*-Cyclohexane-1,2-diyl]bis(N-methylformamide)
Chemical Formula: $C_{10}H_{18}N_2O_2$
Exact Mass: 198,1368

A solution of *N*,*N*'-(±)-*trans*-cyclohexane-1,2-diyl)diformamide, **299** (340 mg, 2.0 mmol) in toluene (5 mL) was added to a suspension of NaH (115 mg, 4.80 mmol) and toluene (20 mL) under argon atmosphere. The resulting mixture was stirred at 70 °C for 1 h. The mixture was allowed to cool to room temperature and iodomethane (852 mg, 6.0 mmol) was added. The mixture was refluxed for 16 h before being allowed to cool to room temperature. The mixture was poured into sat. aq. NaCl (10 mL) and extracted with dichloromethane (3 × 20 mL),

dried over sodium sulfate, filtered, and concentrated to give diformamide **239** (330 mg, 83%) as a colourless oil which solidified on standing. The NMR spectra of this material clearly showed the presence of rotamers. Mp 93–96 °C. ν_{max} (neat)/cm^{-1} 2933, 2860, 1672, 1653, 1427, 1408, 1065, 725 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (2H, s, C*H*O), 4.52–4.33 and 3.54–3.33 (2H, 2m, C*H*N), 2.77 (6H, s, CH_3), 1.91–1.57 (6H, m, CH_2), 1.44–1.22 (2H, m, C*H*H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 163.2, 163.1, 162.5, 58.1, 50.3, 30.8, 30.7, 29.0, 26.0, 25.7, 25.1, 25.0, 24.9. GC-MS (EI) *m/z* 198.2. Data are consistent with the literature.[213] VT–NMR (70 °C and 90 °C in DMSO) were attempted but coalescence of the peaks from the different rotamers was not observed.

5.A1.2 Electron transfer reactions with haloarenes

Electron transfer reactions with 2-iodo-1,3-dimethoxybenzene **292**



292

1,3-Dimethoxybenzene
Chemical Formula: $C_8H_{10}O_2$
Exact Mass: 138,0681

A mixture of 1-iodo-2,6-dimethoxybenzene **292** (264 mg, 1.0 mmol) and KO*t*Bu (224 mg, 2.0 mmol) in 10 mL benzene and 0.1 mL of DMF (1% v/v of solvent) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h in a fumehood behind a blast shield. After cooling to room temperature, the reaction was quenched with water and acidified with HCl 2N, until neutral pH. The mixture was extracted with diethyl ether (30 mL x 3) and washed with brine. The organic layer was dried over sodium sulfate; filtration and concentration gave the residue as a yellow oil. The yield was calculated using 1,3,5-trimethoxybenzene (10 %) as internal standard. The calculated yield of **293** is 79%, whereas 0.5 % of starting material **292** has been identified. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.20 (1 H, t, *J* = 8.2, Ar*H*), 6.53 (2 H, dd, *J* = 8.2, 2.4 Ar*H*), 6.49 (1 H, t, *J* = 2.3, Ar*H*), 3.80 (6 H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 160.4, 129.4, 105.7, 100.0, 54.8. GC-MS (EI) *m/z* 138.1.

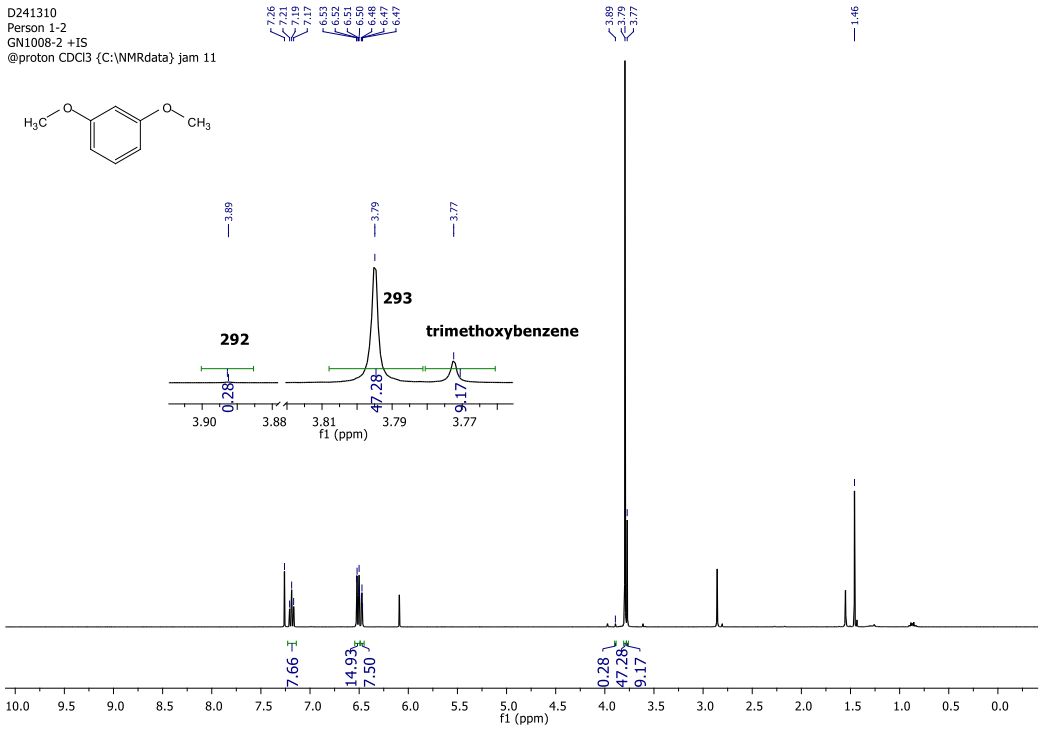
Yield calculation.

For the recovered starting material **292** the integration of the methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methoxy signal of **292** (3.89 ppm) was then measured and the following calculation gave the amount of **292** present:

(0.28/6) × 10 = 0.5%

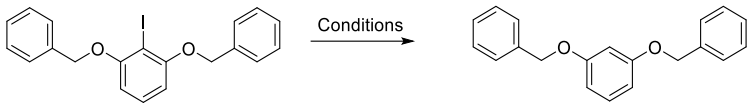
For the deiodinated product **293** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the methoxy signal of **293** (3.77 ppm) was then measured and the following calculation gave the amount of **293** present:

(47.28/6) × 10 = 78.8%



Spectrum 1. Crude mixture from the reaction with 1-iodo-2,6-dimethoxybenzene **292.**

Electron transfer reactions with 2,6-Dibenzyloxy-1-iodobenzene, **290**



290

1,3-Bis(benzyloxy)benzene
Chemical Formula: $C_{20}H_{18}O_2$
Exact Mass: 290,1307

A mixture of 2,6-dibenzyloxy-1-iodobenzene **290** (208 mg, 0.5 mmol), KO*t*Bu (112 mg, 1.0 mmol) in 4.95 mL benzene and 0.05 mL of DMF (1% v/v of solvent) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield inside the fumehood. After cooling to room temperature, the reaction was quenched by water (30 mL). The mixture was extracted with diethyl ether (30 mL) and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to give a yellow solid. The yield of **291** was calculated with internal standard *via* ^{1}H-NMR using 1,3,5-trimethoxybenzene; the calculated values are 80% of deiodinated product **291** and 0.8% of starting material. ν_{max} (neat/cm^{-1}) 2922, 1591, 1145, 1026, 694. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.45 – 7.41 (4 H, m, Ar*H*), 7.41–7.36 (4 H, m, Ar*H*), 7.34 (2 H, dd, m, Ar*H*), 7.19 (1 H, t, *J* = 8.2, Ar*H*), 6.65 (1 H, t, *J* = 2.3, Ar*H*), 6.61 (2 H, dd, *J* = 8.2, 2.4, Ar*H*), 5.05 (4 H, s, CH_2). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 160.2, 137.1, 130.1, 128.7, 128.1, 127.7, 107.6, 102.4, 70.2. GC-MS (EI) *m/z* 290.2.

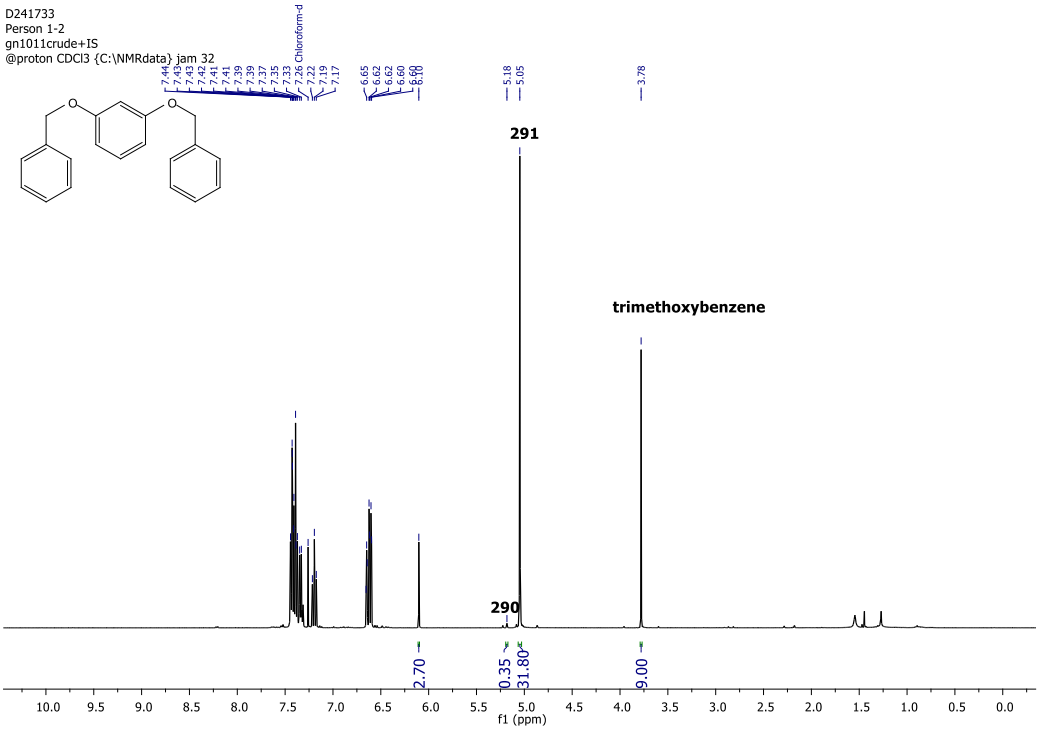
Yield calculation.

For the recovered starting material **290** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **290** (5.18 ppm) was then measured and the following calculation gave the amount of **290** present:

(0.35/4) × 10 = 0.8%

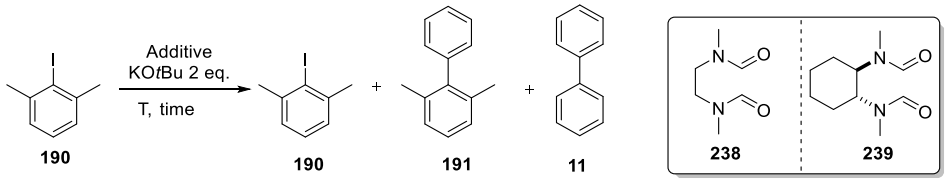
For the deiodinated product **291** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the methyl signal of **291** (3.77 ppm) was then measured and the following calculation gave the amount of **291** present:

(31.80/4) × 10 = 79.5%



Spectrum 2. Crude mixture of the reaction with 2,6-dibenzyloxy-1-iodobenzene, **290**.

Electron transfer reactions with iodo-*m*-xylene, **190**



A mixture of iodo-*meta*-xylene **190** (1.0 mmol or 0.5 mmol), KO*t*Bu (2.0 eq.) and further specified reagents in benzene (10 mL or 5 mL depending on the amount of substrate used respectively) was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at the desired temperature (130 ºC or 110 °C) for the time specified (18 h or 4h) behind a blast shield. After cooling to room temperature, the reaction was quenched by water (30 mL or 15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (30 mL or 15 mL). The organic layer was dried over

sodium sulfate, filtered and concentrated to afford the residue. Since the coupled products **191** and **11** for this reaction are inseparable, the yields have been calculated from NMR spectra *via* internal standard. 1,3,5-Trimethoxybenzene 8.4 mg, (0.050 mmol, 10 mol%) was added as a solid to the reaction mixture, ~1 mL $CDCl_3$ was added and the solution stirred. A portion of the solution was taken and diluted for NMR analysis. (Table 26)

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol) in benzene 10 mL in absence of additive at 130 °C for 18h. 0.5% of coupled products **191** + **11** was detected. (Entry 1).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), DMF (1% v/v) in benzene (99 % v/v, 10 mL total solvent) at 130 °C for 18h. 2.8% of coupled products **191** + **11** was detected. (Entry 2).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), DMF (0.1 mmol) in benzene 10 mL at 130 °C for 18h. 0.6 % of coupled products **191** + **11** was detected. (Entry 3).

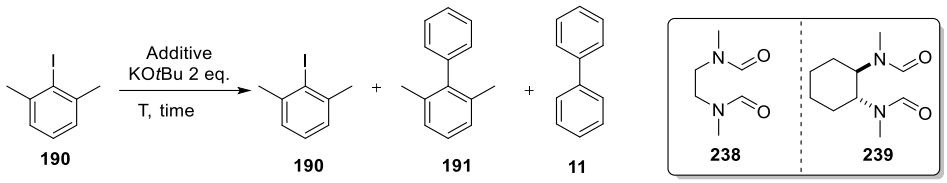
Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), additive **238** (0.05 mmol) in benzene 10 mL at 130 °C for 18h. 8.0% of coupled products **191** + **11** was detected. (Entry 4).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), additive **239** (0.05 mmol) in benzene 10 mL at 130 °C for 18h. 16.1% of coupled products **191** + **11** was detected. (Entry 5).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), DMF (1% v/v) in benzene (99 % v/v, 10 mL total solvent) at 110 °C for 4h. 0.4% of coupled products **191** + **11** was detected. (Entry 6).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), additive **238** (0.05% v/v) in benzene (99.5 % v/v, 10 mL total solvent) at 110 °C for 4h. 19.6% of coupled products **191** + **11** was detected. (Entry 7).

Alternatively, the reaction was conducted using iodo-m-xylene **190** (116 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol), additive **239** (0.05% v/v) in benzene (99.5 % v/v, 10 mL total solvent) at 110 °C for 4h. 31.6% of coupled products **191** + **11** was detected. (Entry 8).



Entry	Additive	190 (%)	191 + 11 (%)[d]
1[a]	none	65	0.5
2[a]	DMF (1%[c])	84	2.8
3[a]	DMF (0.1 mmol)	95.5	0.6
4[a]	**238** (0.05 mmol)	59.4	8.0
5[a]	**239** (0.05 mmol)	55.4	16.1
6[b]	DMF (1%[c])	85	0.4
7[b]	**238** (0.5%[c])	trace	19.6
8[b]	**239** (0.5%[c])	trace	31.6

Table 26. Iodo-*m*-xylene (0.5 mmol), 1 mmol KO*t*Bu, benzene as solvent, 130 °C, 18 h. [b] reaction at 110 °C, 4 h. [c] Relative to benzene (v/v) as solvent. [d] The yields have been calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.[1]

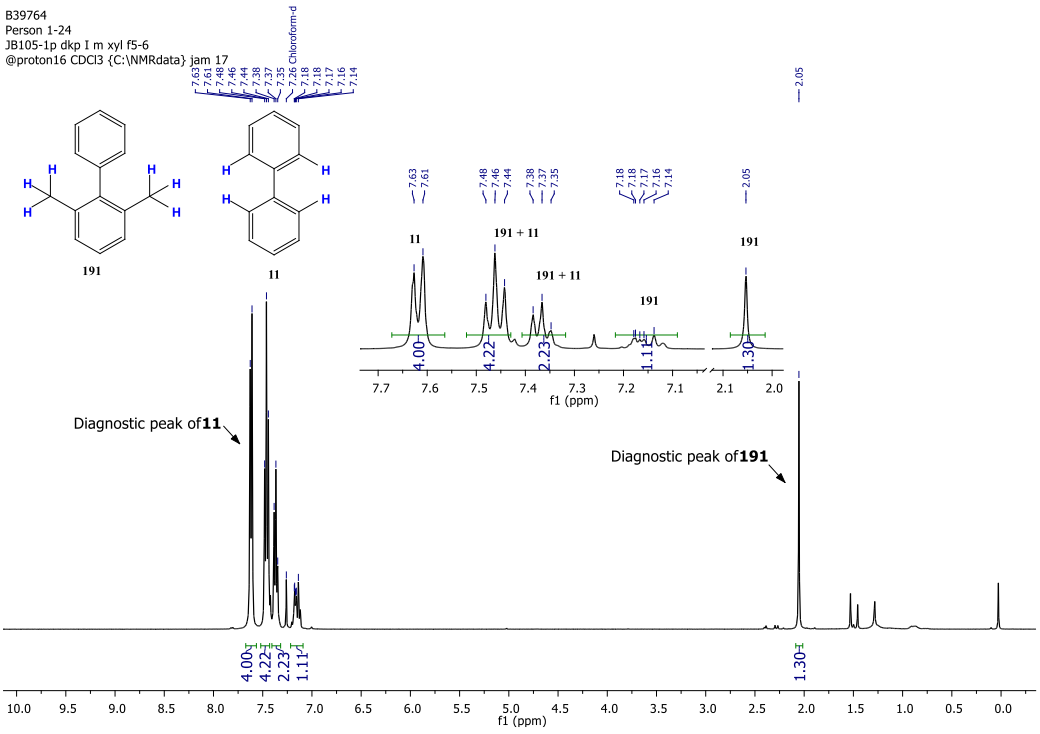
Yield calculation. Example (Entry 5, Table 26).

Biphenyl **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.59 (4H, m), 7.46 (4H, m), 7.38 - 7.34 (2H, m).

2,6-Dimethyl-1,1'-biphenyl **191**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.41 (2H, m), 7.39 - 7.33 (1H, m), 7.19 - 7.10 (5H, m), 2.05 (6H, s).

As shown in spectrum 3, the presence the inseparable mixture of coupled products **191** and **11** can be detected *via* NMR. The peak at 7.62 ppm is diagnostic for biphenyl **11** and integrates 4 protons. The peak at 2.05 ppm is diagnostic for 1,3-dimethylbiphenyl **191**, and it integrates 6 protons.

The yields were therefore calculated using the integration of similar types of peaks: aromatic peaks of biphenyl were compared with the aromatic peak of the internal standard, aliphatic peaks of the 1,3-dimethylbiphenyl were compared with the aliphatic peaks of the internal standard.



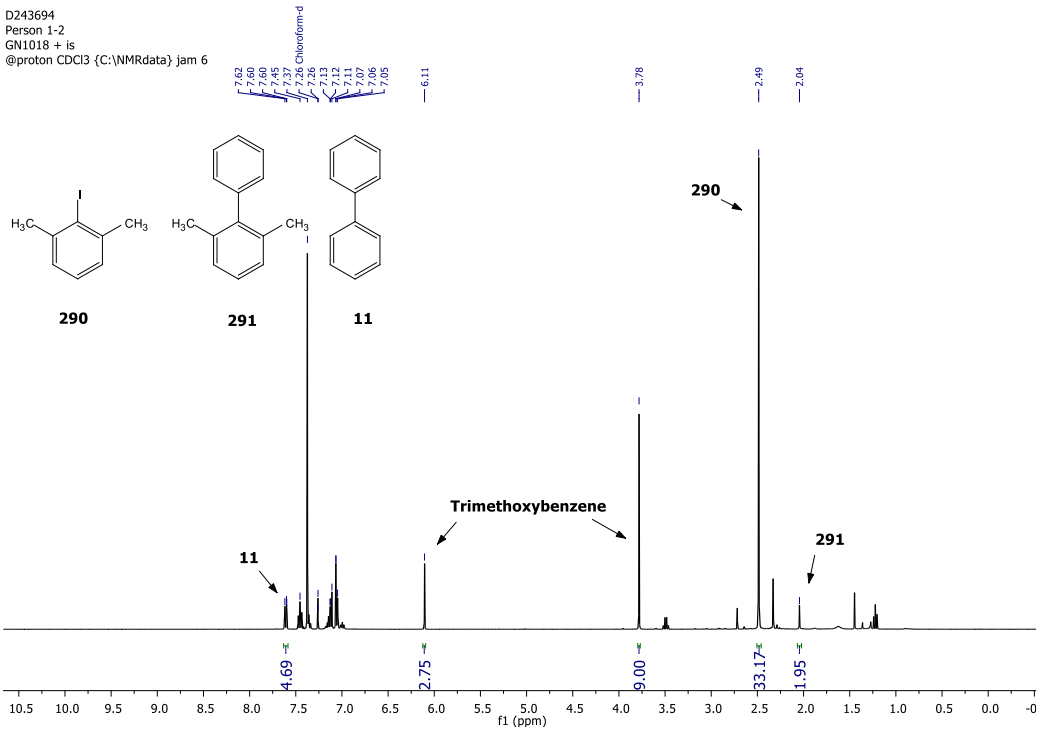
Spectrum 3. 1H-NMR of the inseparable mixture of the coupled products **191** and **11**.

For the recovered starting material **190**, the integration of the methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **190** (2.49 ppm) was then measured and the following calculation gave the amount of **190** present:

(33.17/6) × 10 = 55.4%

For the hetero-coupled product **191** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the methyl signal of **191** (2.04 ppm) was then measured and the following calculation gave the amount of **191** present:

(1.95/6) × 10 = 3.3%

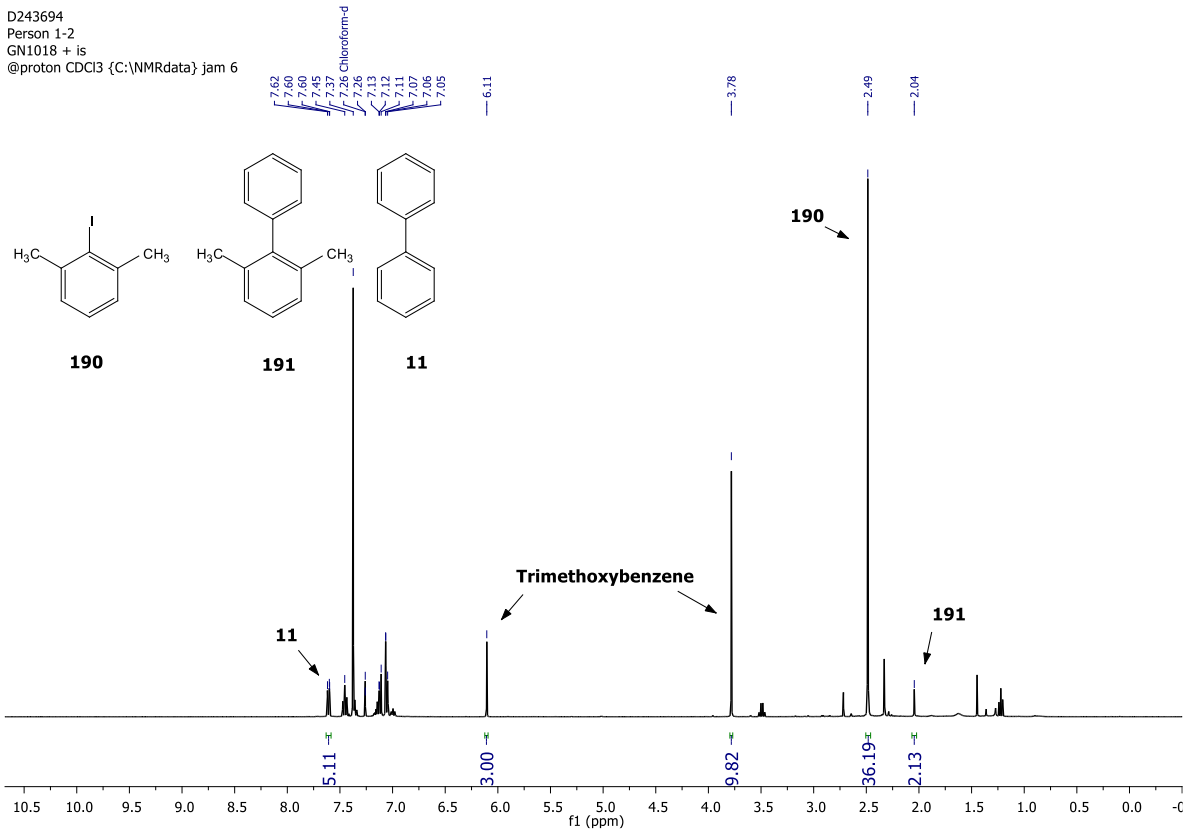


Spectrum 4. Crude mixture of the reaction in Entry 5, Table 26. In this spectrum the integration of aliphatic peak of the internal standard (1,3,5-trimethoxybenzene) is set up to 9.

For the biphenyl product **11** the integration of the aromatic signal of the internal standard was set to 3. The integration of the aromatic signals of **11** at 7.64–7.59 ppm (4 H) was then measured and the following calculation gave the amount of **11** present:

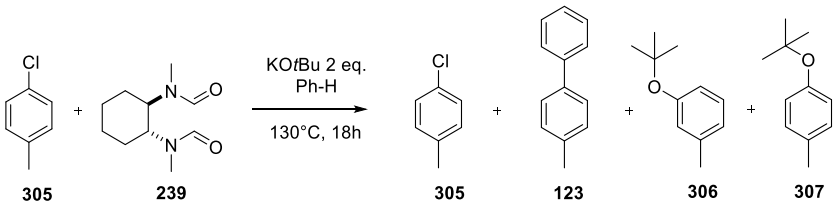
(5.11/4) × 10 = 12.8%

Yield of the mixture **191** + **11**: 3.3% + 12.8% = 16.1% (Entry 5, Table 26)



Spectrum 5. Crude mixture of the reaction in Entry 5, Table 26 In this spectrum the integration of aromatic peak of the internal standard (1,3,5-trimethoxybenzene) is set up to 3.

Electron transfer reactions with 4-chlorotoluene **305**



A mixture of 4-chlorotoluene (63 mg, 0.5 mmol), base (2 eq.) and cyclic formamide **239** (19.8 mg, 0.1 mmol) in 5 mL benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as

a dark yellow oil. The yield of coupled product **123** was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard, following the instruction specified previously. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.61 (2 H, d, *J* = 8.1, Ar*H*), 7.53 (2 H, d, *J* = 8.1. Ar*H*), 7.46 (2 H, t, *J* = 7.6, Ar*H*), 7.35 (1 H, t, *J* = 7.3, Ar*H*), 7.28 (2 H, d, *J* = 8.0, Ar*H*), 2.43 (3 H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 141.3, 138.5, 137.2, 129.6, 128.9 (2 *C*), 127.1 (2 *C*), 21.2. Data were consistent with the literature.[214] (Table 27)

Alternatively, to an oven-dried pressure tube 4-chlorotoluene (63 mg, 0.5 mmol), cyclic formamide **239** (19.8 mg, 0.1 mmol), KO*t*Bu (112 mg, 1 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **123** (10%), **305** (7.8%), **306** + **307** (1.2%). (Entry 1)

Alternatively, to an oven-dried pressure tube 4-chlorotoluene (63 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **305** (25%), **306** + **307** (16.8%).

Alternatively, to an oven-dried pressure tube 4-chlorotoluene (63 mg, 0.5 mmol), cyclic formamide **239** (19.8 mg, 0.1 mmol), KHDMS (199 mg, 1 mmol) and anhydrous benzene (5 mL) were added. The results are reported. No coupled products was observed, the benzyne side products were observed instead. This result is consistent with the literature.[105] **308** + **309** (1.2%). (Entry 2)

Alternatively, to an oven-dried pressure tube 4-chlorotoluene (63 mg, 0.5 mmol), cyclic formamide **239** (19.8 mg, 0.1 mmol), NaH (24 mg, 1 mmol) and anhydrous benzene (5 mL) were added. The results are reported. Only starting material was recovered. **305** (34.5%). (Entry 3)

Entry	Base	R=	305 (%)	123 (%)	Benzyne byproducts (%)
1[a]	KO*t*Bu	-O*t*Bu	7.8	10.0	1.2
2[a]	KHDMS	-N($SiCH_3$)$_2$	n.d.	n.d.	50.4
3[a]	NaH	H	34.5	n.d.	n.d.

Table 27. [a]The reactions were performed using substrate 0.5 mmol, diformamide as additive 0.1 mmol, benzene 5 mL. The yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

Yield calculation

For the recovered starting material **305** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **305** (2.32 ppm) was then measured and the following calculation gave the amount of **305** present:

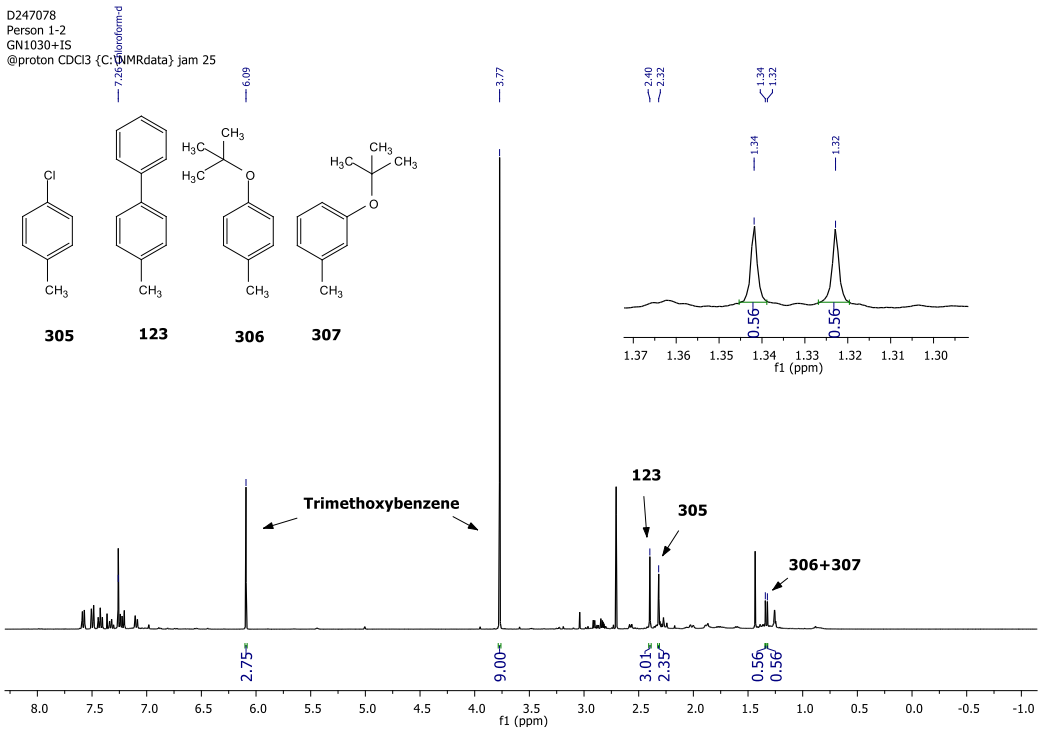
(2.35/3) × 10 = 7.8 %

For the coupled product **123** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the methyl signal of **123** (2.40 ppm) was then measured and the following calculation gave the amount of **123** present:

(3.01/3) × 10 = 10.0%

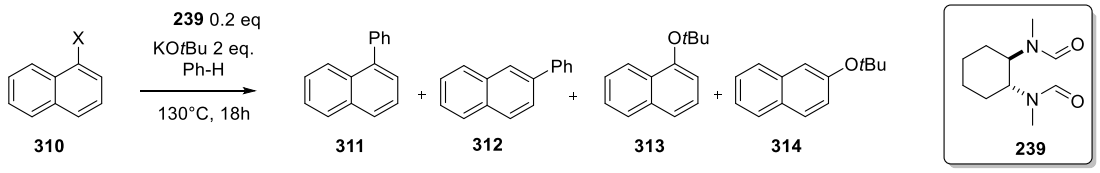
For the benzyne byproducts[215] **306** + **307** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the *t*butyl signal (1.34 ppm and 1.32 ppm) was then measured and the following calculation gave the amount of mixture of **306** + **307** present:

((0.56/9) + (0.56/9)) × 10 = 1.2%



Spectrum 6. Electron transfer reaction using 4-chlorotoluene as substrate. (Table 27, Entry1)

General procedure for the reactions with halo-naphtalene



The mixture of 1-halo-naphthalene **310** (1 mmol), KO*t*Bu (224 mg, 2.0 mmol) and additive **239** (39.6 mg, 0.2 mmol) in 10 mL benzene was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a shield in a fume hood. After cooling to room temperature, the reaction was quenched by water (15 mL) and 1 N HCl until neutral pH was achieved. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate; filtration and concentration followed to give the residue as a dark yellow oil. A column chromathography was then performed using pure hexane as solvent, affording an oil as mixture of the two inseparable products **311**

and **312 (**90 mg, 0.38 mmol). Data of compound **311**. ν_{max} (neat/cm^{-1}) 3054, 1490, 1396, 803, 780, 762, 704. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.93 – 7.89 (2 H, m, Ar*H*), 7.87 (1 H, d, *J* = 8.2, Ar*H*), 7.55 – 7.47 (6 H, m, Ar*H*), 7.46 – 7.41 (3 H, m, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 140.9, 140.4, 133.9, 131.7, 130.2, 128.9, 128.4, 127.7, 127.3, 127.1, 126.2, 125.9, 125.5. GC-MS (EI) *m/z* 204.1. Data for compound **311** were consistent with the literature.[216] Data for compound **312, 313, 313** were compared with spectra from Florimond Cumine, a previous members of the group.

Table 28

Alternatively, to an oven-dried pressure tube 1-iodo-naphthalene (254 mg, 1 mmol), cyclic formamide **239** (39.6 mg, 0.2 mmol), KO*t*Bu (224 mg, 2 mmol) and anhydrous benzene (10 mL) were added. The results are reported. **311** (61%), **312** (traces), **313** + **314** (traces). (Entry 1)

Alternatively, to an oven-dried pressure tube 1-iodo-naphthalene (254 mg, 1 mmol), KO*t*Bu (224 mg, 2 mmol) and anhydrous benzene (10 mL) were added. The results are reported. **311** (24.4%), **313** + **314** (16.6). (Entry 2)

Alternatively, to an oven-dried pressure tube 1-chloro-naphthalene (163 mg, 1.0 mmol), cyclic formamide **239** (39.6 mg, 0.2 mmol), KO*t*Bu (224mg, 2 mmol) and anhydrous benzene (10 mL) were added. The results are reported. **311** (41%), **312** (3%), **313** + **314** (traces). (Entry 3)

Alternatively, to an oven-dried pressure tube 1-chloro-naphthalene (163 mg, 1.0 mmol), KO*t*Bu (224mg, 2 mmol) and anhydrous benzene (10 mL) were added. The results are reported. **310** (35.5%), **313** + **314** (43%). (Entry 4)

Entry	X	Additive	310 (%)	311 (%)	312 (%)	313+314 (%)[d]
1[a]	I	**239**	n.d.	61	trace	trace
2[b]	I	none	n.d.	24.4	n.d.	16.6
3[a]	Cl	**239**	trace	41[c]	3[c]	trace
4[b]	Cl	none	35.5	n.d.	n.d.	42.9

Table 28. [a]The reactions were performed using substrate 1.0 mmol, diformamide as additive 0.1 mmol, benzene 5 mL.[b] The reaction have been performed in absence of additive.[c] Yields calculated by isolation. [d] Yields were calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene (10 mol %) as internal standard.

Yield calculation (Entry 3). Products **311** and **312** were isolated as a inseparable mixture (90 mg, 0.38 mmol).

The following spectrum shows the mixture of **311** and **312** in the crude at the end of the reaction. From this spectrum the ratio can be calculated as following:

The singlet at 8.05 ppm is diagnostic for compound **312** and it refers to 1 proton of the molecule whereas the multiplet at 7.83-7.92 ppm integrates 3 protons of **311** and 3 protons of **312**.

Integrating the peak at 8.05 as 1, the resulting integration of the peak at 7.8-7.92 becomes 43.71 units. From these data, we can create a simultaneous equation as following.

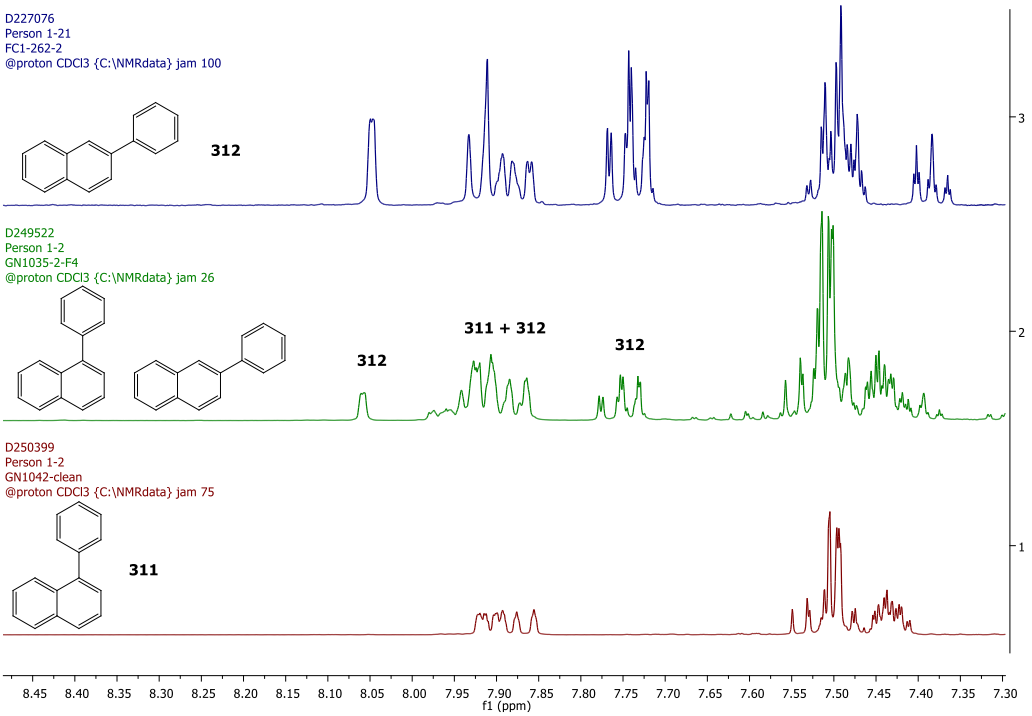
x = units of **312**, y = units of **311**

x = 1.00 3x + 3y = 43.71	x = 1.00 3 + 3y = 43.71	x = 1.00 3y = 40.71	x = 1.00 y = 40.71/3	x = 1.00 y = 13.6

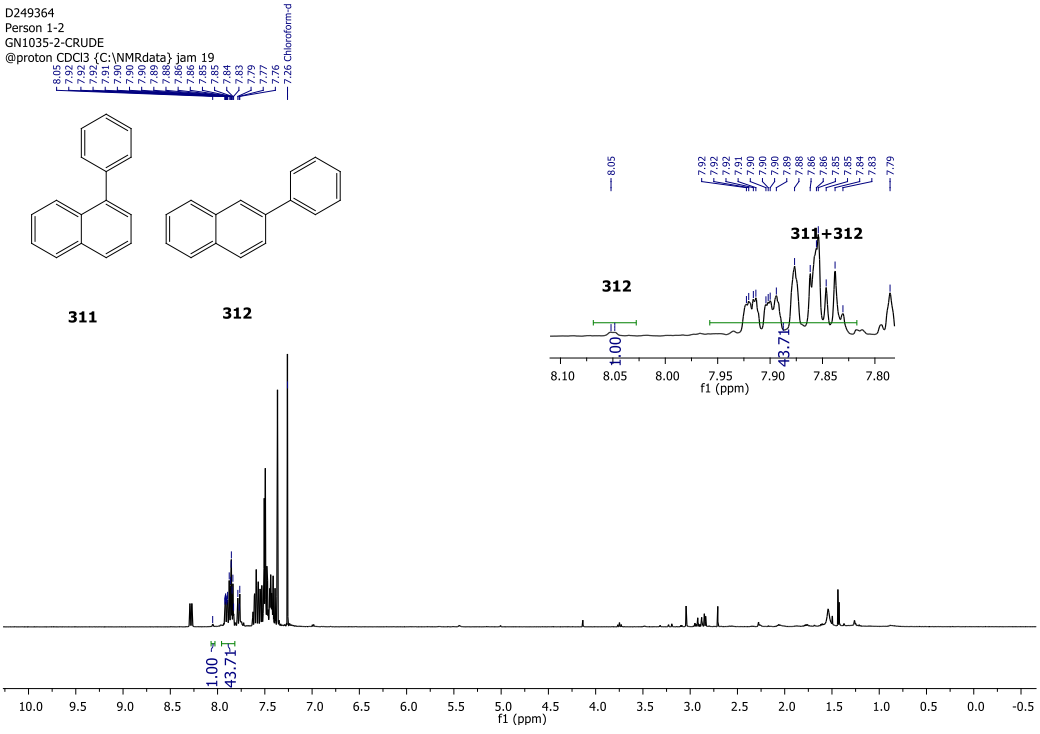
Knowing the ratio (**311** : **312** = 13.6 : 1) of the two products, it is now possible to calculate the products percentages. Since 90 mg of the mixture was isolated then the amounts of the equimass products are:

311 : 90 mg x 13.6/14.6 = 84 mg, 0.41 mmol, 41%

312: 90 mg x 1/14.6 = 6.2 mg, 0.03 mmol, 3 %.



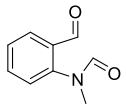
Spectrum 7. Spectra comparison of the isolated mixture **311** + **312** (green), clean **312** (blue) and clean **311** (red).



Spectrum 8. Crude reaction mixture used for yield calculation.

5.A2 Exploring the Deprotonation of Non-Enolisable Aldehydes

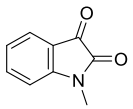
N-(2-Formylphenyl)-*N*-methylformamide, **7**



N-(2-Formylphenyl)-*N*-methylformamide
Chemical Formula: $C_9H_9NO_2$
Exact Mass: 163,0633

A solution of 1-methylindole (750 mg, 5.73 mmol) in methanol (45 mL) was cooled at -78 °C and a stream of ozone (2.5 % in oxygen) passed through until a blue/green colour persisted (6 h). Oxygen was then passed through the solution until the blue/green colour faded and excess of ozone passed into and was quenched by a KI saturated solution connected with the reaction flask, during the whole reaction. Dimethyl sulfide (3.5 g, 4.13 mL, 57.3 mmol) was added and stirred at -78°C for 10 min before the cooling bath was removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure to give the product (note: a blast shield was put in place around the rotary evaporator during this operation). The crude material was purified by flash chromatography with petroleum ether : ethyl acetate as 7:3 as eluent, affording the title product as an orange viscous oil (330 mg, 2.02 mmol, 35% yield). The NMR spectra of this material showed the presence of rotamers. ν_{max} (neat/cm^{-1}) 2860, 2752, 1668, 1595, 1485, 1333, 1192, 1085, 768, 733. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 10.08 (1 H, s, C*H*OC), 8.23 (1 H, s, *HC*ON), 7.96 (1 H, dd, *J* = 7.7, 1.5, Ar*H*), 7.69 (1 H, td, *J* = 7.8, 1.6, Ar*H*), 7.52 (1 H, t, *J* = 7.5, Ar*H*), 7.29 (1 H, d, *J* = 8.1, Ar*H*), 3.33 (3 H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 189.4, 189.2, 163.1, 162.8, 143.6, 135.4, 135.2, 131.9, 131.1, 130.7, 128.6, 127.9, 127.6, 38.0, 34.7. GC-MS (EI) *m/z* 163.1. NMR spectra was consistent with the literature.[217]

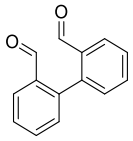
N-methylisatin, **8**



N-methylisatin
Chemical Formula: $C_9H_7NO_2$
Exact Mass: 161,0477

A mixture of KO*t*Bu (112 mg, 1.0 mmol) and **7** (52.2 mg; 0.65 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed, placed in the fumehood and heated at 130 ºC for 18 h behind a shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil. *N*-methylisatin **8** was isolated *via* column chromatographic using petroleum ether : ethyl acetate as 9:1 as eluent as a red solid (41 mg,0.26 mmol, 40% yield). Mp 130-133 °C [lit., 130-132 °C].[218] ν_{max} (neat/cm^{-1}) 3054, 2923, 1742, 1723, 1599, 1467, 1091. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.64 – 7.58 (2 H, m, Ar*H*), 7.13 (1 H, t, *J* = 7.6, Ar*H*), 6.89 (1 H, d, *J* = 7.6, Ar*H*), 3.26 (3 H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 182.9, 157.8, 151.0, 137.9, 124.8, 123.3, 117.0, 109.4, 25.7. GC-MS (EI) *m/z* 161.1. Data were consistent with the literature. [219]

[1,1'-Biphenyl]-2,2'-dicarbaldehyde, **5**

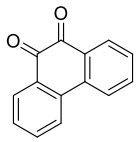


[1,1'-Biphenyl]-2,2'-dicarbaldehyde
Chemical Formula: $C_{14}H_{10}O_2$
Exact Mass: 210,0681

A suspension of phenanthrene (1.0 g, 5.62 mmol) in DCM (25 mL) was cooled to -78°C and O_3 (2.5 % in O_2) was passed through the mixture until the phenanthrene was consumed as monitored by TLC (8 h). To the cooled reaction mixture, potassium iodide (2.8 g, 17.0 mmol) and 5 mL of acetic acid were added. After the addition, the reaction mixture was allowed to stand at room temperature for 30 min to 1 h. The released iodine was reduced with 10% sodium thiosulfate solution (10 mL), after which the reaction mixture was placed immediately under an air blast. As the methanol evaporated, a solid began to crystallise. The

dried solid was then purified by chromatography, using hexane : ethyl acetate as 9:1 eluent to afford the title compound as a colorless oil (330 mg, 1.57 mmol; 28% yield).[127] ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 9.85 (2 H, s, C*H*O), 8.07 (2 H, dd, *J* = 7.7, 1.4, Ar*H*), 7.68 (2 H, td, *J* = 7.5, 1.5, Ar*H*), 7.61 (2 H, t, *J* = 7.4, Ar*H*), 7.36 (2 H, dd, *J* = 7.5, 1.0, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 191.2, 141.3, 134.7, 133.5, 131.8, 128.9, 128.7. GC-MS (EI) *m/z* 210.1. Data were consistent with the literature. [220]

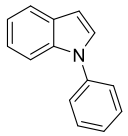
Phenanthrene-9,10-dione, **6**



phenanthrene-9,10-dione
Chemical Formula: $C_{14}H_8O_2$
Exact Mass: 208,0524

A mixture of KO*t*Bu (159 mg, 1.42 mmol) and [1,1'-biphenyl]-2,2'-dicarbaldehyde **5** (100 mg, 0.48 mmol) in 5 mL benzene was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a shield in the fumehood. After cooling to room temperature, the reaction was quenched with water (15 mL), acidified with 1N HCl until neutral pH and extracted with diethyl ether (15 mL). The organic layers were separated, dried over sodium sufate, filtered and concentrated by rotary evaporator to give a residue as a yellow solid (70 mg). The crude material has been purified by chromatography affording phenanthrenequinone **6** as an orange solid (50 mg, 0.24 mmol, 50% yield). The data of the product **6** are given. Mp 201-204 °C [lit., 204-205 °C][221] ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 8.22 (2 H, dd, *J* = 7.8, 1.5, Ar*H*), 8.05 (2 H, d, *J* = 8.0, Ar*H*), 7.75 (2 H, td, *J* = 8.0, 1.4, Ar*H*), 7.50 (2 H, td, *J* = 7.7, 1.0, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 180.5, 136.1, 136.0, 131.2, 130.7, 129.7, 124.1. GC-MS (EI) *m/z* 208.1. NMR data were consistent with the literature.[222]

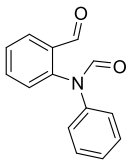
1-phenyl-1H-indole, **382**



1-phenyl-1*H*-indole
Chemical Formula: $C_{14}H_{11}N$
Exact Mass: 193.0891

To a solution of indole (2.0 g, 17.0 mmol) in NMP (36 mL), CuBr (5.1 g, 35.7 mmol), Na_2CO_3 (3.8 g, 35.7 mmol) and iodobenzene (12.0 g; 58.2 mmol) were added and the mixture was heated at 170°C for 6h. After cooling to rt, 5 % HCl (15 mL) and ethyl acetate (15 mL) were added and the mixture was filtered on a celite pad. The filtrate was separated and the organic layer was washed with brine, dried over sodium sulfate and concentrated by rotary evaporator. The crude product was then purified by chromatography using pure hexane as eluent affording the title compound **382** as a yellow oil (2.2 g, 11.9 mmol, 67% of yield). IR ν_{max} (film/cm^{-1}) 3051, 1595, 1454, 1329, 1233, 1211, 748. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 – 7.72 (1 H, m, Ar*H*), 7.62 (1 H, ddd, *J* = 8.4, 1.7, 0.8, Ar*H*), 7.57 – 7.55 (4 H, m, Ar*H*), 7.41 (1 H, dd, *J* = 7.0, 2.4, Ar*H*), 7.39 (1 H, d, *J* = 3.2, Ar*H*), 7.28 (1 H, ddd, *J* = 8.3, 6.3, 1.4, Ar*H*), 7.25 – 7.20 (1 H, m, Ar*H*), 6.74 (1 H, dd, *J* = 3.3, 0.8, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 139.4, 135.4, 129.1, 128.9, 127.0, 126.0, 123.9, 121.9, 120.7, 119.9, 110.0, 103.1. GC-MS (EI) *m/z* 193.0. NMR spectrum consistent with the literature.[223]

N-(2-formylphenyl)-*N*-phenylformamide, **383**

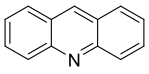


N-(2-formylphenyl)-*N*-phenylformamide
Chemical Formula: $C_{14}H_{11}NO_2$
Exact Mass: 225.0790

A solution of 1-phenyl-1H-indole, **382** (1 g, 5.2 mmol) in DCM (60 mL) was cooled at -78 °C and a stream of ozone (2.5% in oxygen) passed through until a blue/green colour persisted (6 h). O_2 was then passed through the solution until the blue/green colour faded and excess of ozone passed into and was quenched by a KI saturated solution connected with the reaction flask, during the whole reaction. Triphenylphosphine (2.7 g, 10.4 mmol) was added and

stirred at -78°C for 10 min before the cooling bath was removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure to give the product (note: a blast shield was put in place around the rotary evaporator during this operation). The crude material was purified by flash chromatography with hexane : ethyl acetate as 7:3 as eluent, affording the title compound as a yellow oil (380 mg, 1.68 mmol, 32 % yield). The NMR spectra of this material showed the presence of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.09 (s, 1H,C*H*O), 8.85 (s, 1H, C*H*ON), 8.02 (dd, *J* = 1.6, 7.7 Hz, 1H, Ar*H*), 7.69 (td, *J* = 1.7, 7.7 Hz, 1H, Ar*H*), 7.54 (tt, *J* = 0.9, 7.6 Hz, 1H, Ar*H*), 7.47 – 7.27 (m, 3H, Ar*H*), 7.25 (dd, *J* = 1.2, 7.9 Hz, 1H, Ar*H*), 7.19 – 7.14 (m, 2H, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 188.6, 188.4, 161.9, 161.1, 141.1, 134.9, 134.7, 131.7, 130.1, 129.7, 129.5, 129.2, 128.8, 128.5, 128.2, 126.4, 126.1, 124.0, 123.0. *m*/*z* (APCI) calcd. for $C_{14}H_{12}NO_2$ $[M+H]^+$: 226.0868, found: 226.0865.

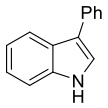
Acridine, **384**



acridine
Chemical Formula: $C_{13}H_9N$
Exact Mass: 179.0735

A mixture of KO*t*Bu (224 mg, 2.0 mmol) and *N*-(2-formylphenyl)-N-phenylformamide, **383** (225 mg, 1.0 mmol) in 5 mL benzene was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a shield in the fumehood. After cooling to room temperature, the reaction was quenched with water (15 mL), acidified with 1N HCl until neutral pH and extracted with diethyl ether (15 mL). The organic layers were separated, dried over sodium sufate, filtered and concentrated by rotary evaporator to give a residue The crude material was purified by chromatography using hexane : ethyl acetate 9:1, affording acridine **384** as yellow needles (170 mg, 0.94 mmol, 94 % yield). Mp 100-103 °C [lit., 105-106 °C].[224] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.78 (1 H, s, Ar*H*), 8.27 (2 H, ddd, *J* = 8.8, 1.7, 0.8, Ar*H*), 8.01 (2 H, dd, *J* = 8.4, 1.3, Ar*H*), 7.80 (2 H, ddd, *J* = 8.8, 6.6, 1.4, Ar*H*), 7.55 (2 H, ddd, *J* = 8.3, 6.6, 1.0, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 148.6, 135.5, 129.8, 128.9, 127.7, 126.1, 125.2. GC-MS (EI) *m/z* 179.0. Data were consistent with the literature.[130]

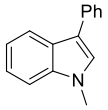
3-phenyl-1H-indole, **392**



3-phenyl-1*H*-indole
Chemical Formula: $C_{14}H_{11}N$
Exact Mass: 193.0891

A mixture of phenylhydrazine hydrochloride (1.45 mg, 10.0 mmol), 2-phenylacetaldehyde (1.17 mL, 10 mmol) and 2,4,6-trichloro-1,3,5-triazine (184 mg, 1.0 mmol) in ethanol (20 mL) was heated to 85 °C.[131] After 2 h the starting material was absent as monitored by TLC. The reaction mixture was cooled to ambient temperature and diluted with water. The organic mixture was extracted into ethyl acetate (25 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated via rotary evaporator and purified by column chromatography using hexane : ethyl acetate as 9 : 1 to yield 3-phenyl-1H-indole **392** as a yellow solid (920 mg, 4.76 mmol, 47.6 %). Mp 80-81 °C [lit., 81 – 83 °C].[225] IR ν_{max} (neat/cm^{-1}) 3080, 1602, 1548, 1466, 1240, 1222, 765, 738. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.22 (s, 1H, N*H*), 7.95 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.68 (dd, *J* = 8.3, 1.2 Hz, 2H, Ar*H*). 7.45 (tt, *J* = 8.1, 1.6 Hz, 3H, Ar*H*), 7.37 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.25 - 7.33 (m, 1H, Ar*H*), 7.23 - 7.27 (m, 1H, Ar*H*), 7.20 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H, Ar*H*). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm 136.7, 135.6, 128.9, 127.6, 126.0, 125.8, 122.5, 121.9, 120.4, 119.9, 118.3, 111.5. GC-MS (EI) *m/z* 193.1. Data were consistant with the literature.[225]

1-Methyl-3-phenyl-1H-indole, **393**

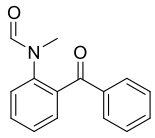


1-methyl-3-phenyl-1*H*-indole
Chemical Formula: $C_{15}H_{13}N$
Exact Mass: 207.1048

To a solution of 3-phenyl-1H-indole, **392** (2.0 g, 10.4 mmol) in DMF (20 ml) sodium hydride (0.6 g, 16.6 mmol) was added at 0 °C under nitrogen atmosphere. The reaction was warmed to RT and stirred for 15 min, then cooled down to 0 °C again. Neat iodomethane (2.35 g, 1.03 ml, 16.6 mmol) was added dropwise and the reaction was allowed to warm to RT and

stirred for 3 h. Upon disappearance of the starting material as indicated by TLC, the reaction mixture was poured into ice water and extracted with EtOAc (3 × 100 mL). The organic layer was combined and dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography on silica gel (hexane : EtOAc as 95:5) to yield 1-methyl-3-phenyl-1H-indole as a yellow oil (2.0 g, 93 %). IR ν_{max} (neat/cm^{-1}) 3050, 1603, 1465, 1375, 1240 1222, 765, 736, 698. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.95 (1H, dt, *J* = 8.0, 1.0 Hz, ArH), 7.64 - 7.68 (2H, m, ArH), 7.44 (2H, tt, *J* = 8.1, 1.6 Hz, ArH), 7.38 (1H, dt, *J* = 8.2, 0.9 Hz, ArH), 7.27 - 7.32 (2H, m, ArH), 7.24 (1H, s, ArH), 7.20 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz, ArH), 3.85 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm 137.5, 135.7, 128.7, 127.3, 126.5, 126.2, 125.7, 122.0, 119.9, 119.9, 116.8, 109.5, 32.9. *m/z* (APCI) calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1126, found: 208.1131.

N-(2-Benzoylphenyl)-*N*-methylformamide, **394**

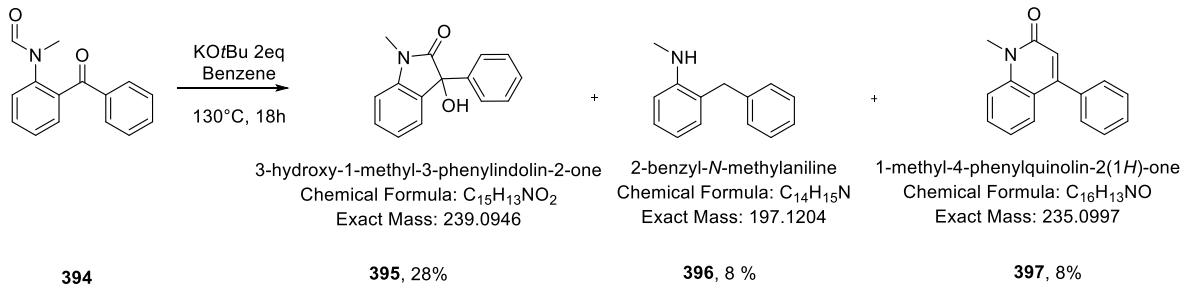


N-(2-benzoylphenyl)-*N*-methylformamide
Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239.0946

3-Phenyl-1H-indole, **393** (1 g, 4.84 mmol) in DCM (60 mL) and pyridine (1.1 g, 1.17 mL, 14.5 mmol) were cooled at -78 °C and a stream of ozone (2.5 % in O_2) passed through until a blue/green colour persisted (6 h). O_2 was then passed through the solution until the blue/green colour faded and excess of ozone passed into and was quenched by a KI saturated solution connected with the reaction flask, during the whole reaction. Triphenylphosphine (1.4 g, 5.3 mmol) was added and stirred at -78°C for 10 min before the cooling bath was removed and the reaction mixture stirred at room temperature overnight.[129,226] The reaction mixture was then concentrated under reduced pressure to give a residue (note: a blast shield was put in place around the rotary evaporator during this operation). The crude residue was dissolved in ethyl acetate and the byproduct triphenylphosphinoxide was filtered off. The resulting mother liquor was then concentrated and purified by chromatographic column using Hex/ EtOAc as 9:1 ratio, giving the title product **394** (340 mg, 1.42 mmol, 29.4 % yield) as

a yellow solid. The NMR spectra of this material showed the presence of rotamers. Mp 70-73 °C [lit., 96 °C from benzene/hexane].[227] IR ν_{max} (neat/cm^{-1}) 3055, 1673, 1654, 1533, 1230, 1244, 925, 704. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (1H, s, C*H*N), 7.74 (2H, dd, *J* = 8.4, 1.3 Hz, Ar*H*), 7.67 – 7.56 (2H, m, Ar*H*), 7.56 (1H, dd, *J* = 7.6, 1.6 Hz, Ar*H*), 7.53 – 7.43 (3H, m, Ar*H*), 7.31 (1H, dd, *J* = 7.9, 1.2 Hz, Ar*H*), 3.06 (3H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 195.4, 162.0, 139.9, 136.3, 136.0, 133.3, 132.9, 132.7, 131.3, 131.2, 129.8, 129.6, 129.4, 129.2, 128.2, 127.9, 127.8, 126.8, 126.8, 126.6, 126.6, 37.5, 33.3. *m*/*z* (APCI) calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1019, found: 240.1019.

Testing *N*-(2-benzoylphenyl)-*N*-methylformamide, **394** with KO*t*Bu



A mixture of KO*t*Bu (224 mg, 2.0 mmol) and **394** (239 mg, 1.0 mmol) in 5 mL benzene was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a shield in the fumehood. After cooling to room temperature, the reaction was quenched with water (15 mL), acidified with 1N HCl until neutral pH and extracted with diethyl ether (15 mL). The organic layers were separated, dried over sodium sufate, filtered and concentrated by rotary evaporator to give a residue. The crude material was purified by chromatography using hexane : ethyl acetate from 8:2 to 2:8 affording 3 different oils: **395** (67 mg, 0.28 mmol, 28% yield), 2-benzyl-*N*-methylaniline **396** (16 mg, 8 mmol, 8% yield), **397** (19 mg, 8 mmol, 8% yield).

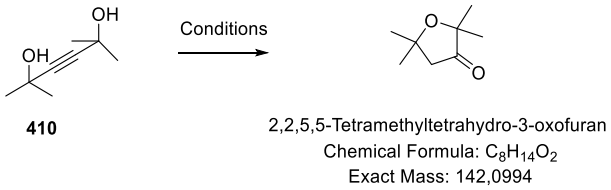
3-hydroxy-1-methyl-3-phenylindolin-2-one, **395**: IR ν_{max} (film/cm^{-1}) 3333, 1701, 1610, 1375, 1354, 1111, 1091, 752, 694. ^{1}H NMR (400 MHz $CDCl_3$) δ ppm 7.42 – 7.27 (7 H, m, Ar*H*), 7.09 (1 H, td, *J* = 7.6, 0.9, Ar*H*), 6.91 (1 H, d, *J* = 7.8, Ar*H*), 3.29 (1 H, s, O*H*), 3.26 (3 H, s, CH_3). The presence of the OH was confirmed by adding D_2O into the NMR tube:

the fast D-H exchange causes peak disappearance. ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 177.0, 143.1, 139.6, 131.0, 129.4, 128.1, 127.8, 124.8, 124.5, 123.0, 108.2, 77.5, 26.0. GC-MS (EI) *m/z* 239.1. Data were consistent with the literature.[228]

2-Benzyl-*N*-methylaniline, **396**: IR ν_{max} (film/cm^{-1}) 3435, 1603, 1584, 1512, 1493, 1310, 746, 731. ^{1}H NMR (400 MHz $CDCl_3$) δ ppm 7.31 (2 H, tt, *J* = 8.2, 1.6, Ar*H*), 7.28 – 7.21 (2 H, m, Ar*H*), 7.19 (2 H, d, *J* = 7.3, Ar*H*), 7.06 (1 H, d, *J* = 6.0, Ar*H*), 6.75 (1 H, t, *J* = 7.9, Ar*H*), 6.68 (1 H, d, *J* = 8.1, Ar*H*), 3.90 (2 H, s, CH_2), 3.57 (1 H, s, N*H*), 2.80 (3 H, s, CH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 146.7, 138.8, 130.0, 128.1, 128.0, 127.4, 126.0, 124.0, 116.5, 109.5, 37.4, 30.3. GC-MS (EI) *m/z* 197.1. Data were consistent with the literature.[229]

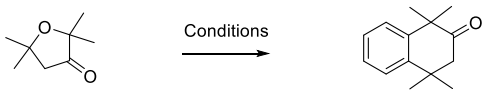
1-Methyl-4-phenylquinolin-2(1H)-one, **397**: IR ν_{max} (film/cm^{-1}) 2920, 1628, 1440, 1273, 1117, 1067, 752, 698. ^{1}H NMR (400 MHz $CDCl_3$) δ ppm 7.62 – 7.54 (2 H, m, Ar*H*), 7.53 – 7.40 (6 H, m, Ar*H*), 7.17 (1 H, ddd, *J* = 8.2, 7.2, 1.1, Ar*H*), 6.69 (1 H, s, C*H*CO), 3.79 (3 H, s, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 161.5, 150.4, 139.9, 136.6, 130.2, 128.4, 128.2, 128.1, 127.2, 121.4, 120.8, 120.1, 114.0, 29.0. GC-MS (EI) *m/z* 235.1. Data were consistent with the literature.[230]

2,2,5,5-Tetramethyltetrahydro-3-oxofuran, **411**



A mixture of mercury (II) acetate (1.12 g, 3.5 mmol), sulfuric acid (1.0 mL), water (100 mL) and 2,5-dimethyl-3-hexyne-2,5-diol **410** (10 g, 70 mmol) was heated at 80 °C for 4 h. After cooled to RT, the mixture was extracted with diethyl ether (3 x 50 mL) and the organic phases were combined, washed with water, dried over sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound **411** as a colourless oil (8.4 g, 24 mmol, 84% yield).[132] IR ν_{max} (film/cm^{-1}) 2974, 2931, 1753, 1369, 1145, 991. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 2.50 (2 H, s, CH_2), 1.38 (6 H, s, CH_3), 1.28 (6 H, s, CH_3).^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 218.4, 80.9, 76.3, 48.6, 30.3, 26.5. GC-MS (EI) *m/z* 142.1. Data were consistent with the literature.[231]

1,1,4,4-Tetramethyl-2-tetralone, **412**

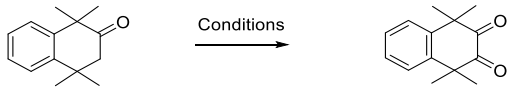


411

1,1,4,4-Tetramethyl-2-tetralon
Chemical Formula: $C_{14}H_{18}O$
Exact Mass: 202,1358

Aluminium chloride (16 g, 121 mmol) was added portionwise (15 min) to a solution of **411** (8.4 g, 59 mmol) in 50 mL of benzene at 0 °C. After the addition was completed the reaction mixture was allowed to warm to room temperature. After 16 h the reaction was carefully poured onto ice and the resulting water solution was extracted with ethyl acetate. The organic fraction was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material obtained was crystallised (after 1 month *circa*) from petroleum ether at -20 °C to afford the title product **412** (1.64 g, 8.12 mmol, 13.8%) as a white solid.[132] Mp 64-66 °C [lit., 68-71 °C].[232] ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.38 (1 H, dd, *J* = 7.1, 2.1, Ar*H*), 7.33 (1 H, dd, *J* = 7.3, 2.1, Ar*H*), 7.29–7.24 (1 H, m, Ar*H*), 7.26–7.19 (1 H, m, Ar*H*), 2.65 (2 H, s, CH_2), 1.46 (6 H, s, CH_3), 1.32 (6 H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 214.0, 143.7, 143.3, 127.4, 127.1, 126.7, 124.6, 51.6, 48.2, 38.1, 30.7, 28.6. HRMS (ESI) *m/z* calculated for $C_{14}H_{19}O$ $[M+H]^+$ 203.1430; found: 203.1430.

1,1,4,4-Tetramethyltetralin-2,3-dione: **413**



412

1,1,4,4-Tetramethyltetralin-2,3-dione
Chemical Formula: $C_{14}H_{16}O_2$
Exact Mass: 216,1150

1,1,4,4-Tetramethyl-2-tetralone, **412** (500 mg, 2.48 mmol) was dissolved in dioxane (4 mL), and selenium dioxide (288 mg, 2.6 mmol) was added. The reaction mixture was stirred and refluxed for 44 h. After cooling and filtering, the solvent was removed under reduced pressure on the rotary evaporator to yield a crude crystalline product. The product was purified by chromatography using petroleum ether : ethyl acetate as 9:1 as eluent to afford the title product **413** as a yellow oil (860 mg, 3.9 mmol, 80.3% yield).[132] ν_{max} (neat/cm^{-1}) 2978, 2359, 2340, 1724. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.38 – 7.30 (4 H, m, Ar*H*), 1.52

(12 H, s, C*H*$_3$). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 205.5, 140.4, 128.4, 126.5, 51.2, 26.8. HRMS (ESI) *m/z* calculated for $C_{14}H_{17}O_2$ $[M+H]^+$ 217.1223; found: 217.1224.

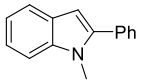
2,2'-(1,2-Phenylene)bis(2-methylpropanoic acid), **414**

413

2,2'-(1,2-Phenylene)bis(2-methylpropanoic acid)
Chemical Formula: $C_{14}H_{18}O_4$
Exact Mass: 250,1205

1,1,4,4-tetramethyltetralin-2,3-dione, **413** (800 mg, 3.70 mmol) was dissolved in 10 mL of dioxane/water and H_5IO_6 (980 mg, 4.30 mmol) was added. The reaction mixture was stirred and heated at 70 °C for a total of 40 h. The solvent was removed by rotary evaporator to afford a solid. This solid was then dissolved in diethyl ether, filtered and extracted with 10% sodium hydroxide. On acidification of the alkaline extract, product **414** was obtained as a flocculent white precipitate (360 mg, 1.7 mmol, 38.9 % yield).[132] Mp 205-208 °C [lit., 218-219 °C].[132] ν_{max} (film/cm^{-1}) 2980, 1701, 1315.5, 1207, 1047, 912, 767, 750.^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 12.11 (2 H, s, COO*H*), 7.36 (2 H, m, Ar*H*), 7.18 (2 H, m, Ar*H*), 1.57 (12 H, s). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 179.5, 142.3, 129.6, 126.2, 48.1, 28.9.[132] HRMS (ESI) *m/z* calculated for $C_{14}H_{17}O_4$ $[M-H]^-$ 249.1132; found, 249.1133.

1-Methyl-2-phenyl-1H-indole. **417**

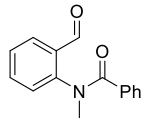


1-methyl-2-phenyl-1*H*-indole
Chemical Formula: $C_{15}H_{13}N$
Exact Mass: 207.1048

To a solution of 2-phenyl-1H-indole (4.83 g, 25 mmol) in DMF (47.5 ml) sodium hydride (1.600 g, 40.00 mmol) was added at 0 °C under nitrogen atmosphere The reaction was warmed to RT and stirred for 15 min, then cooled down to 0 °C again. Neat iodomethane (2.490 ml, 40.00 mmol) was added dropwise and the reaction was allowed to warm to RT and stirred for 3 h. Upon disappearance of the starting material as indicated by TLC, the reaction mixture was poured into ice water and extracted with EtOAc (3 × 100 mL). The organic layer was combined and dried over Na_2SO_4 and the solvent was removed *in vacuo*.

The crude material was purified by flash column chromatography on silica gel hexane : EtOAc as 95:5 to yield1-methyl-2-phenyl-1H-indole **417** (4.81 g, 93 %) as a yellow oil. IR ν_{max} (neat/cm^{-1}) 3120, 1466, 1341, 1308, 757, 748, 731, 702. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.68 (1Hd, t, *J* = 7.9, 1.0 Hz, Ar*H*), 7.56 (2H, dd, *J* = 8.3, 1.4 Hz, Ar*H*), 7.51 (2H, ddd, *J* = 7.7, 6.8,1.2 Hz, Ar*H*), 7.4 - 7.48 (1H, m, Ar*H*), 7.40 (1H, dd, *J* = 8.2, 0.8 Hz, Ar*H*), 7.29 (1H, ddd, *J* =8.2, 7.0, 1.2 Hz, Ar*H*), 7.19 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, Ar*H*), 6.61 (1H, d, *J* = 0.8 Hz, Ar*H*), 3.78 (3H, s, CH_3). ^{13}C-NMR (126 MHz, $CDCl_3$) δ ppm 141.6, 138.4, 132.9, 129.4, 128.5, 128.0, 127.9, 121.7, 120.5, 119.9, 109.6, 101.7, 31.2. *m*/*z* (APCI) calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.1121, found: 208.1122.

N-(2-Formylphenyl)-*N*-methylbenzamide, **418**



N-(2-formylphenyl)-*N*-methylbenzamide
Chemical Formula: $C_{15}H_{13}NO_2$
Exact Mass: 239.0946

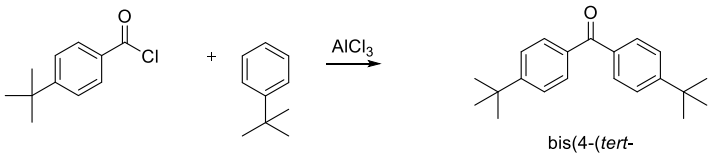
1-Methyl-2-phenyl-1H-indole **417** (1 g, 5.2 mmol) in DCM (60 mL) and pyridine (1.1 g, 1.17 mL, 14.5 mmol) were cooled at -78 °C and a stream of ozone (2.5 % in O_2) passed through until a blue/green colour persisted (6 h). O_2 was then passed through the solution until the blue/green colour faded and excess of ozone passed into and it was quenched by a KI saturated solution connected with the reaction flask, during the whole reaction. Triphenylphosphine (1.4 g, 5.3 mmol) was added and stirred at -78°C for 10 min before the cooling bath was removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure to give the product (note: a blast shield was put in place around the rotary evaporator during this operation). The crude material was purified by flash chromatography with hexane : ethyl acetate as 8:2 as eluent, affording the title product **418** as an oil (1.1 g, 4.6 mmol, 95.1 % yield).[226] The NMR spectra of this material showed the presence of rotamers. IR ν_{max} (neat/cm^{-1}) 3052 , 2841, 1693, 1644, 1597, 1363, 1235, 1210, 730. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.14 (1H, s, C*H*O), 7.78 (1H, d, *J* = 7.6 Hz), 7.58 – 7.52 (1H, m, Ar*H*), 7.43 – 7.32 (1H, m, Ar*H*), 7.27 – 7.06 (6H, m, Ar*H*), 3.54 (3H, s, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 188.6, 134.7, 134.5, 132.9,

131.4, 130.1, 129.6, 129.5, 128.8, 128.0, 127.5, 127.4, 38.8. *m/z* (APCI) calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1019, found: 240.1020.

5.A3 KO*t*Bu (but not NaO*t*Bu) Photoreduces Benzophenone under Activation by Visible Light

5.A3.1 Preparation of the substrates

4,4'-Di-*tert*-butylbenzophenone, **440**



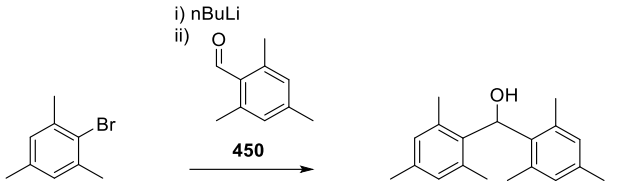
447 **448**

bis(4-(*tert*-butyl)phenyl)methanone
Chemical Formula: $C_{21}H_{26}O$
Exact Mass: 294.1984

p-tert-Butylbenzoyl chloride **447** (1.18 g, 1.17 ml, 6 mmol) was slowly added to *tert*-butylbenzene **448** (1.93 mg, 2.22 mL, 14.4 mmol) and aluminium trichloride (2.22 g, 15.2 mmol) at RT. During the addition of *p-tert*-butylbenzoyl chloride, the reaction turned from a yellow suspension to a dark reddish brown solution. After the addition was complete, the reaction was warmed at 80 °C for 2.5 h. Vigorous bubbling was observed throughout the reaction. Afterwards, the hot reaction mixture was poured into crushed ice (30 g) and concentrated hydrochloric acid (10.5 mL). This yielded a tar-like substance which metamorphosed to a yellow solid after decomposition was complete (few minutes). This yellow solid was filtered, dissolved in toluene (15 mL), washed with water and 5% aqueous sodium hydroxide and dried over sodium sulfate. Recrystallisation from toluene produced a white powder which was washed with hexane to give the title compound **440** as a white solid (625 mg, 0.68 mmol, 35.5%).[147] Mp: 122-124 °C (lit: 123-124°C).[233] ν_{max} (neat, cm^{-1}) 2959, 2903, 2864, 1643, 1605, 1280, 1186, 1104, 932. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (4 H, d, *J* = 8.6, Ar*H*), 7.49 (4 H, d, *J* = 8.8, Ar*H*), 1.37 (18 H, s, C*H*$_3$) ppm. ^{13}C-NMR (101

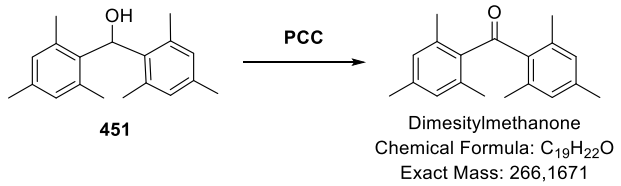
MHz, $CDCl_3$) δ 195.7, 155.4, 134.7, 129.5, 124.7, 34.6, 30.7 ppm. GC-MS (EI) *m/z* 294.1. Data were consistent with the literature.[147]

Dimesitylmethanol, **451**



To a cooled (-78 °C) solution of mesityllithium, prepared by addition of *n*-butyllithium (2.2 mmol) to a solution of mesityl bromide **449** (478 mg, 0.37 mL, 2.4 mmol) in 8 mL of THF, a solution of mesitylaldehyde (296 mg, 0.294 mL, 2.0 mmol) in 2 mL of THF. After 30 min, the solution was allowed to warm and was quenched with aqueous ammonium chloride. The product was extracted with diethyl ether, dried over sodium sulfate and concentrated. The crude product was washed with pentane to give dimesitylmethanol **451** as a white solid (315 mg, 1.18 mol, 59%). Mp: 145-147 (lit: 149-150 °C)[234] IR ν_{max} (neat, cm^{-1}) 3472, 2908, 1608, 1476, 1420, 1375, 1126, 1045, 1003, 851, 694. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.82–6.78 (4 H, s, Ar*H*), 6.37–6.33 (1 H, s, C*H*OH), 2.27–2.24 (6 H, s, CH_3), 2.23–2.19 (12 H, s, CH_3), 1.73–1.68 (1 H, s, O*H*) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$) δ 136.7 (2 *C*), 130.7 (2 *C*), 73.5, 21.2, 20.8 ppm. GC-MS (EI) *m/z* 268.1. Data were consistent with the literature.[148]

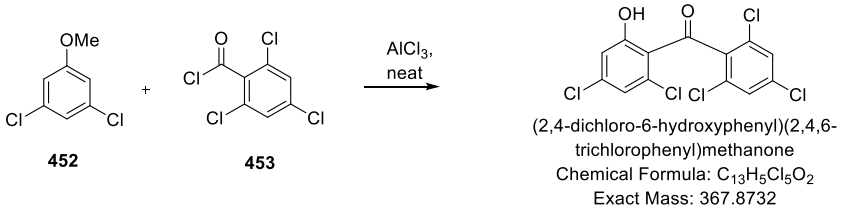
Dimesitylmethanone, **441**



Pyridinium chlorochromate (2.53 g, 11.8 mmol) was added to a solution of dimesitylmethanol **441** (2.10 g, 7.8 mmol) in 35 mL of DCM and allowed to stir at RT for 3 h. The crude product was filtered on a celite pad, the solution concentrated and crystallised from methanol to give dimesitylmethanone, **441** as a white solid (1.4 g, 5.2 mmol, 67%). [148] Mp: 140-143 °C (lit: 138-140 °C)[148]. IR ν_{max} (neat, cm^{-1}) 2916, 1643, 1605, 1422, 1242,

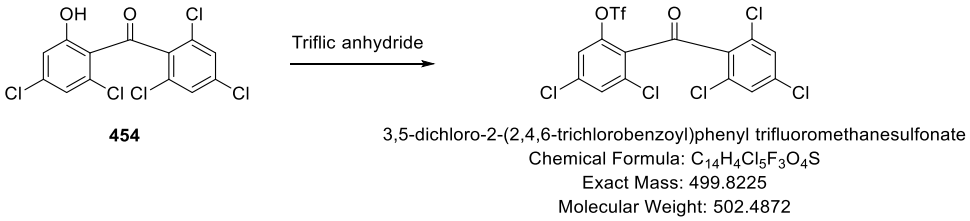
887, 855, 696. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.84 (4 H, s, Ar*H*), 2.29 (6 H, s, CH_3), 2.12 (12 H, s, CH_3) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$) δ 202.8, 140.1, 138.6, 136.8, 129.9, 21.3, 20.9 ppm. GC-MS (EI) *m/z* 266.1 (M^+). Data were consistent with the literature.[148]

(2,4-Dichloro-6-hydroxyphenyl)(2,4,6-trichlorophenyl)methanone, **454**



3,5-Dichloroanisole **452** (2.8 mg, 16 mmol) and aluminium chloride (2.55 g, 19.2 mmol) were cooled to 0 °C in a flask under inert atmosphere. 2,4,6-Trichlorobenzoyl chloride **453** (4.65 g, 19.2 mmol) was then added and the reaction mixture was stirred at 110 °C for 15 h. At the end of the reaction (monitored by TLC), water (15 mL) was added and the mixture stirred. The mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated *in vacuo*. Purification by silica gel chromatography with pure hexane afforded (2,4-dichloro-6-hydroxyphenyl)(2,4,6-trichlorophenyl)methanone, **454** (1.7 g, 4.69 mmol, 58.6 %) as a white solid. Mp: 82-84 °C. IR ν_{max} (neat, cm^{-1}) 1626, 1543, 1386, 1365, 1298, 1224, 1184, 1089, 960, 916. ^{1}H NMR (400 MHz $CDCl_3$) δ 12.58 (1 H, s, O*H*), 7.38 (2 H, s, Ar*H*), 7.06 (1 H, d, *J* = 2.1, Ar*H*), 6.96 (1 H, d, *J* = 2.1, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 165.9, 143.0, 137.8, 136.6, 136.44, 132.2, 128.5, 123.0, 118.4, 117.0 ppm. *m/z* (APCI) calcd. for $C_{13}H_6Cl_5O_2$ $[M+H]^+$: 368.8805, found: 368.8798.

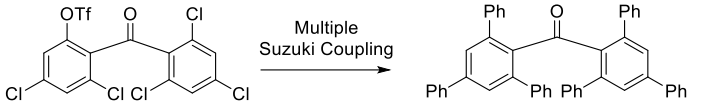
3,5-Dichloro-2-(2,4,6-trichlorobenzoyl)phenyl trifluoromethanesulfonate, **455**



Ketone **454** (1.61 g, 4,4 mmol), anhydrous DCM (8 mL) and pyridine (695.2 mg, 8,8 mmol) were added to a round-bottomed flask, under argon atmosphere. The mixture was cooled to 0° C in an ice bath, then was treated with dropwise addition of triflic anhydride (4.49 g, 5.28

mmol). The resulting mixture was allowed to warm to RT and was stirred for an additional 4 h. The mixture was then filtered and concentrated *in vacuo*. The product was purified by chromatography (hexane), affording ketone **455** (1.24 g, 2.48 mmol, 56.4 %). Mp: 110-112 °C. IR ν_{max} (neat, cm^{-1}) 1686, 1427, 1207, 1136, 1091, 953, 910, 798. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.46 (1 H, d, *J* = 1.9, Ar*H*), 7.40 – 7.36 (3 H, m, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 185.8, 148.5, 138.8, 137.9, 134.9, 134.6, 134.5, 130.4, 129.3, 121.5, 118.5 (q, *J* = 320.6, *C*F_3) ppm. *m/z* (APCI) calcd. for $C_{14}H_5Cl_5F_3O_4S$ $[M+H]^+$: 500.8298, found: 500.8287.

Bis(5'-phenyl-[1,1':3',1"-terphenyl]-2'-yl)methanone, **251**



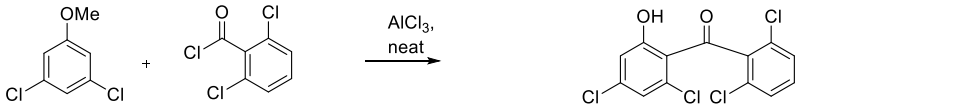
455

bis(5'-phenyl-[1,1':3',1"-terphenyl]-2'-yl)methanone
Chemical Formula: $C_{49}H_{34}O$
Exact Mass: 638.2610
Molecular Weight: 638.8100

Six different oven-dried microwave vials were charged, independently, with **455** (100.4 mg, 0,2 mmol), bis(acetonitrile)dichloropalladium(II) (2,6 mg, 0,01 mmol, 5%), Sphos (8,2 mg, 0,02 mmol, 10 %), phenylboric acid (292,8 mg, 2,4 mmol) and K_3PO_4 (508,8 mg, 2,4 mmol). The mixture was then introduced into the glovebox and anhydrous toluene (10 mL) was added. The vial was then sealed inside the glovebox and transferred into the fumehood, where it was heated at 110 °C for 4 days. The six cooled reaction mixtures were then combined and diluted with water and extracted with toluene. The combined organic layers were combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography (hexane) affording a white solid which was recrystallised using small amounts of toluene (very soluble) and hexane (almost insoluble) giving rise to the title ketone **251** (454 mg, 0.71 mmol, 59.3% combined yield from the 6 vials). The reaction was found to work better in a system under pressure such as a microwave vial. A bigger scale in a normal three-necked flask was tried, but only traces of product were detected.[150] Mp: 246-248 °C. IR ν_{max} (neat, cm^{-1}) 3053, 1665, 1590, 1491, 1229, 1074, 1029. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.52 – 7.48 (4 H, m, Ar*H*), 7.43 (4 H, t, *J* = 7.3, Ar*H*), 7.39 – 7.35 (2 H, m, Ar*H*), 7.33 – 7.26 (12 H, m, Ar*H*), 7.20 – 7.17 (8 H, m, Ar*H*), 7.09 (4 H, s, Ar*H*) ppm. ^{13}C NMR (101

MHz, $CDCl_3$) δ 193.7, 143.4, 141.2, 140.9, 139.4, 136.2, 129.8, 128.7, 128.3, 127.3, 126.7, 126.7, 126.2 ppm. *m*/*z* (APCI) calcd. for $C_{49}H_{35}O$ $[M+H]^+$: 639.2682, found: 639.2678.

(2,4-Dichloro-6-hydroxyphenyl)(2,6-dichlorophenyl)methanone, **461**

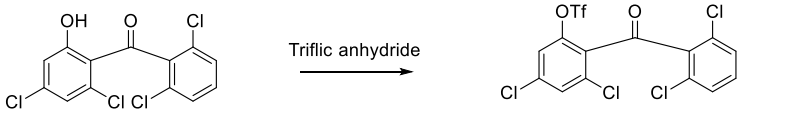


452 **460**

(2,4-dichloro-6-hydroxyphenyl)(2,6-dichlorophenyl)methanone
Chemical Formula: $C_{13}H_6Cl_4O_2$
Exact Mass: 333.9122
Molecular Weight: 335.9890

Aluminium chloride (1.8 g, 13.2 mmol) and 3,5-dichloroanisole **452** (1.0 g, 6 mmol) were added to a flask under inert atmosphere and this was then cooled at 0 °C. 2,6-Dichlorobenzoyl chloride **460** (1.5 g mg, 7.2 mmol) was then added. The reaction mixture was stirred at 110°C for 15 h. The mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated *in vacuo*. Purification with silica gel chromatography using pure hexane as eluent afforded the title compound **461** as a white solid (1.91 g , 5.72 mmol, 72 % yield). Mp: 98-100 °C. IR ν_{max} (neat, cm^{-1}) 3080, 1618, 1593, 1545, 1425, 1396, 1296, 1223, 1175, 956, 912, 846, 804. ^1H NMR (400 MHz $CDCl_3$) δ 12.70 (1 H, s, O*H*), 7.37 – 7.31 (3 H, m, Ar*H*), 7.05 (1 H, d, *J* = 2.0, Ar*H*), 6.94 (1 H, d, *J* = 2.1, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 165.3, 142.1, 138.5, 136.1, 131.2, 130.9, 130.5, 127.7, 122.3, 120.3, 117.6, 116.5 pm. *m*/*z* (APCI) calcd. for $C_{13}H_7Cl_4O_2$ $[M+H]^+$: 334.9200, found 334.9209. Analogous demethylation of anisole using $AlCl_3$ was previously reported in the literature.[149]

3,5-Dichloro-2-(2,6-dichlorobenzoyl)phenyl trifluoromethanesulfonate, **462**



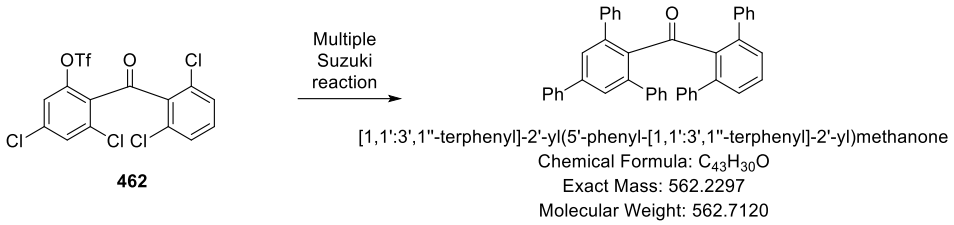
461

3,5-dichloro-2-(2,6-dichlorobenzoyl)phenyl trifluoromethanesulfonate
Chemical Formula: $C_{14}H_5Cl_4F_3O_4S$
Exact Mass: 465.8615

Ketone **461** (1.6 g, 4.8 mmol), anhydrous DCM (8 mL) and pyridine (758.4 mg, 9.6 mmol) were added to a round-bottomed flask, under argon atmosphere. The solution was cooled to 0° C in an ice bath and then was treated with dropwise addition of triflic anhydride (1.62 g, 5.76 mmol). The resulting mixture was allowed to warm to RT and stirred for additional 4 h.

At the end of the reaction (monitored by TLC), the mixture was filtered and concentrated *in vacuo*. The product was purified by chromatography (hexane), affording ketone **462** (2.0 g, 4.40 mmol, 92%) as a white solid. Mp: 95-97 °C. IR ν_{max} (neat, cm^{-1}) 1690, 1591, 1429, 1211, 1138, 955, 910, 868, 800, 781. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.46 (1 H, d, *J* = 1.8, Ar*H*), 7.38 (1 H, d, *J* = 1.8, Ar*H*), 7.36 – 7.34 (3 H, m, Ar*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0, 147.9, 137.9, 135.8, 134.0, 133.2, 131.7, 129.9, 129.7, 128.6, 120.7, 117.9 (q, *J* = 320 Hz, *C*F_3) ppm. *m/z* (APCI) calcd. for $C_{14}H_9Cl_4F_3NO_4S$ $[M+NH_4]^+$: 483.8953, found 483.8950.

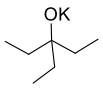
[1,1':3',1''-Terphenyl]-2'-yl(5'-phenyl-[1,1':3',1''-terphenyl]-2'-yl)methanone, **252**



Six oven-dried microwave vials were charged, independently, with ketone **462** (93.6 mg, 0.2 mmol), bis(acetonitrile)dichloropalladium(II) (2.59 mg, 0.01 mmol, 5%), Sphos (8.2 mg, 0.02 mmol, 10%) phenylboronic acid (244 mg, 2 mmol) and K_3PO_4 (424 mg, 2 mmol). The mixture was then introduced into the glovebox and anhydrous toluene (10 mL) was added. The vials were then closed, removed from the glovebox and placed in the fumehood, where they were heated at 110 °C for 5 days (monitored *via* NMR). The cooled reaction mixture was diluted with water and extracted with toluene. The combined organic layers were combined, dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The mixture was purified *via* chromatography (hexane : ethyl acetate as 9.5 : 0.5), affording the title product **252** (420 mg, 0.75 mmol, 62 % combined yield) as a white powder. The reaction was found to work better in a system under pressure such as a microwave vial. Reaction conditions were inspired by prior literature.[150] Mp: 90-93 °C. IR ν_{max} (neat/cm^{-1}) 3048, 1667, 1589, 1491, 1231, 926, 885, 756, 694. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.51 – 7.47 (2 H, m), 7.45 – 7.39 (2 H, m), 7.39 – 7.33 (1 H, m), 7.33 – 7.23 (13 H, m), 7.18 – 7.13 (4 H, m), 7.13 – 7.09 (4 H, m), 7.06 (2 H, s), 6.87 (2 H, d, *J* = 7.6) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 143.4, 142.6, 141.1, 140.9, 140.9, 139.4, 137.3, 135.8, 130.2, 129.8, 128.8, 128.6,

128.3, 127.3, 126.8, 126.7, 126.6, 126.2, 126.0 ppm. *m/z* (APCI) calcd. for $C_{43}H_{31}O$ $[M+H]^+$: 563.2375, found 563.2388.

Potassium 3-ethylpentan-3-olate, **237**

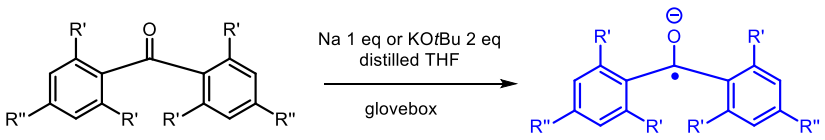


potassium 3-ethylpentan-3-olate
Chemical Formula: $C_7H_{15}KO$
Exact Mass: 154.0760

In the glovebox, previously washed potassium hydride (400 mg, 10 mmol) was added to a flame-dried three-necked flask, equipped with a vacuum tap. The flask was then sealed, removed from the glovebox and placed in a -78 ^oC bath in a fumehood. A solution of triethylcarbinol (1160 mg, 10 mmol) in anhydrous diethyl ether (20 mL) was added. The reaction mixture was stirred at -78 °C for 1 h, then at RT overnight. The solvent was removed on the house vacuum line and the crude material was dried for 3 h, put under an argon atmosphere and transferred into the glove box immediately giving rise to **237** (1.3 g, 8.4 mmol, 84 %). ^1H NMR (400 MHz, C_6D_6) δ 1.22 (6 H, q, J = 7.5, CH_2CH_3), 0.85 (9 H, t, J = 7.5, CH_2CH_3) ppm. ^{13}C NMR (101 MHz, C_6D_6) δ 71.8, 33.1, 8.1 ppm.

5.A3.2 Qualitative and quantitative tests

General procedure for testing the reduction of benzophenone and benzophenone derivatives with Na or KO*t*Bu.



The aromatic ketone (1 eq, 0.77 mmol) was added to distilled THF (5 mL) in a pressure tube containing sodium (18 mg, 0.77 mmol) or KO*t*Bu (172 mg 1.54 mmol) in the glovebox. The sealed pressure tube was then removed from the glovebox and placed on a stirrer hotplate in the fumehood. Where specified, the reaction was heated to 70°C behind a blast shield. The

ketyl radical formation was detected through development of a blue coloration in the solution. The reaction was quenched with isopropyl alcohol and the blue coloration disappeared soon after the addition.

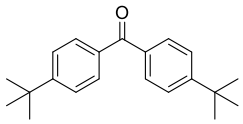
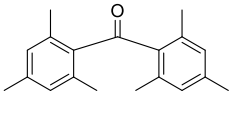
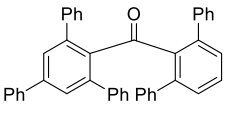
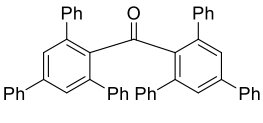
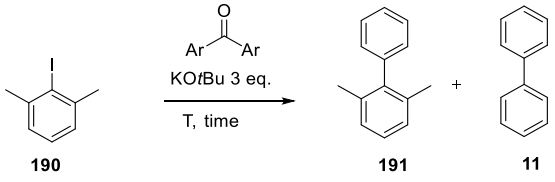
Ketone	 440	 441	 252	 251
Conditions				
Na, rt				
time	10 min	1h	1h	5h
KO*t*Bu, 70°C				
time	36 h	36 h	36 h	36 h

Table 29. All the reactions were performed in a glovebox in THF as solvent. A picture was taken at the mentioned time.

Reactions with iodo-*m*-xylene using the aromatic ketones as additives

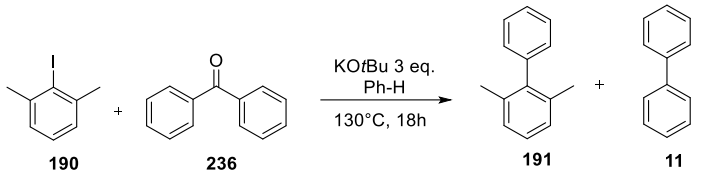


190 191 11

A mixture of iodo-*m*-xylene **190** (0.5 mmol), KO*t*Bu (3.0 eq.) and the desired aromatic ketone (0.2 eq) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N hydrochloric acid until neutral pH. The mixture was extracted with diethyl ether (3

x 15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue. Since the coupled products **191** and **11** are inseparable, the yields were calculated from NMR spectra *via* internal standard. 1,3,5-trimethoxybenzene 8.4 mg, (0.050 mmol, 10 mol%) which was added as a solid to the reaction mixture, ~1 mL $CDCl_3$ was added to form a homogeneous solution and the solution stirred. A portion of the solution was taken and diluted for NMR analysis.

General conditions and yield calculations for cross coupling reactions



A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **236** (18.2 mg; 0.01 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard. Biphenyl **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.59 (4H, m), 7.46 (4H, m), 7.38 - 7.34 (2H, m). 2,6-Dimethyl-1,1'-biphenyl **191**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.41 (2H, m), 7.39 - 7.33 (1H, m), 7.19 - 7.10 (5H, m), 2.05 (6H, s).

Yield calculation

The quantity of each product was determined as following (also see annotated example spectrum below):

For the recovered starting material **190** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **190** (2.50 ppm) was then measured and the following calculation gave the amount of **190** present:

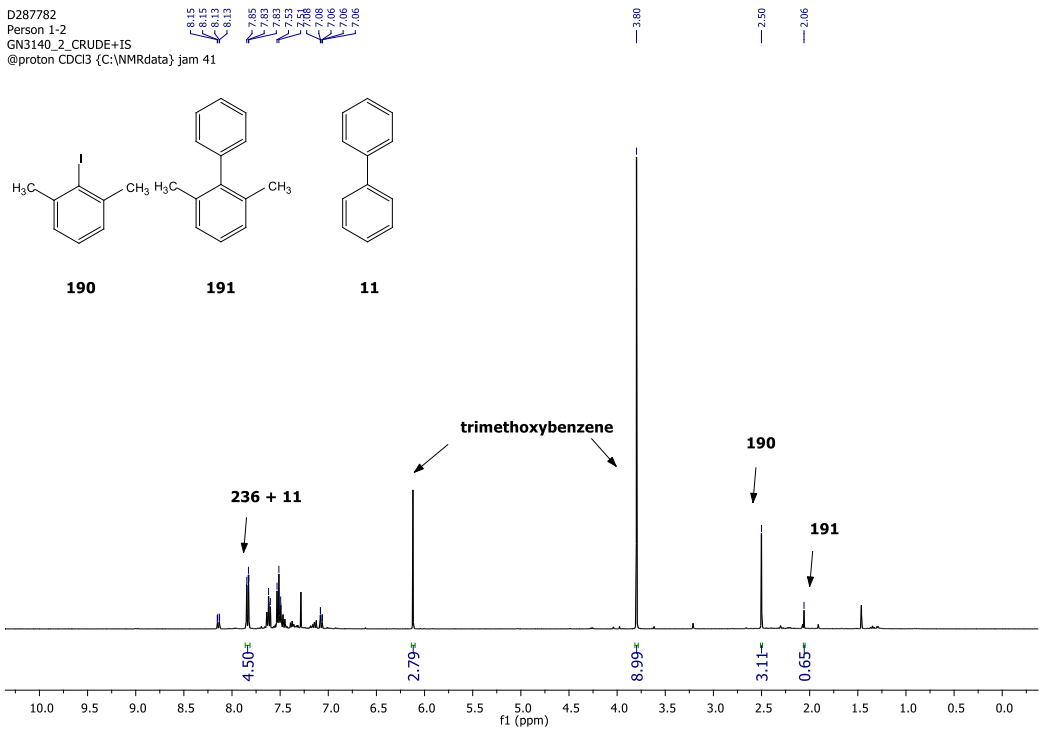
(3.11/6) × 10 = 5.2%

For the coupled product **191**, the integration of the methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **191** (2.04 ppm) was then measured and the following calculation gave the amount of **191** present:

(0.65/6) × 10 = 1.1%

For the biphenyl product **11** the integration of the aromatic signal of the internal standard was set to 3 units. The integration of the aromatic signals of **7** at 7.64–7.59 ppm (4 H) was then measured and the following calculation gave the amount of **7** present:

(int/4) × 10 = yield % but see text below the next spectrum**



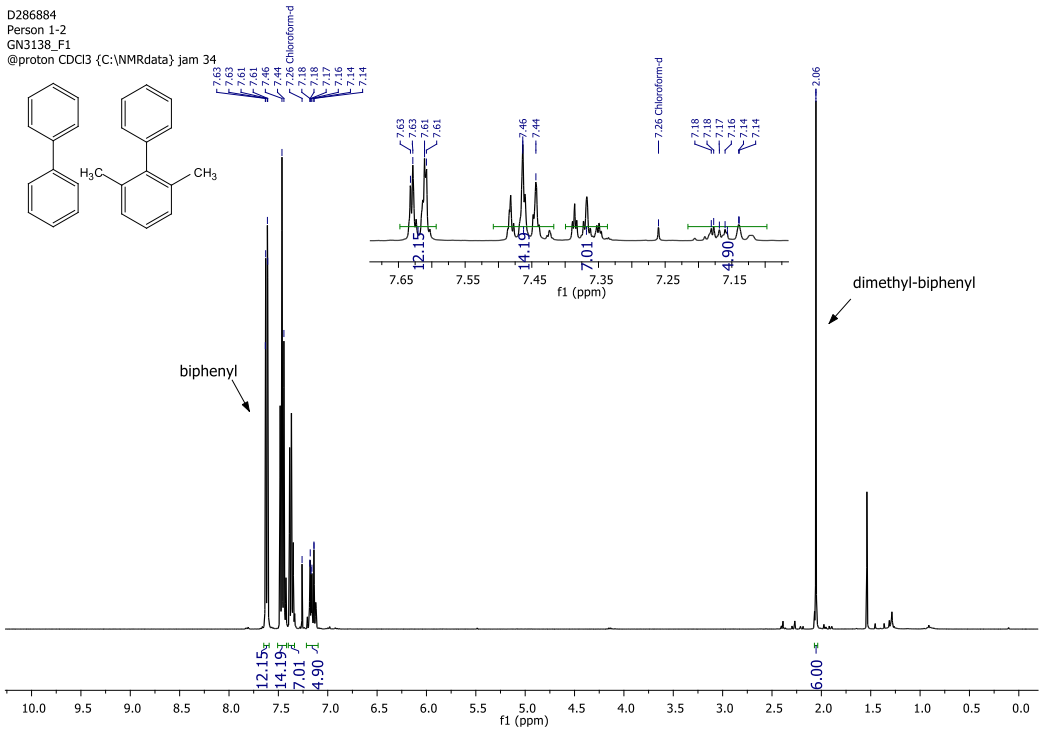
Spectrum 9. NMR of the crude mixture.

**In this particular case the diagnostic peak of biphenyl overlaps with one of the benzophenone peak. In the BHAS mediated mechanism the ratio between biphenyl and heterocoupled product is always 3:1. In fact, after purification by chromatography the inseparable mixture was indeed in 3:1 ratio. Integrating the methyl group (6H, 2.06 ppm) as 6 the ratio of biphenyl (4H, 7.62 ppm) is:

(12.15/4) = 3.0

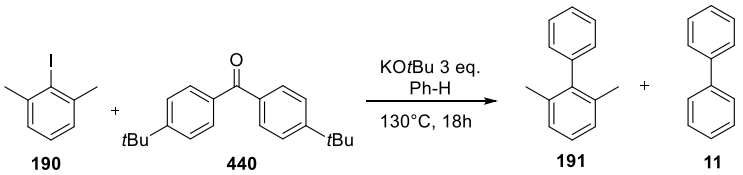
Since the ratio was found to be 3:1, the tiled of biphenyl present in the mixture was 3.3%. Number of runs: (a) Biphenyl 3.3 % ; 1,3-dimethylbiphenyl 1.1 %. (b) Biphenyl 3.6 % ; 1,3-dimethylbiphenyl 1.2%. (c) Biphenyl 3.6 % ; 1,3-dimethylbiphenyl 1.2%

Average of 3 runs: Biphenyl 3.5 % ; 1,3-dimethylbiphenyl 1.2%.



Spectrum 10. ^{1}H-NMR of the mixture of the coupled products.

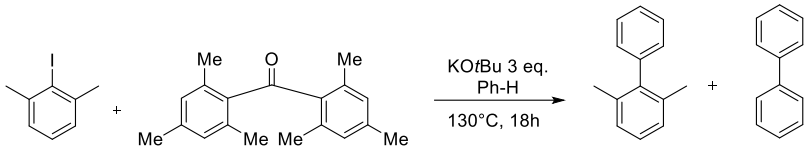
Cross coupling reaction using **440** as additive.



A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **440** (29.4 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube

in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 1.0 % of **191** and 3.2 % of **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

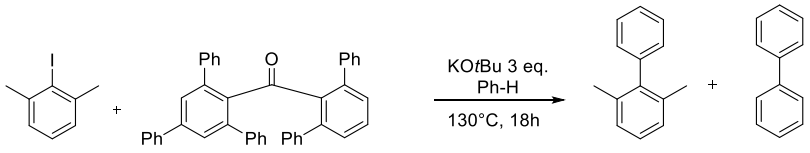
Cross coupling reaction using **441** as additive.



190 **441** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **441** (26.6 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 0.7 % of **191** and 1.8 % of **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

Cross coupling reaction using **252** as additive.

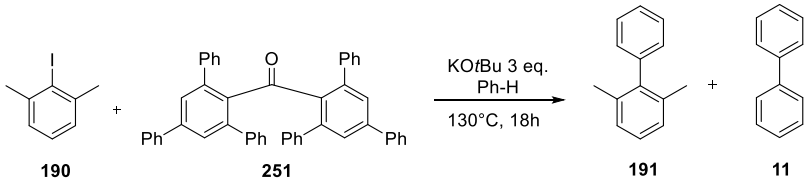


190 **252** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **252** (56.2 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether

(15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 0.8 % of **191** and 2.4 % of **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

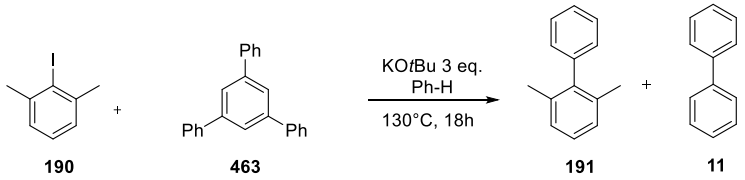
Cross coupling reaction using **251** as additive.



190 **251** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **251** (63.8 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 0.4 % of **191** and 1.2 % of **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

Cross coupling reaction using **463** as additive.

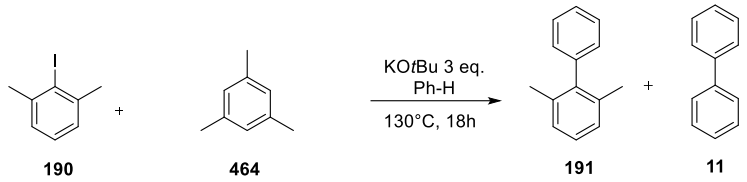


190 **463** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **463** (29.4 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give

the residue as a dark yellow oil which yielded 0.9 % of **191** and **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

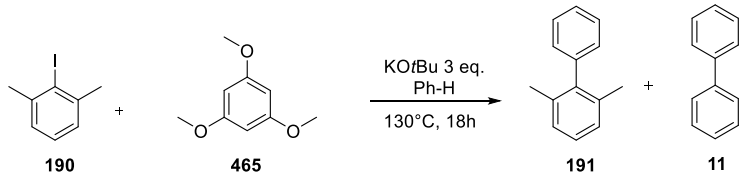
Cross coupling reaction using **464** as additive.



190 **464** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **464** (12.0 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 1.1 % of **191** and **11**. The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard.

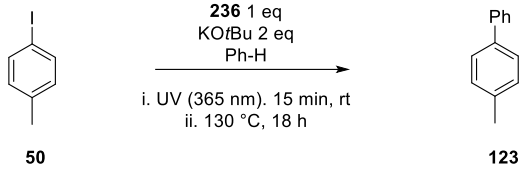
Cross coupling reaction using **465** as additive.



190 **465** **191** **11**

A mixture of 1-iodo-2,6-dimethylbenzene **190** (116 mg, 0.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and **465** (16.8 mg; 0.1 mmol) in benzene (5 mL) was sealed in a 15 mL pressure tube in a glovebox. The tube was removed from the glovebox and heated at 130 ºC for 18 h behind a blast shield. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give the residue as a dark yellow oil which yielded 2.8 % of **191** and **11**. The yield was calculated using CH_2Br_2 (100%) as internal standard.

Reactions with iodo-*para*-toluene using **236** as additive



50 **123**

A mixture of iodo-*p*-toluene **50** (0.5 mmol), KO*t*Bu (112 mg, 1 mmol), **236** (91 mg, 0.5 mmol, if added) in benzene (2.5 mL) was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and placed RT for 15 min under UV (365 nm) irradiation and then transferred into an oil bath at 130 °C for 18h. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (3 x 15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give rise to the residue. 1,3,5-Trimethoxybenzene 8.4 mg, (0.050 mmol, 10 mol%) was added as a solid to the reaction mixture, ~1 mL $CDCl_3$ was added and the solution stirred. A portion of the solution was taken and diluted for NMR analysis. The quantity of product was determined as following. For the recovered starting material the integration of methoxy signal (3.81 ppm) of the internal standard in the ^{1}H-NMR spectrum was set to 9 units.

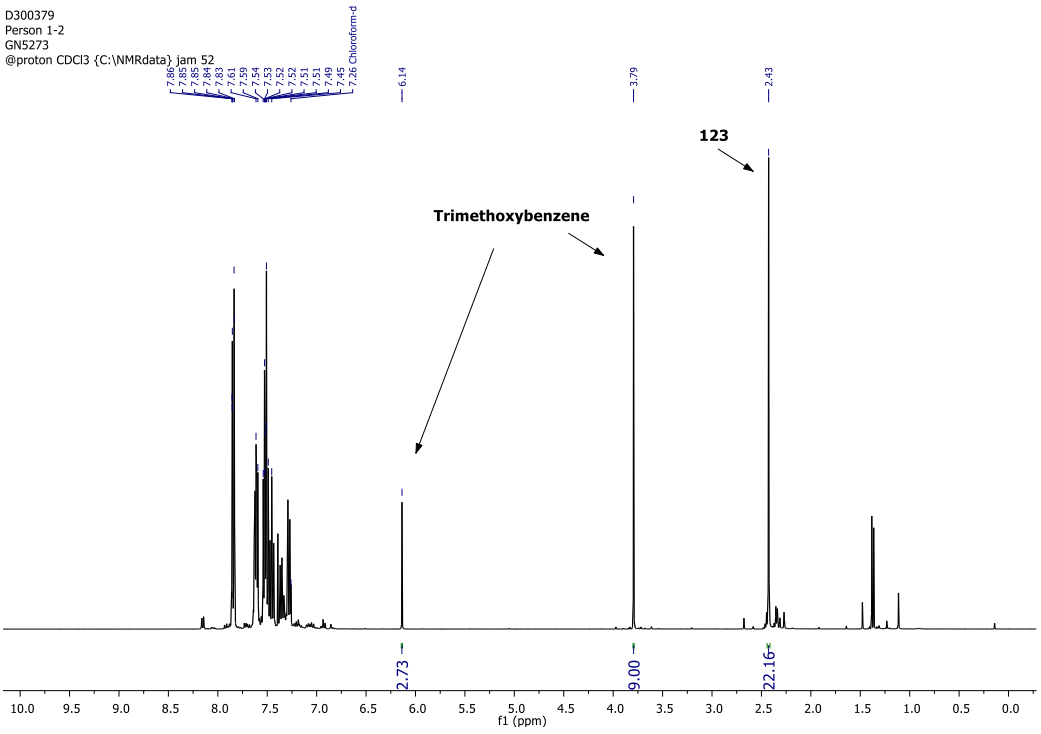
Yield calculation:

The integration of the methyl signal of **50** (3H, 2.33 ppm) was then measured and the following calculation gave the amount of **50** present:

(6.24/3) × 10 = 21 %

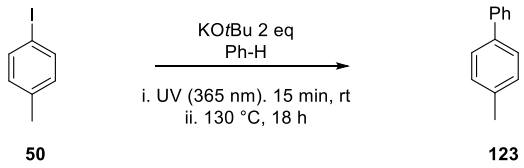
For the product **123** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9. The integration of the methyl signal of **123** (3H, 2.46 ppm) was then measured and the following calculation gave the amount of **123** present.

(22.25/3) × 10 = 74 %



Spectrum 11. ^{1}H-NMR of the crude mixture of the reaction with 4-iodo-toluene.

Reactions with iodo-*p*-toluene **50** with no additive (blank reaction)



50 **123**

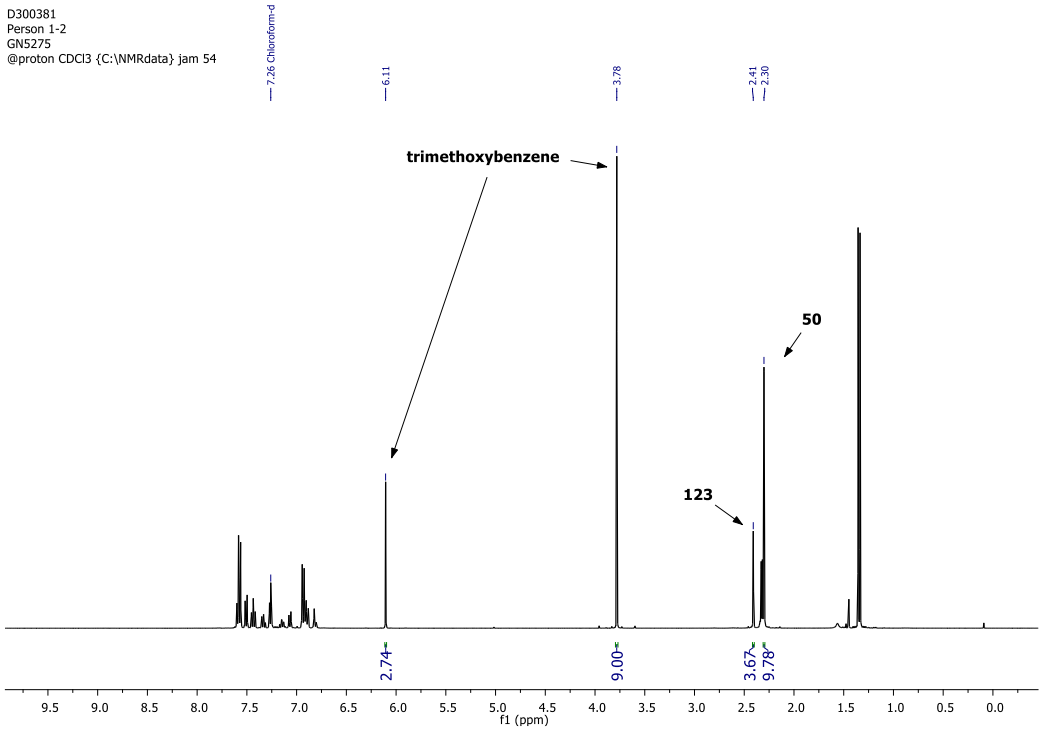
A mixture of iodo-*p*-toluene **50** (0.5 mmol), KO*t*Bu (112 mg, 1 mmol) in benzene (2.5 mL) was sealed in a 15 mL pressure tube in glovebox. The tube was removed from the glovebox and placed RT for 15 min under UV (365 nm) irradiation and then transferred into an oil bath at 130 °C for 18h. After cooling to room temperature, the reaction was quenched by water (15 mL) and acidified with 1N HCl until neutral pH. The mixture was extracted with diethyl ether (3 x 15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give rise to the residue. 1,3,5-Trimethoxybenzene 8.4 mg, (0.050 mmol, 10 mol%) was added as a solid to the reaction mixture, ~1 mL $CDCl_3$ was added and the solution stirred. A portion of the solution was taken and diluted for NMR analysis. The quantity of product was determined as following. For the recovered starting material the integration of methoxy signal

(3.81 ppm) of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **50** (3H, 2.33 ppm) was then measured and the following calculation gave the amount of **50** present:

(9.78/3) × 10 = 33 %

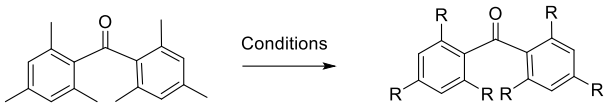
For the product **123** the integration of methoxy signal of the internal standard in the ^{1}H-NMR spectrum was set to 9 units. The integration of the methyl signal of **123** (3H, 2.46 ppm) was then measured and the following calculation gave the amount of **123** present.

(3.68/3) × 10 = 12 %



Spectrum 12. Crude mixture of the reaction in absence of benzophenone.

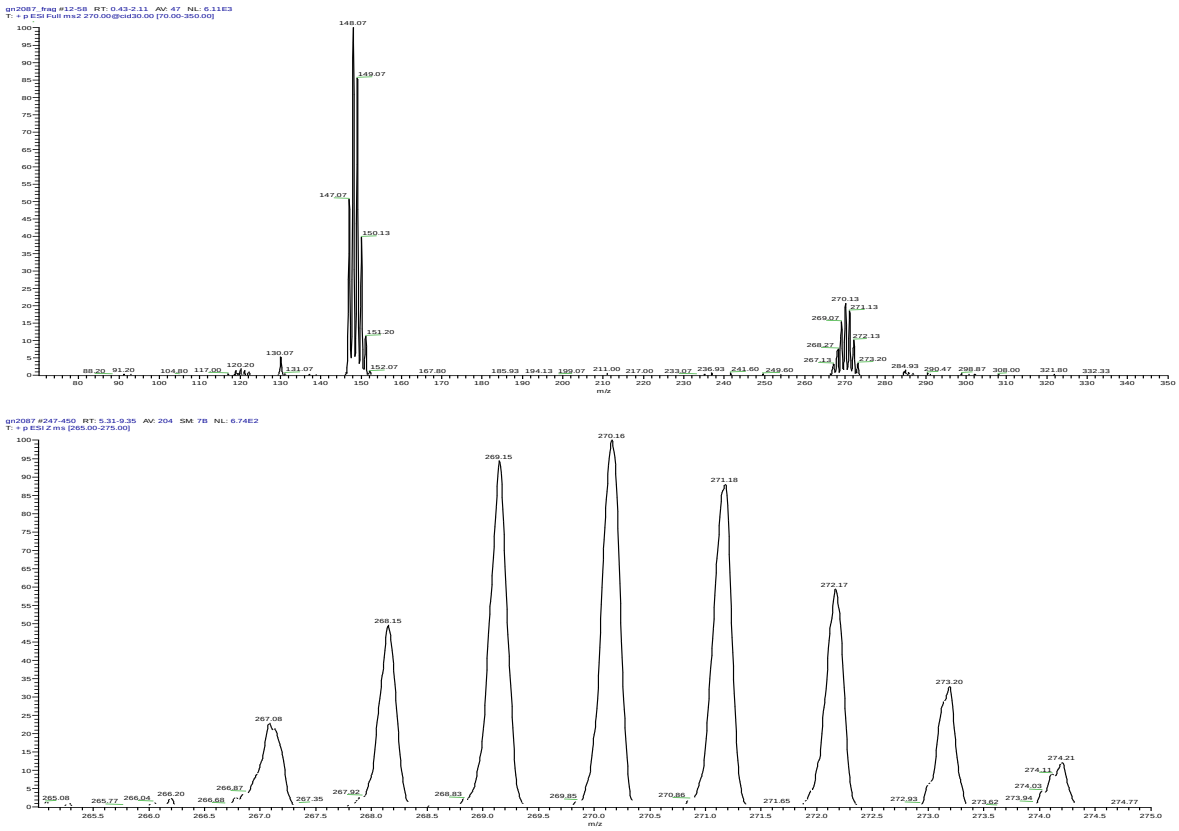
Testing the deuterium incorporation on dimesitylmethanone **441**



Dimesitylmethanone-d_{mix}
Chemical Formula: $C_{19}H_{22}O$
Exact Mass: 266,1671

441 **441-d_{mix}**,R= CH_3,CH_2D, CHD_2,CD_3

KO*t*Bu (170 mg, 1.54 mmol) was added to a solution of dimesitylmethanone **441** (205 mg, 0.77 mmol) in distilled THF (5 mL) into a 5 mL microwave vial in the glovebox. The sealed vial was afterward removed from the glovebox and placed on the stirrer hotplate where, behind a blast shield, deuterium oxide was carefully added (0.5 mL). The reaction mixture was allowed to stirrer for 24 h at 70 °C. Afterwards the reaction was quenched with water and extracted with diethyl ether (3x10 mL), dried over sodium sulfate, filtered and concentrated in *vacuo* to give a series of products **441-d_{mix}**: non-, mono- and poly-deuterated on the methyl groups. ^{1}H-NMR, ^{13}C-NMR, ^{2}H-NMR, ESI-MS were collected.



Spectrum 13. ESI-MS of the mixture **400-d_{mix}.**

5.A3.3 Reactions with lights

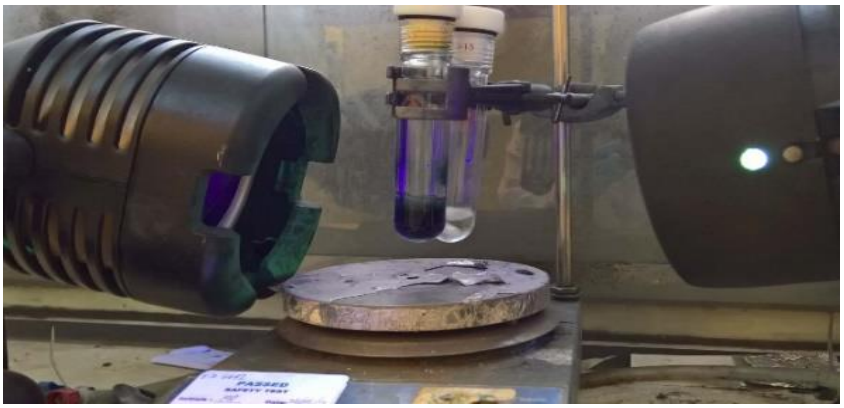


Figure S1 Above is a typical example of reaction performed under UV lamps (365 nm, 100 W x 2) at RT.Left: THF + **236** (0.5 mmol) + KO*t*Bu (2eq). Right: blank reaction THF + **236** (0.5 mmol). Picture taken after 30 min.

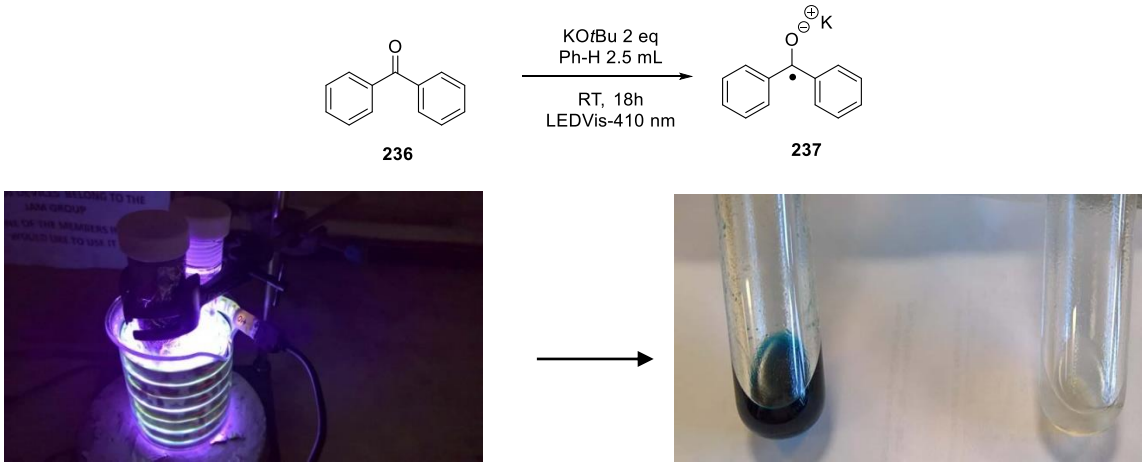
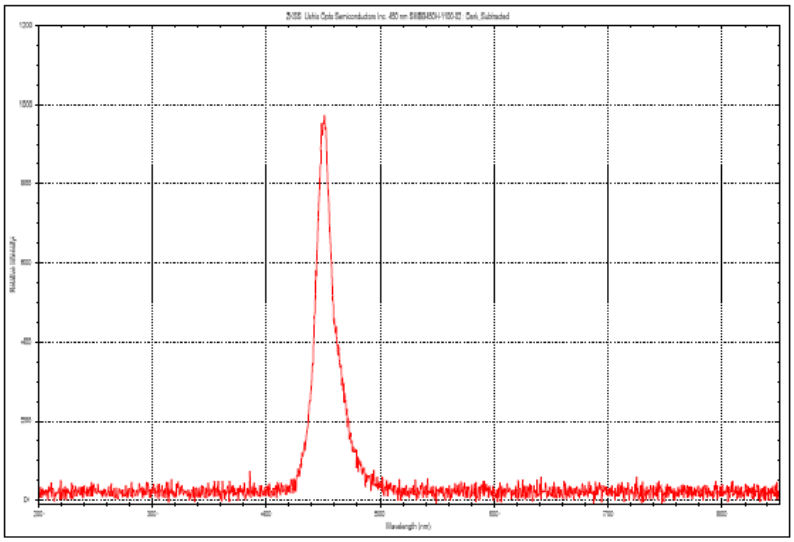


Figure S2. Above is a typical example of reaction **236** + KO*t*Bu 2 eq in benzene 2.5 mL performed under Vis LEDs light (400 nm, 14.4 W) at RT. Only the tube with a direct exposition to the light gives the typical blue coloration of the ketyl radical, afterwards confirmed by UV measurement.

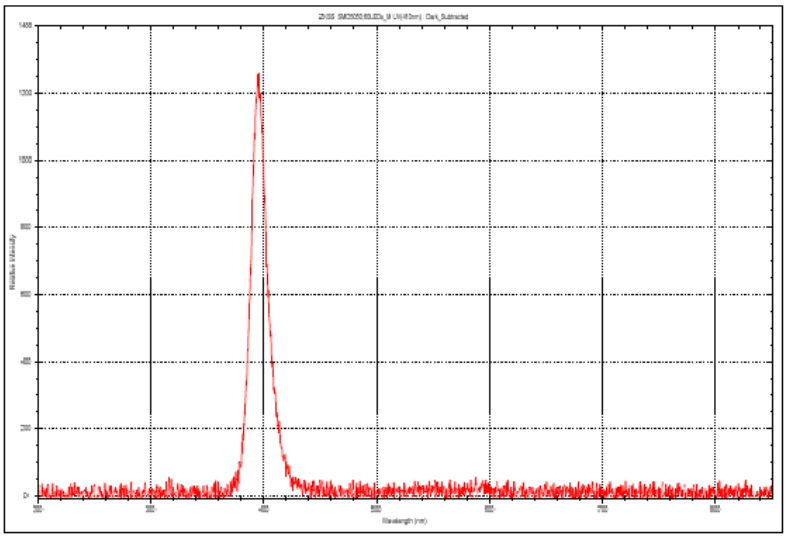
LED Output Spectra

These measurements has been taken by thank Dr. Glynn Williams and Lee Edwards (GSK).

These spectra were produced using a BWTEK Inc, Exemplar LS (Low Straylight Smart CCD Spectrometer, http://bwtek.com/products/exemplar-ls/). Reference spectrum taken of a Ushio Opto Semiconductors Inc. 450 nm: SMBB450H-1100-02. (Full details in SI of https://doi.org/10.1002/cptc.201800082 page S10)



Spectrum of SMD5050;60LEDs/M; Color: UV('410nm')



Luminous flux measurements

These measurements has been taken by thank Dr. Glynn Williams and Lee Edwards (GSK). Luminous flux measurements were taken with a Traceable® Dual-Display Light Meter

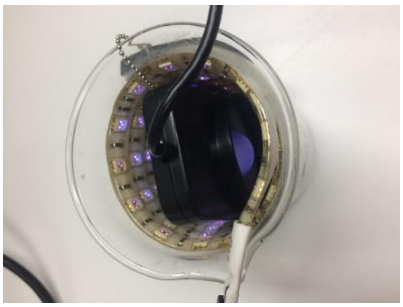


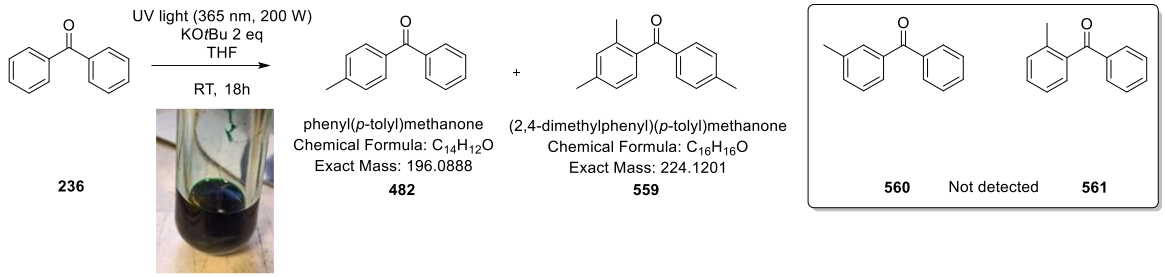
Figure 13. Lux measurement set up

(https://traceable.com/3252-traceable-dual-displaylight-meter.html purchased from Fisher Scientific). The Lux sensor was placed inside the coil of SMD5050;60LEDs Figure X, and the setup covered with tin foil to remove any external light.

Traceable® Dual-Display Light Meter was set to F= fluorescent mode, the LEDs where turned on a LUX reading taken, 39 LUX.

Detection of methylated and ethylated benzophenone

Phenyl(*p*-tolyl)methanone, **482** and (2,4-dimethylphenyl)(p-tolyl)methanone, **559**



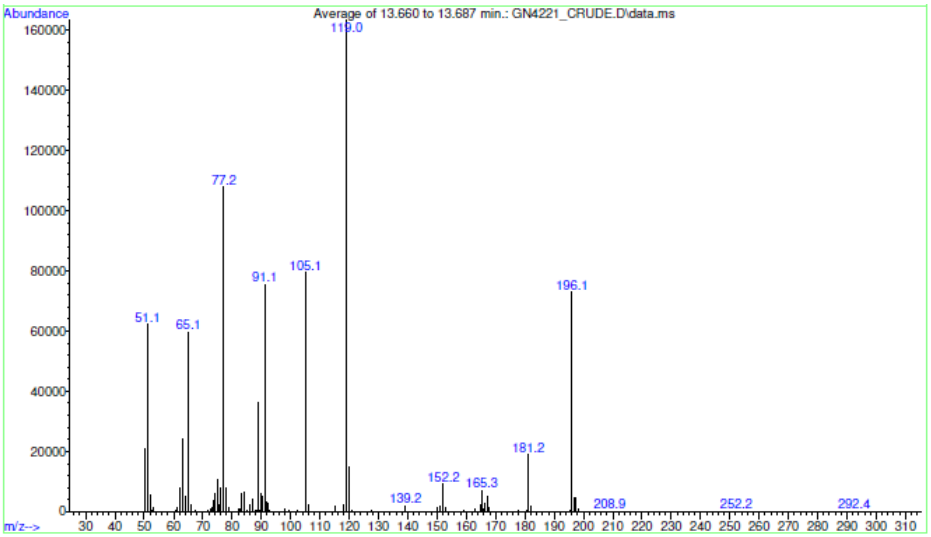
Benzophenone **236** (91 mg, 0.5 mmol), KO*t*Bu (112 mg, 1 mmol) were loaded in a 15 mL pressure tube with THF (2.5 mL). The sealed tube was then moved out from the glovebox and placed under UV light for 18h. The dark green/blue colour gradually developed from the start of the reaction. After 18 h the tube was opened and water was added. The dark coloration disappeared after few seconds of air exposure or water contact. The mixture was then extracted with ether, dried over sodium sulfate and concentrated *in vacuo*. The ratio of the peaks on the GC-MS defines the type of substitution on the compound. The observed ratio is: GCMS (EI) (%): 196.1 (M^+, 47%), 181.2 (11%), 165.3 (4%), 152.2 (5%), 119.0 (100%), 105.1 (50%), 91.1 (48%), 77 (68%). (See Spectrum 12 below).

The fragmentation pattern for ketone **482** found in the literature: GCMS (EI) (%): 196 (M^+, 43), 181(9), 165 (4), 152(4), 119(100), 105(32), 91(46), 77(43).[235]

The fragmentation pattern for ketone **560** found in the literature: GCMS (EI) (%): 196(M^+ , 67), 195 (100), 178 (11), 119 (29), 105 (21), 91 (33), 77(33), 51 (13).[235]

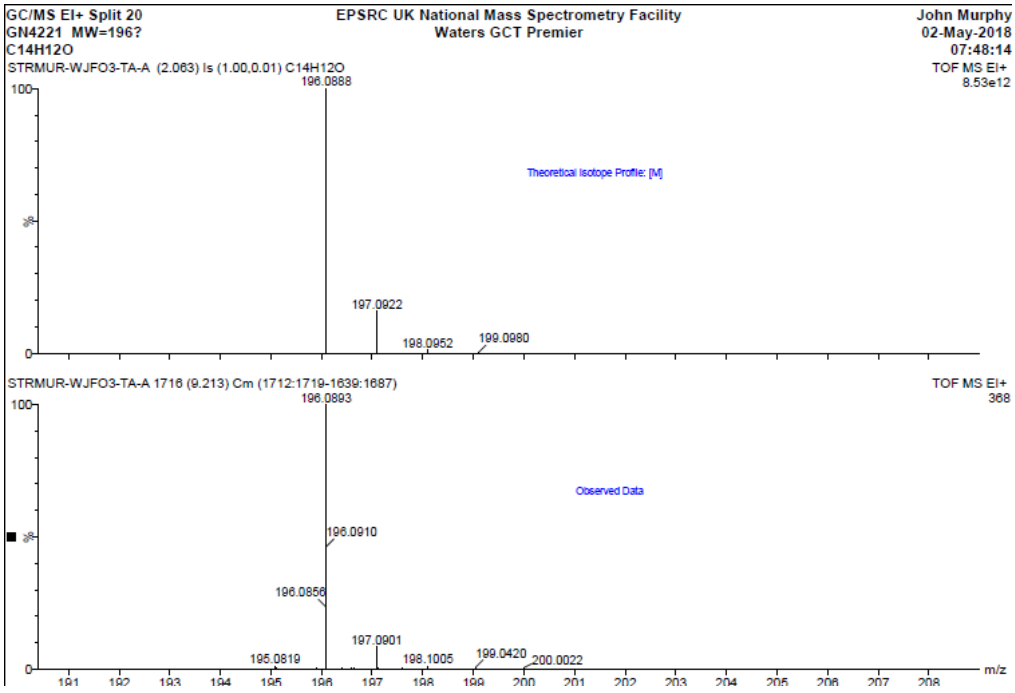
The fragmentation pattern for ketone **561** found in the literature: GCMS (EI) (%): 197 ($M+1^+$, 27), 196 (M^+, 82), 119 (100), 105 (64), 91 (43), 77 (44), 65 (24), 51 (22), 41 (2).[235]

The observed fragmentation pattern is consistent with the literature data for the ketone **482**.



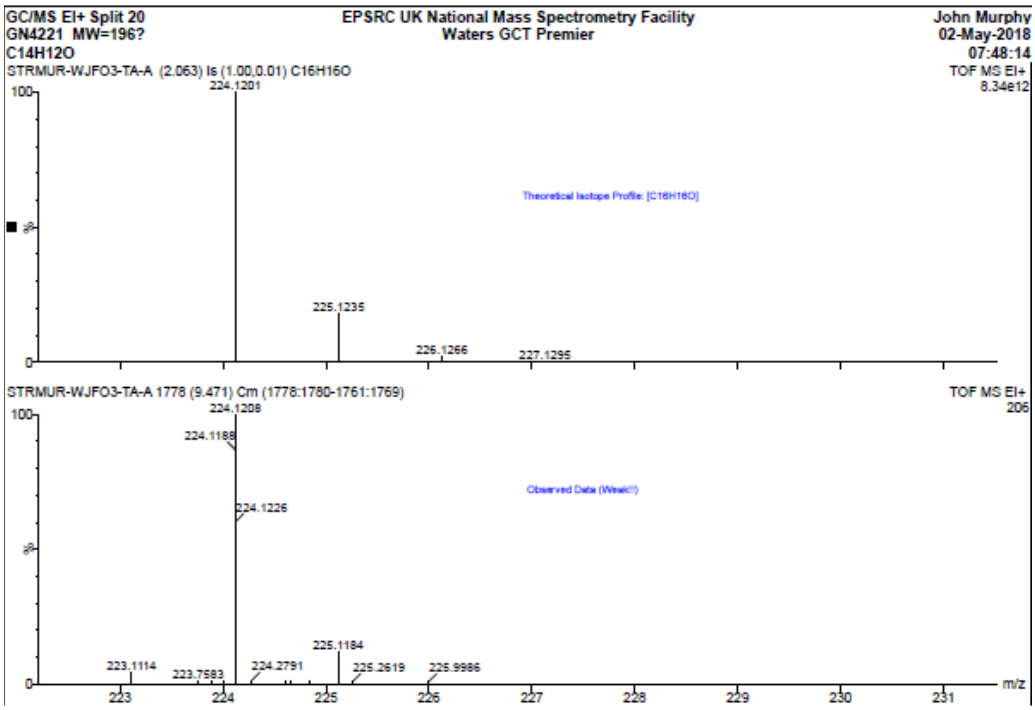
Spectrum 14. GC-MS (EI) fragmentation pattern obtained with product **482**.

The residue was analysed via TOF MS EI$^+$ (HRMS) (see spectrum below) and the presence of phenyl(p-tolyl)methanone **482** was therefore confirmed. *m/z* (TOF MS EI$^+$) calcd. for $C_{14}H_{12}O$ $[M]^+$: 196.0888, found 196.0893.



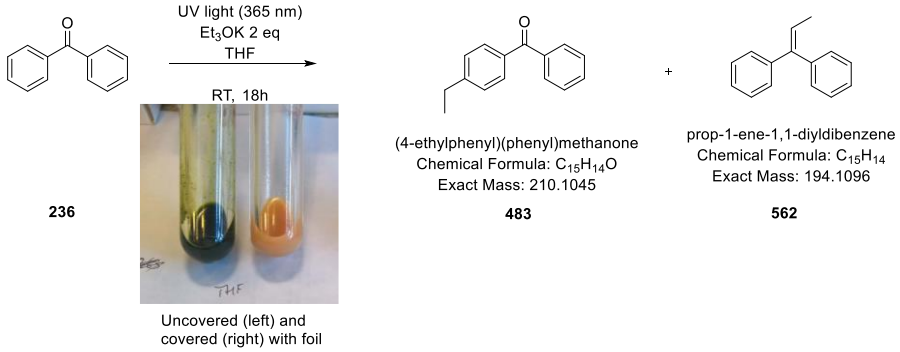
Spectrum 15. Calculated and observed high resolution mass spectra of phenyl(*p*-tolyl)methanone **482.**

The residue was analysed via TOF MS EI$^+$ (HRMS) (see spectrum below) and the presence of (2,4-dimethylphenyl)(p-tolyl)methanone **559** was therefore confirmed. *m/z* (TOF MS EI$^+$) calcd. for $C_{14}H_{12}O$ [M]$^+$: 224.1201, found 224.1208 (weak signal).



Spectrum 16. Calculated and observed high resolution mass spectra (2,4-dimethylphenyl)(p-tolyl)methanone **572.**

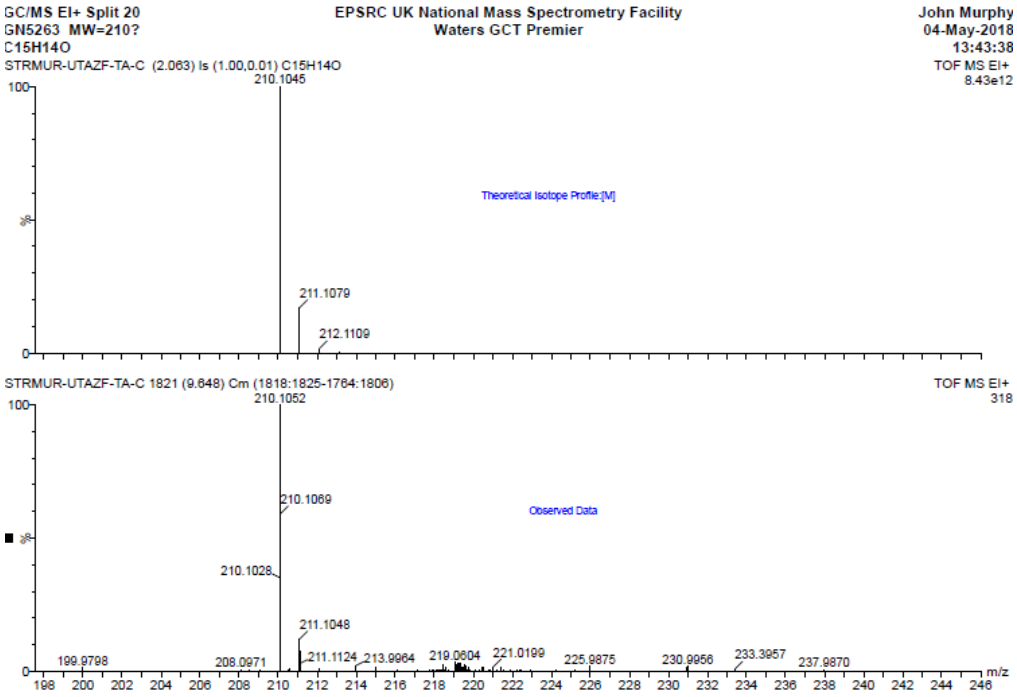
(4-Ethylphenyl)(phenyl)methanone, **483** and prop-1-ene-1,1-diyldibenzene, **562**



Benzophenone **236** (91 mg, 0.5 mmol), $KOEt_3$ (154 mg, 1 mmol) were loaded in a 15 mL pressure tube with THF (2.5 mL). The sealed tube was then moved out from the glovebox and placed under UV light for 18h. The dark green/blue colour was gradually developed since

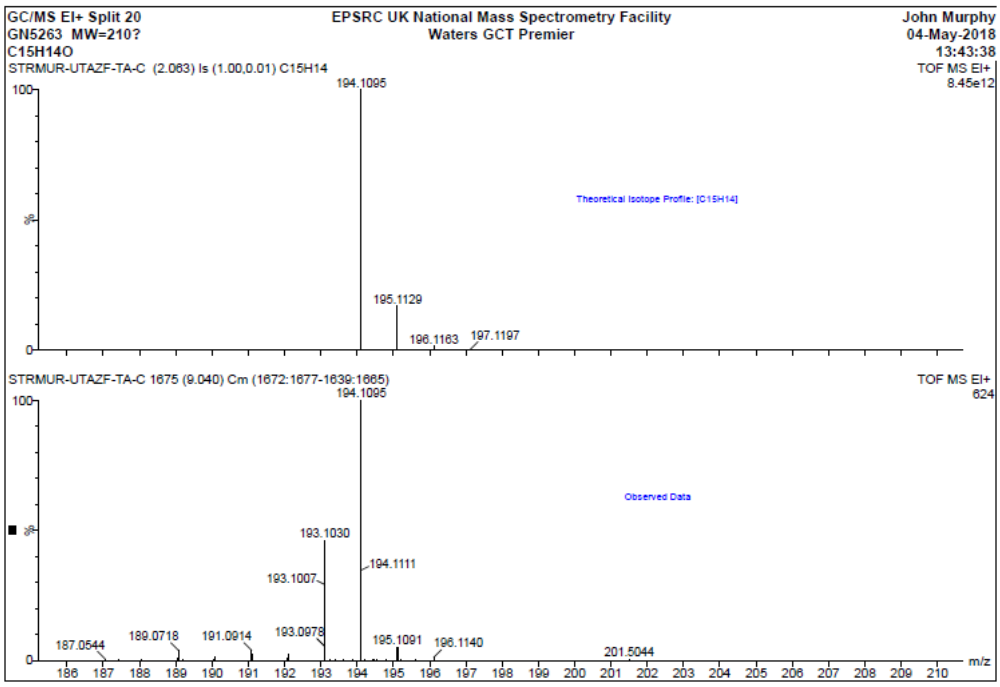
the start of the reaction. The blank reaction (absence of any source of lights) does not give any blue/green colour throughout the entire course of the reaction. After 18 h the tube was opened and water was added. The dark coloration disappeared after few seconds of air exposure or water contact. The mixture was then extracted with ether, dried over sodium sulfate and concentrated *in vacuo*.

The residue was analysed via TOF MS EI$^+$ (HRMS) (see spectrum below) and the presence of (4-ethylphenyl)(phenyl)methanone **483** was therefore confirmed. *m*/*z* (TOF MS EI$^+$) calcd. for $C_{14}H_{12}O$ [M]$^+$: 210.1045, found 210.1052.



Spectrum 17. Calculated and observed high resolution mass spectra of of 4-ethylphenyl)(phenyl)methanone **483**.

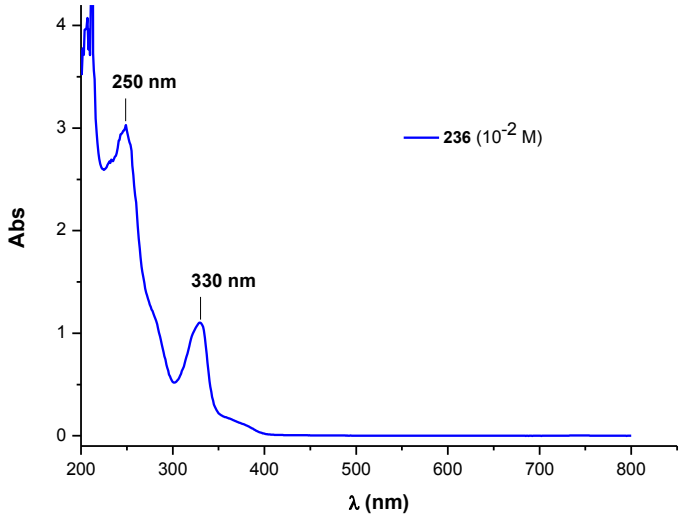
The residue was analysed via TOF MS EI$^+$ (HRMS) (see spectrum below) and the presence of prop-1-ene-1,1-diyldibenzene **562** was therefore confirmed. *m*/*z* (TOF MS EI$^+$) calcd. for $C_{14}H_{12}O$ [M]$^+$: 194.1095, found 194.1095.



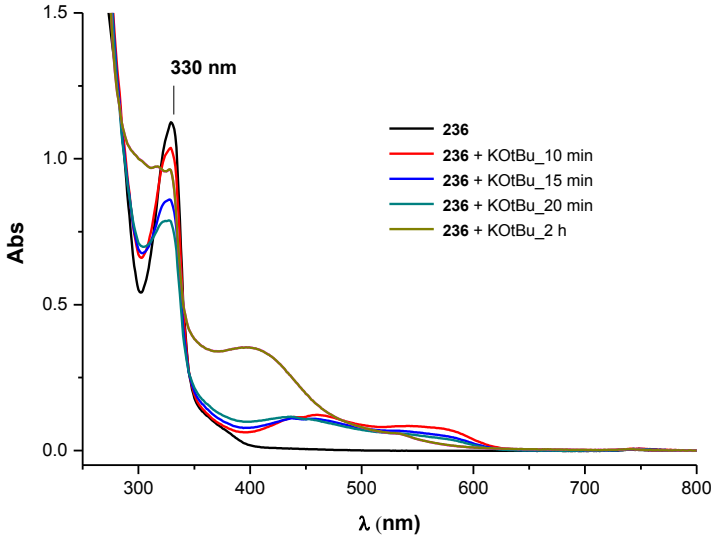
Spectrum 18. Calculated and observed high resolution mass spectra of of prop-1-ene-1,1-diyldibenzene **562**.

5.A3.4 UV measurements

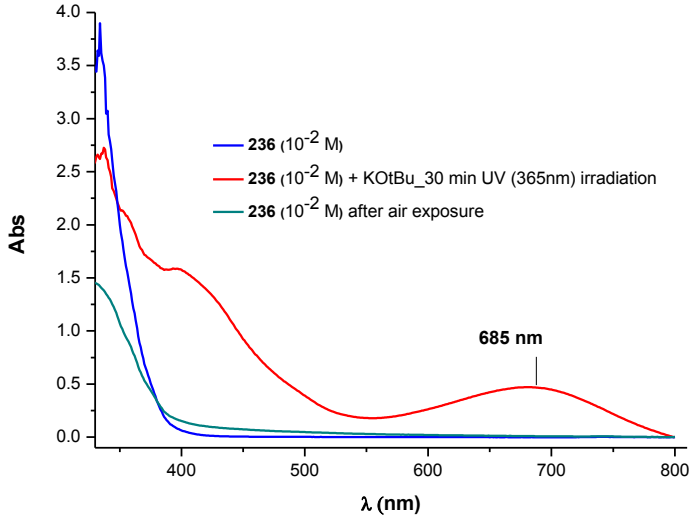
Every solution was prepared in the glovebox using distilled THF (3 mL) and a quartz standard cuvette.



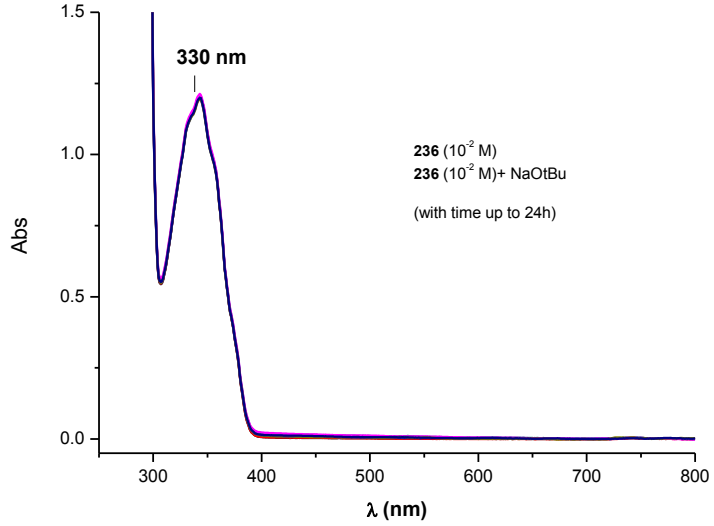
Spectrum 19. UV spectrum of benzophenone **236** (10^{-2} M) in THF.



Spectrum 20. UV spectrum of benzophenone (10^{-2} M) in THF; In the presence of KO*t*Bu, a charge-transfer band (hvCT) occurs with the time.

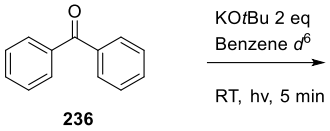


Spectrum 21. Formation of the ketyl radical anion **237** after irradiating the complex **236**+KO*t*Bu with UV light (365 nm, 100W x 2). Literature peak in THF: 656 nm.[153]



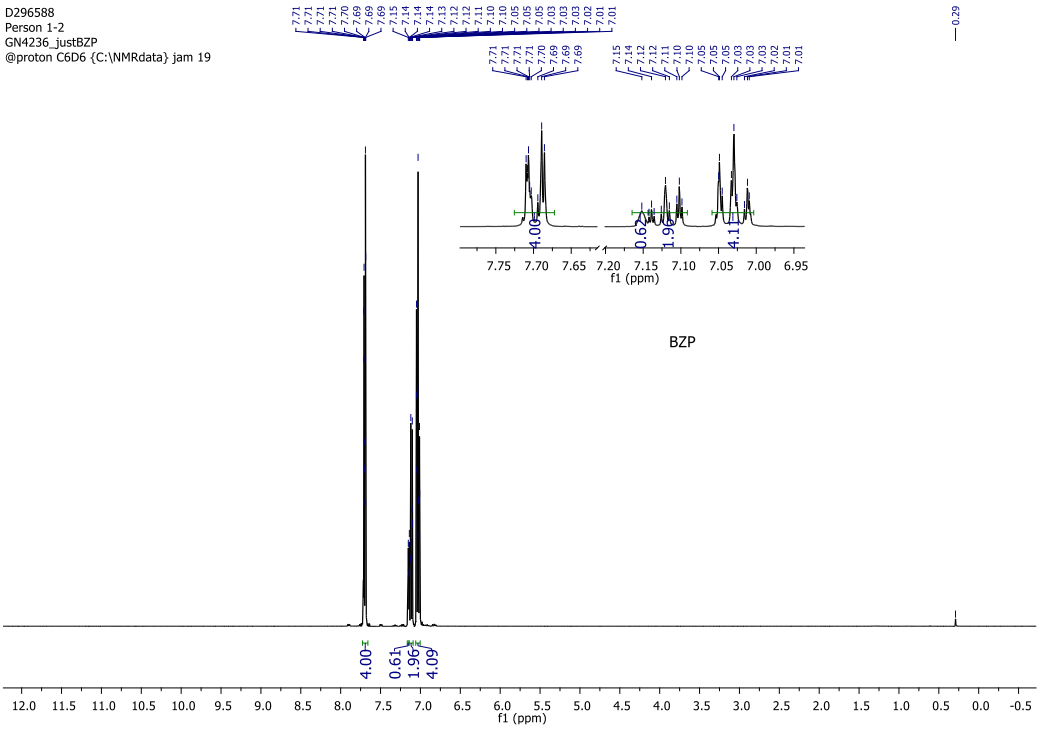
Spectrum 22. UV measurements of benzophenone (10^{-2} M) before and after adding NaO*t*Bu. The cuvette was agitated and measurements were taken every 10 min for 1h. The cuvette was then left overnight and no shift was observed the following day. No colour change in the cuvette was observed.

NMR tests throughout the reaction

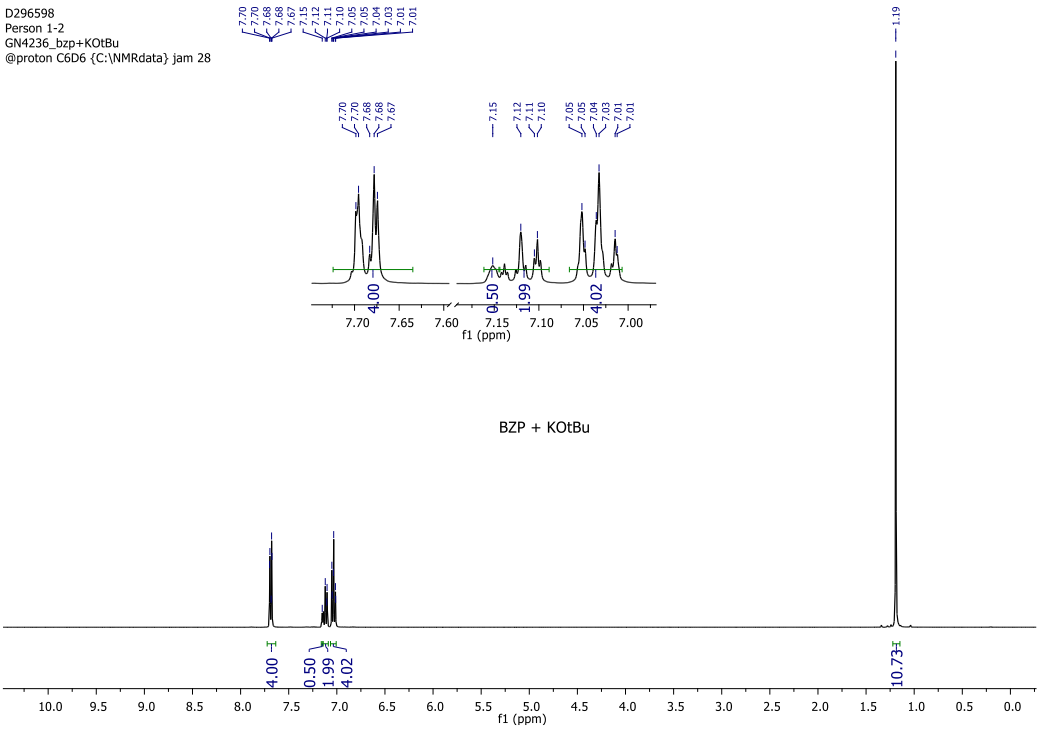


236

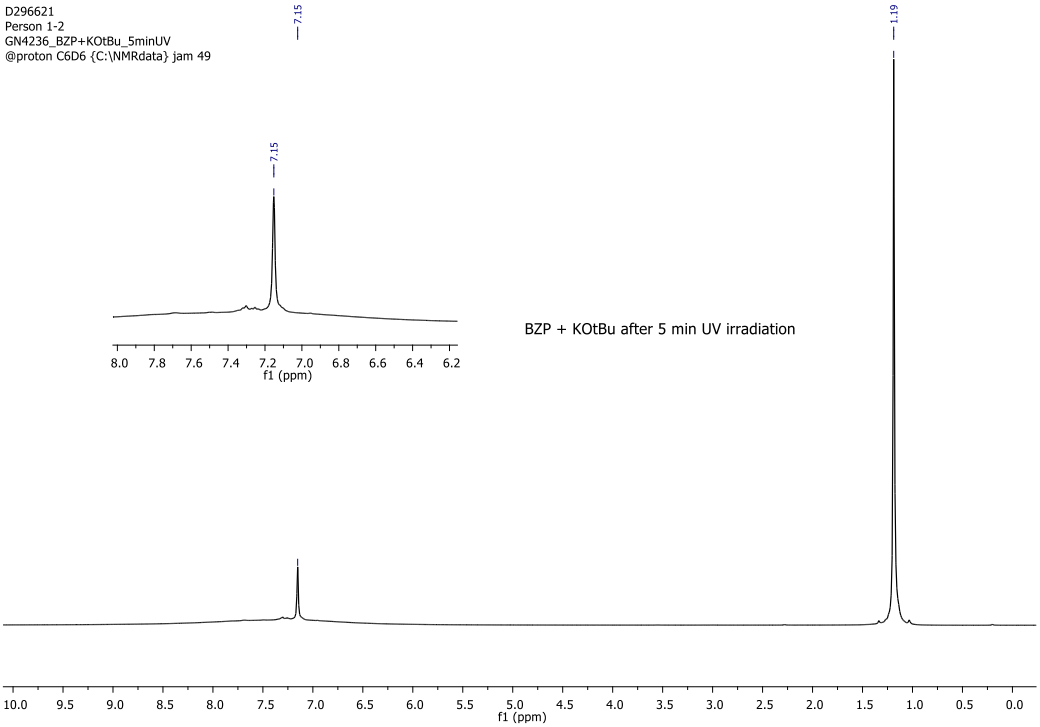
The signals from structure **236** disappear just after 5 minutes UV exposure (Spectra 23-25), indicating that radical species are formed in the reaction. After leaving the NMR tube in the darkness for 24h, the benzophenone peaks re-sharpened (Spectra 26).



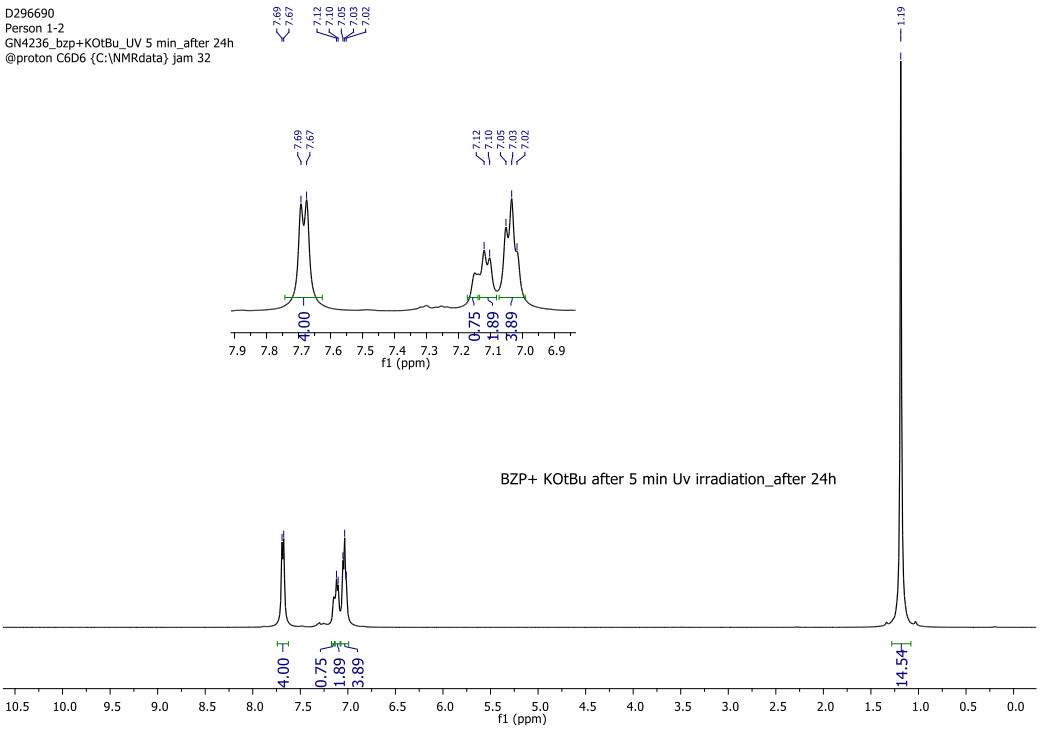
Spectrum 23. ^{1}H NMR spectrum of benzophenone.



Spectrum 24. ^{1}H NMR spectrum of benzophenone + KO*t*Bu.



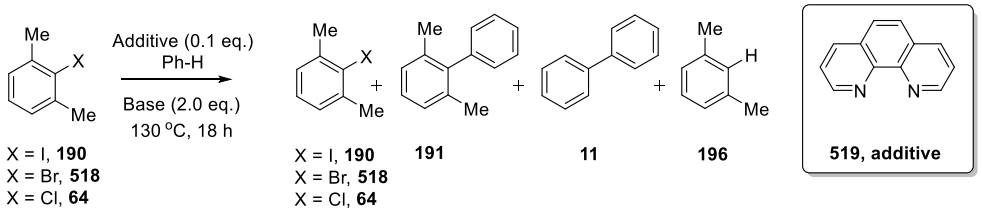
Spectrum 25. ^{1}H NMR spectrum of benzophenone + KO*t*Bu after 5 min irradiation with UV (365 nm, 200 W).



Spectrum 26. ^{1}H NMR spectrum of benzophenone + KO*t*Bu after 5 min irradiation with UV (365 nm), then standing for 24 h. Re-sharpening of benzophenone peaks.

5.B4 Role of KH in benzene in electron transfer reactions

5.B4.1 Dehalogenation procedure for 2,6-dimethylhalobenzenes



General procedure: to an oven-dried pressure tube was added 2,6-dimethylhalobenzene (0.5 mmol), base (1.0 mmol), additive **519** (0.05 mmol, if stated) and benzene (5 mL). The tube was sealed in a glovebox and heated at 130 °C for 18 h. After cooling to rt, the reaction was quenched carefully with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (8.4 mg, 0.05 mmol) was added to the crude reaction and the yield calculated as general procedure. Biphenyl **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.59 (4H, m), 7.46 (4H, m), 7.38 - 7.34 (2H, m). 2,6-Dimethyl-1,1'-biphenyl **191**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.41 (2H, m), 7.39 - 7.33 (1H, m), 7.19 - 7.10 (5H, m), 2.05 (6H, s).

Table 30

Alternatively, to an oven-dried pressure tube 2,6-dimethyliodobenzene **190** (116 mg, 0.5 mmol) and KO*t*Bu (112 mg, 1.0 mmol) were added. These experiments were set up, quenched, and analysed by the same general method. Trace amounts of **191** + **11** were detected. (Entry 1)

Alternatively, to an oven-dried pressure tube 2,6-dimethyliodobenzene **190** (116 mg, 0.5 mmol), 1,10-phenanthroline **519** (9 mg, 0.05 mmol) and KO*t*Bu (112 mg, 1.0 mmol) were added. These experiments were set up, quenched, and analysed by the same general method. **11** + **191**: 18.2% combined yield, 3.7:1 ratio. (Entry 2)

Alternatively, to an oven-dried pressure tube 2,6-dimethyliodobenzene **190** (116 mg, 0.5 mmol), 1,10-phenanthroline **519** (9 mg, 0.05 mmol) and KH (40 mg, 1.0 mmol) were added. These experiments were set up, quenched, and analysed by the same general method. **11** + **191**: 16.3% combined yield, 3.9:1 ratio. (Entry 3)

Alternatively, to an oven-dried pressure tube 2,6-dimethyliodobenzene **190** (116 mg, 0.5 mmol) and KH (40 mg, 1.0 mmol) were added. These experiments were set up, quenched, and analysed by the same general method. **11** + **191**: 5.5% combined yield, 7.7:1 ratio. (Entry 4)

The reactions in entries 5-7 were performed by Dr Samuel Dalton and Dr Joshua Barham and added here for completeness.

Alternative procedure for dehalogenation reactions in the presence of 1,10-phenanthroline **519**: To an oven-dried pressure tube was added 2,6-dimethyliodobenzene **190** (0.5 mmol), base (1.0 mmol), 1,10-phenanthroline (0.05 mmol) and benzene (5 mL). The tube was sealed in a glovebox and heated at 130 °C for 18 h. Work up and quantification of biaryls by internal standard (10 mol% 1,3,5-trimethoxybenzene) was conducted in the same way as the general procedure. Purification by column chromatography (hexane) afforded an inseparable mixture of biphenyl **11** and 2,6-dimethyl-1,1'-biphenyl **191** as a white microcrystalline solid.

Entry	**Additive /Base**	**Ratio[a] 11:191**	**11 + 191 yield[b]**	**Recovered 190 (%)[b]**
1	-/KO*t*Bu	-	<0.5	72
2	**519**/KO*t*Bu	3.7:1	18.2	33
3	**519**/KH	3.9:1	16.3	<1
4[c]	-/KH	7.7:1	5.5	14
5	-/NaH	No reaction detected		
6[d]	-/KH	7.4:1	3.9	3
7[e]	-/KH	7.0:1	1.5	9

Table 30. [a]2,6-Dimethyliodobenzene **190** was used as a substrate unless otherwise stated. Ratios are determined by ^{1}H NMR of the crude reaction mixture. [b]Yield (%) of combined biaryls, or yield (%) of returned starting material determined by ^{1}H NMR. [c]Average of two runs. [d] **518** was used as a substrate. [e]**64**was used as a substrate.

Yield calculation. Example (Table 30, Entry 2).

The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard. The quantity of each product was determined as follows (also see annotated example spectra below):

For the starting material **190** the integration of the methoxy signals of the internal standard in the ^{1}H-NMR spectrum (3.78 ppm) was set to 9 units. The integration of the methyl signal of **190** at 2.49 ppm (6 H) was then measured and the following calculation gave the amount of **190** present:

(20.07/6) x 10 = 33.4%

For 2,6-dimethyl-1,1'-biphenyl **191**, the integration of the methoxy signal of the internal standard in the 1H-NMR spectrum (3.78 ppm) was set to 9 units. The integration of the methyl signal of **191** 2.05 ppm (6 H) was then measured and the following calculation gave the amount of **191** present:

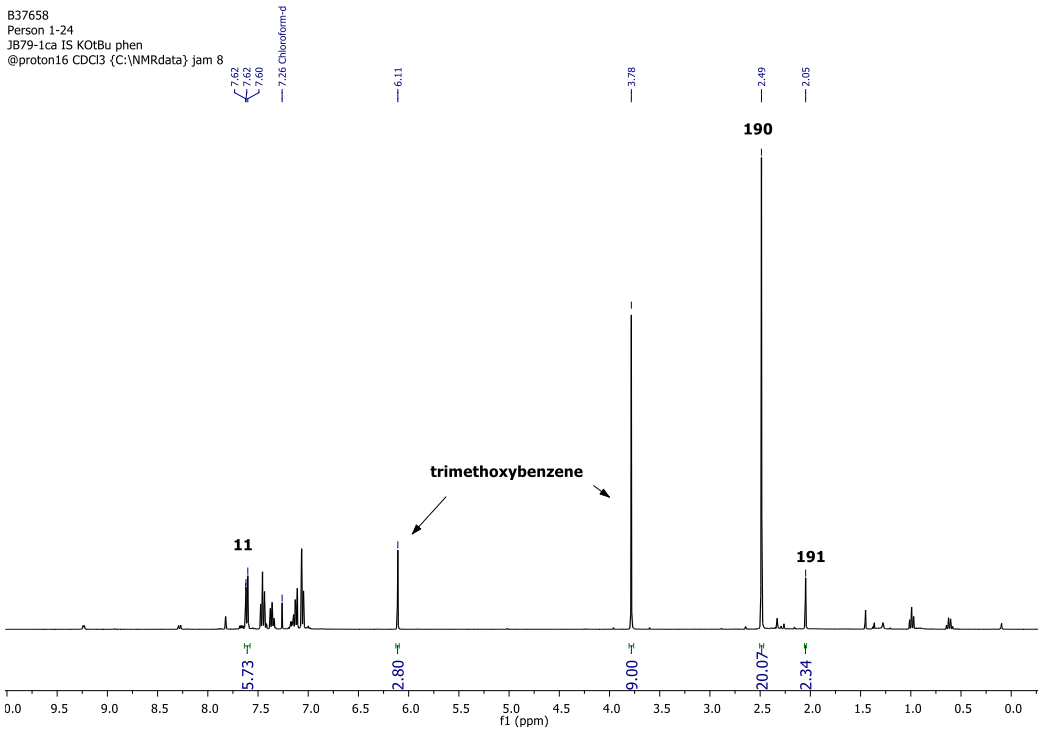
(2.34/6) × 10 = 3.9 %

For the biphenyl product **11** the integration of the aromatic signal of the internal standard (6.10 ppm) was set to 9 units. The integration of the aromatic signals of **11** at 7.64–7.59 ppm (4 H) was then measured and the following calculation gave the amount of **11** present:

(5.73/4) × 10 = 14.3 %

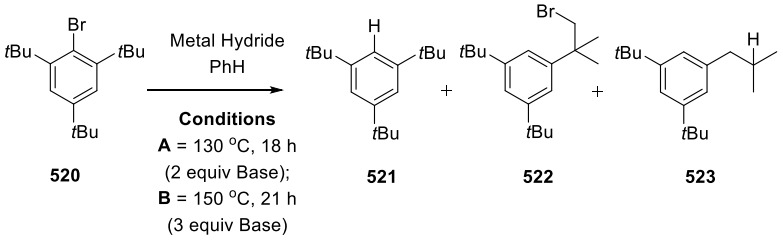
Ratio **11 : 191** = 14.3% : 3.9% = 3.7:1

Yield **11 + 191 =** 14.3% + 3.9% = 18.2%.



Spectrum 27. Mixture of coupled products (Entry 2, Table 30).

5.B4.2 Dehalogenation of 2,4,6-tri-*t*-butylbromobenzene



General procedure: To an oven-dried pressure tube was added 2,4,6-tri-*tert*-butylbromobenzene **520** (0.5 mmol), metal hydride (1.0 mmol, 2 eq.) and benzene (5 mL). The tube was sealed in a glovebox and heated at 130 °C for 18 h (conditions **A**). After cooling to rt, the reaction was quenched carefully with water (50 mL) under an Ar flow, and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (8.4 mg, 0.05 mmol) was added to the crude reaction mixture, the residue dissolved in $CDCl_3$ and the yields determined by

^{1}H NMR. (Table 32) Compounds were previously characterised by Dr Samuel Dalton and Dr Joshua Barham, previous members of the Murphy group.

Alternatively, the reaction was conducted under Conditions **A**, in the absence of metal hydride. No reaction occurred (Entry 1).

Alternatively, the reaction was conducted under Conditions **A**, using KO*t*Bu (2 eq.) as a base No reaction occurred (Entry 2).

Alternatively, the reaction was conducted under Conditions **A**, using KH (2 eq.) as a base. A series of 8 different experiments were performed using 3 different batches. Some of the experiments were performed by Dr Samuel Dalton and Dr Joshua Barham. The results are shown in the following table and the average reported (Entry 3).

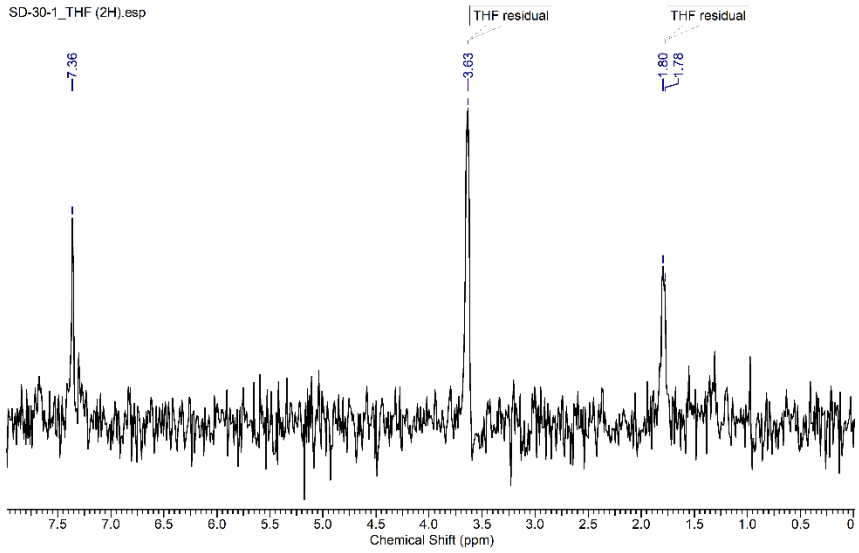
	Expt 1	**Expt 2**	**Expt 3**	**Expt 4**	**Expt 5**	**Expt 6**	**Expt 7**	**Expt 8**	**Average of 8 expts**
520	50.5%	66.1%	42.8%	60.5%	61.8%	28.5%	61.1%	75%	55.8%
521	32%	31.4%	39.1%	33.7%	20.3%	31.4%	18.3%	14%	27.5%
522	7.9%	13%	3.4%	4.4%	3.1%	1.4%	4%	3.5%	5.1%
523	4.5%	3.2%	7.6%	5.2%	6.3%	12.8%	4.4%	3%	5.9%

Table 31. Outcome from the all the replicates of Entry 3.

The reactions in entries 4-5 were performed by Dr Samuel Dalton and Dr Joshua Barham and added here for completeness.

Entry	Base	Solvent/ Quench	Yields (%)[a] 521	522	523	520	D-incorporation
1[b]	-	C_6H_6/H_2O	No reaction				-
2[b]	KO*t*Bu	C_6H_6/H_2O	No reaction				-
3[c]	KH	C_6H_6/H_2O	28	5	6	56	No[d]
4	KH	C_6D_6/D_2O	18	11	3	66	Yes[e,f]
5[g]	KH	C_6H_6/H_2O	31	1	13	29	-

Table 32. D-incorp. = Deuterium incorporation. Unless otherwise stated, conditions **A** were used. [a]Yields determined by ^{1}H NMR of the crude reaction mixture. [b]No products were observed, **520** was recovered in quantitative (ca. 100%) yield. [c]Average of eight replicates. [d]After quenching with D_2O, D-incorporation was not detected. [e]D-incorporated was detected by ^{2}H NMR. [f]After quenching with H_2O, D-incorporation was still detected. [g]Reaction conducted under conditions **B**.



Spectrum 28. Deuterium incorporation of products in the crude mixture (Entry 4, Table 32).

Yield calculation. Example (Table 32, Entry 3).

For the returned starting material **520**, the integral of the aromatic signal of the internal standard (6.10 ppm) was set to 3. The integration of the aromatic signal of **520** (7.43 ppm, 2H) was measured and the following calculation gave the amount of **520** present:

(12.35/2) x 10 = 61.8%

For the dehalogenated product **521**, the integration of the aromatic signal of **521** (7.28 ppm, 3H) was measured and the following calculation gave the amount of **521** present:

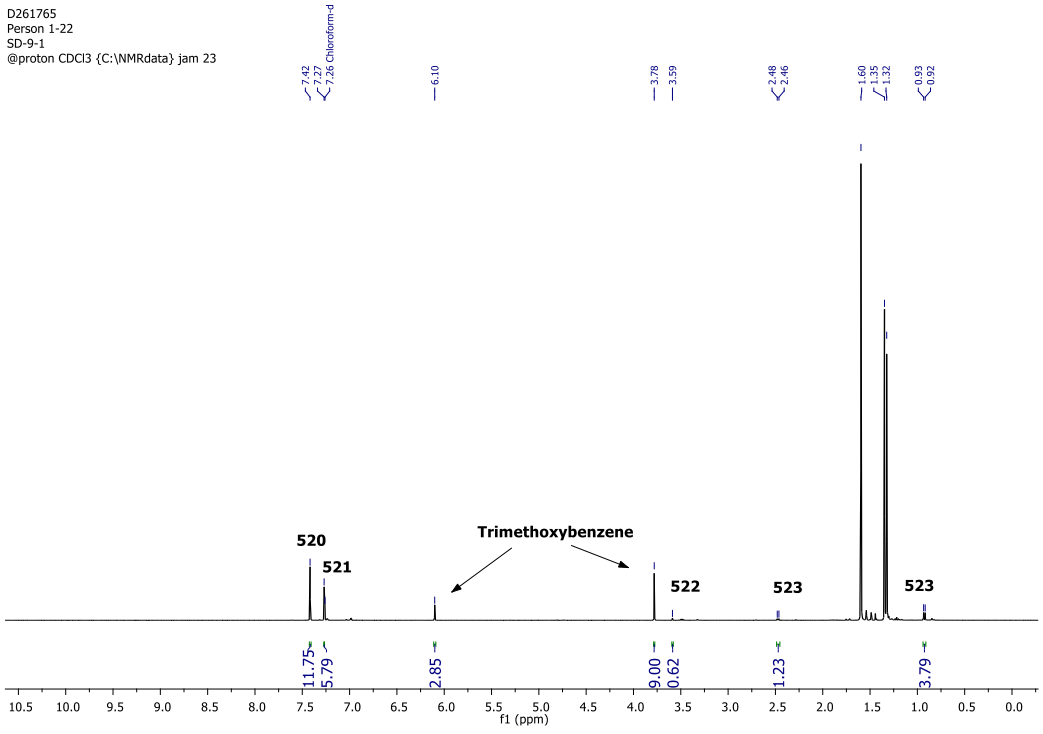
(6.08/3) x 10 = 20.3%.

For bromide **522**, the methoxy signal of the internal standard (3.78 ppm) was set to 9. The integration of the benzylic CH_2 signal of **522** (3.60 ppm, 2H) was measured and the following calculation gave the amount of **522** present:

(0.62/2) x 10 = 3.1%.

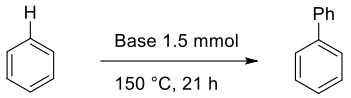
For rearranged dehalogenated product **523**, the methoxy signal of the internal standard (3.78 ppm) was set to 9. The integrations of the benzylic CH_2 signal (2.47 ppm, 2H) and the isopropyl CH_3 signals (0.93 ppm, 6H) of **523** were measured and the following calculation gave the amount of **523** present:

((1.23+3.79)/8) x 10 = 6.3%.



Spectrum 29. Crude mixture of the reaction in Table 32 Entry 3.

5.B4.3 Formation of biphenyl *via* deprotonation of benzene with KH



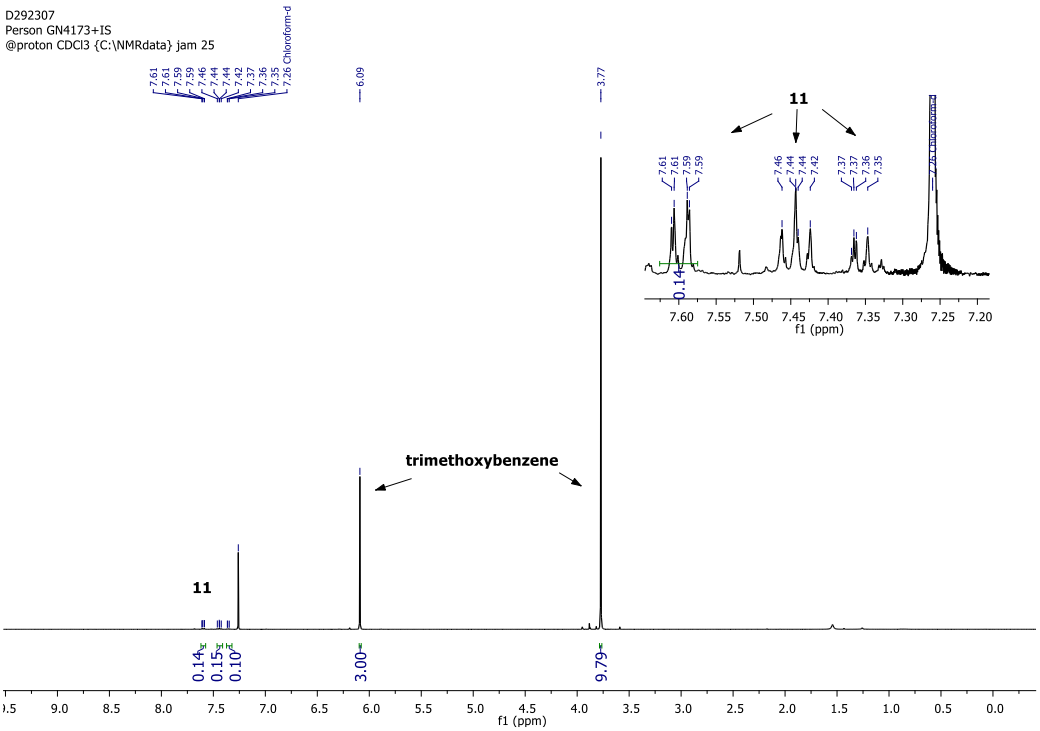
1,1'-biphenyl
Chemical Formula: $C_{12}H_{10}$
Exact Mass: 154.0783

To an oven-dried pressure tube was added potassium *tert*-butoxide (168 mg, 1.5 mmol) and benzene (5 mL). The tube was sealed in a glovebox and stirred at 150 °C for 21 h. After cooling to rt, the reaction was quenched carefully with water (30 mL) and the pH neutralised with hydrochloric acid (5 %) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*, but no product was observed.

To an oven-dried pressure tube was added potassium hydride (60 mg, 1.5 mmol) and benzene (5 mL). The tube was sealed in a glovebox and stirred at 150 °C for 21 h. After cooling to rt, the reaction was quenched carefully with IPA/water (30 mL) and the pH neutralised with hydrochloric acid (5 %) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford biphenyl **11** (0.3 mg; 0.002 mmol) calculated via internal standard as previously shown.

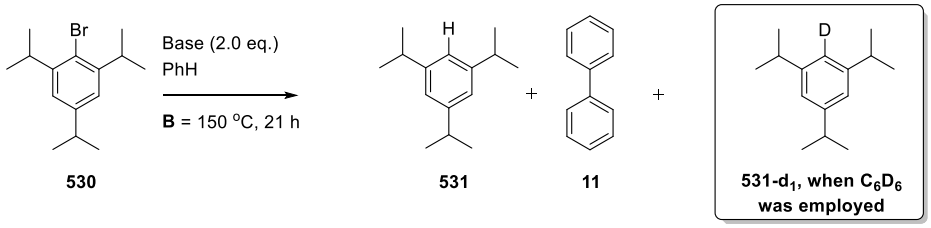
This small amount of biphenyl **11** was calculated via 1H-NMR using trimethoxybenzene (8.4 mg; 0.05 mmol) as internal standard. The integration of the aromatic signal of the internal standard (6.10 ppm) was set to 9 units. The integration of the aromatic signals of **11** at 7.64–7.59 ppm (4 H) was then measured and the following calculation gave the amount of **11** present:

(0.14/4) x 0.05 mmol (IS_{mmol}) x 154 mg/mmol ($\mathbf{11}_{MW}$) = 0.3 mg



Spectrum 30. Formation of little amount of biphenyl from the reaction of benzene + KH.

5.B4.4 Dehalogenation of 2,4,6-tri-*iso*-propylbromobenzene



General reaction procedure: To an oven-dried pressure tube was added 2,4,6-tri-*iso*-propylbromobenzene **530** (0.5 mmol), metal hydride (1.0 mmol, 2 eq.) and benzene (5 mL). The tube was sealed in a glovebox and heated at 150 °C for 21 h (conditions **A**). After cooling to rt, the reaction was quenched carefully with water (50 mL) under an Ar flow, and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. 1,3,5-trimethoxybenzene (8.4 mg, 0.05 mmol) was added

to the crude reaction mixture, the residue dissolved in $CDCl_3$ and the yields determined by ^1H NMR (Table 33).

Alternatively, the reaction was conducted under Conditions **B**, in C_6H_6 (5 mL) on 0.5 mmol scale of bromoarene **530** and 2 eq of KH (Entry 1). The values resulting from three experiments are reported. (a) **531** (17%), **11** (9%), **530** (71%) (b) **531** (19%), **11** (6%), **530** (56%). (see spectrum + calculations below) (c) **531** (38%), **11** (15%), **530** (59%) Average: **531** (25%), **11** (10%), **530** (62%).

Alternatively, the reaction was conducted under Conditions **B**, in C_6D_6 (5 mL) on 0.1 mmol scale of bromoarene **530** and 2 eq of KH (Entry 2). The value resulting from three experiments are reported. (a) **531**+**531-d$_1$** (55%), **11** (12%); (b) **531**+**531-d$_1$** (61%), **530** (14%); (c) **531**+**531-d$_1$** (49%), **11** (17%). Average: **531**+**531-d$_1$** (55%), **11** (14%).

Alternatively, the reaction was conducted under Conditions **B**, in C_6H_6 (5 mL) on 0.5 mmol scale of bromoarene **517** and 2 eq of NaH (Entry 3). (a) **518** (4%), **11** (1%), **517** (95%).

Entry	**Base**	**Solvent/ Quench**	**Yields (%)[a]**			**D-incorporation**
			531	**11**	**530**	
1	KH	C_6H_6/H_2O	25	10	62	-
2[b]	KH	C_6D_6/D_2O	55	0	14	Yes
3[c]	NaH	C_6H_6/H_2O	4	1	95	-

Table 33. Reactions were conducted using conditions **B**. [a]Yields determined by ^1H NMR of the crude reaction mixture. [b]Average of three replicates. [b]The yield of **531**+**531-d$_1$** is reported.

Yield calculation when C_6H_6 was employed. Example (Table 33, Entry 1).

The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard. The quantity of each product was determined as follows (also see annotated example spectra below).

For the returned starting material **530**, the integral of the aromatic signal of the internal standard (6.10 ppm) was set to 3. The integration of the aromatic signal of **530** (6.99 ppm, 2H) was measured and the following calculation gave the amount of **530**:

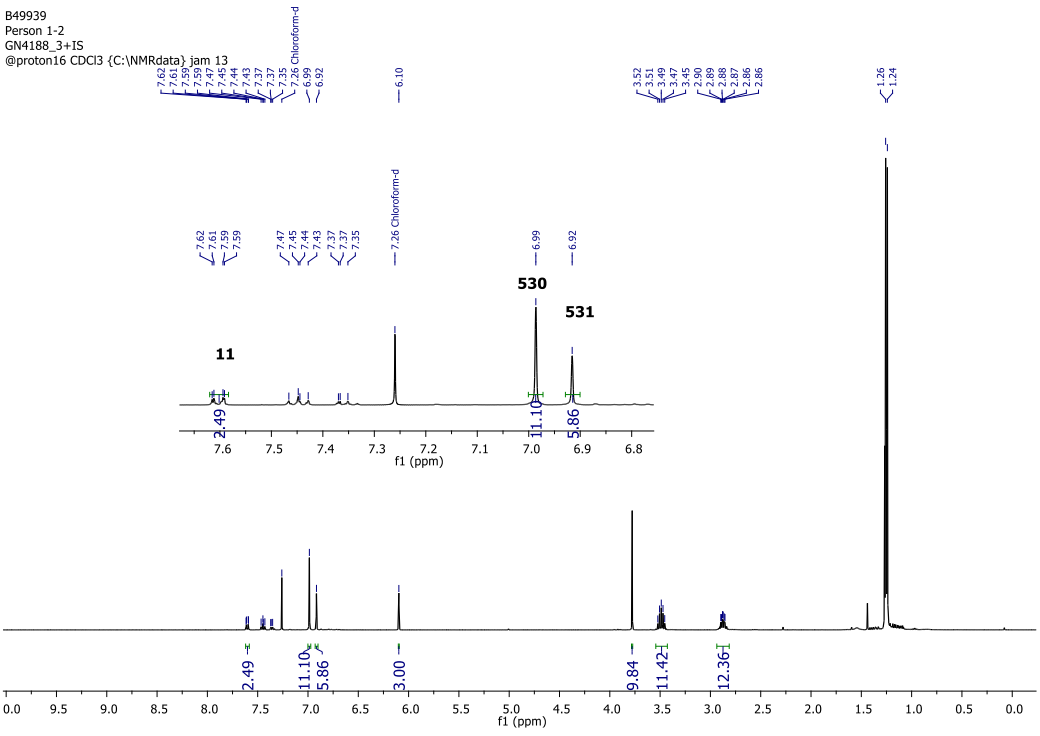
(11.10/2) x 10 = 55.5%.

For the dehalogenated products, the integration of the aromatic signal of **531** (6.91 ppm, 3H) was measured and the following calculation gave the amount of **531** present:

(5.86/3) x 10 = 19.5%.

For biphenyl, The integration of the aromatic signal of **11** (7.62-6.59 ppm, 4H) was measured and the following calculation gave the amount of **11** present:

(2.49/4) x 10 = 6.2%.



Spectrum 31. Spectrum of the reaction mixture (Entry 1, Table 33).

Yield calculation when C_6D_6 was employed. Example (Table 33, Entry 2).

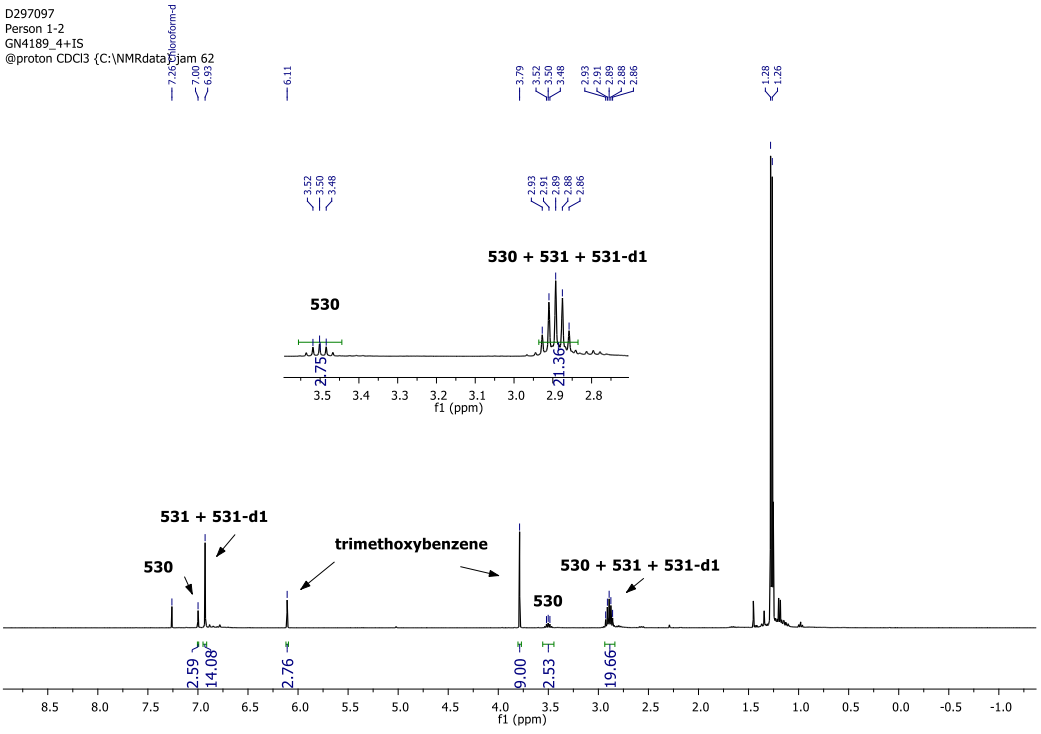
The yield was calculated using 1,3,5-trimethoxybenzene (10%) as internal standard. The quantity of each product was determined as follows (also see annotated example spectra below).

The yield of returned **530** was calculated as 14.1% as shown in the previous example with the integral of the aromatic signal of the internal standard (6.10 ppm) set to 3.

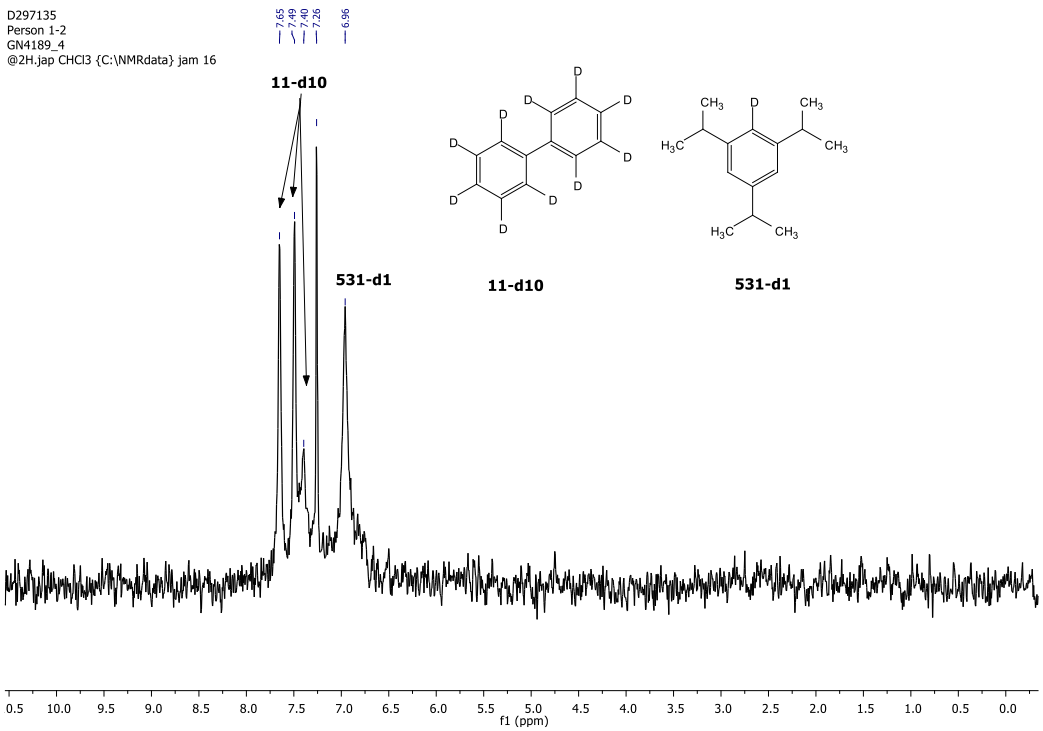
For the combined yield of **531** + **531-d$_1$**, it is assumed that no D-incorporation occurred in the aliphatic region. Therefore, the contribution of **530** to the integral of the peak at 2.89 ppm, 1H from **530** and 3H from **531** can be subtracted by the following calculation:

19.66 - (2.53/2) = 18.4 integration units (for the 3x aliphatic CH peaks of **530** + **531-d$_1$**).

The combined yield of **531** + **531-d$_1$** is given by: [(18.4/3) x 10] = 61.3 %. (From the integral of the resonance at 6.93 ppm, in the ^{1}H spectrum below, it is clear that at least 70% of product **531** is monodeuterated, but more precise determination is complex).



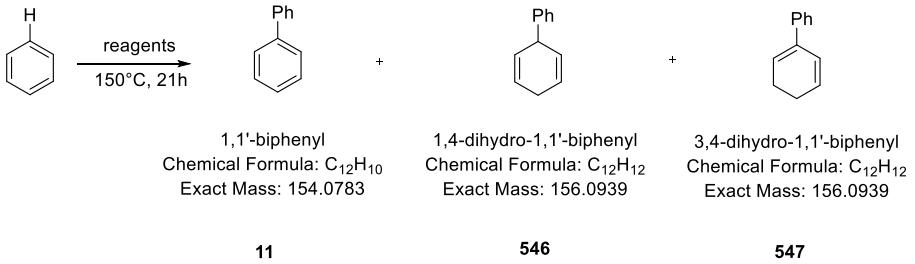
Spectrum 32. Spectrum of the reaction mixture (Entry 2, Table 33).



Spectrum 33. ^{2}H-NMR of the mixture of the products in Entry 2 of Table 33.

5.B5 Special K^+? Potassium Salts Facilitates Reductive Coupling of Arenes by Potassium Metal

5.B5.1 Reactions with K metal



General reaction procedure: To an oven-dried pressure tube the metal (potassium or sodium), a possible additive and anhydrous benzene were added in a glovebox. The tube was sealed and transferred in a fumehood. The reaction was stirred at 150 °C. After 21h the reaction was cooled to 0 °C, it was quenched carefully with IPA/water (20 mL), the pH was adjusted to neutral by using HCl 5% and the organic fraction was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the crude product. The calculations of the yields reactions *via* internal standard 1,3,5-trimethoxybenzene (^{1}H-NMR internal standard) were performed as general procedure.

Variation from general procedure. Table 34.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added The results of the four experiments using different reagents are reported. (a) **11** (108 mg, 0.70 mmol), **546** (traces), **547** (traces) (Old batch of K metal and KO*t*Bu stored in the glovebox); (b) **11** (115 mg, 0.70 mmol), **546** (traces), **547** (traces). (isolated yield using the same batches of K and KO*t*Bu metal used in a); (c) **11** (182 mg, 1.18 mmol), **546** (28 mg, 0.17 mmol), **547** (6 mg, 0.04 mmol). (This result comes from a newly obtained batch of K metal); (d) **11** (83 mg, 0.54 mmol), **546** (14 mg, 0.09 mmol), **547** (11 mg, 0.07 mmol) (Third different batch of K metal

and different batch of KO*t*Bu, this latter stored on the bench). Average:) **11** (122 mg, 0.79 mmol), **546** (12 mg, 0.07 mmol), **547** (3 mg, 0.02 mmol). (Entry 1)

Alternatively, to an oven-dried pressure tube potassium metal (19.5 mg, 0.5 mmol), KO*t*Bu (56 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (32 mg, 0.21 mmol). (Entry 2)

Alternatively, to an oven-dried pressure tube potassium metal (3.9 mg, 0.1 mmol), KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (1 mg, 0.01 mmol). (Entry 3)

Alternatively, to an oven-dried pressure tube potassium metal (19.5 mg, 0.5 mmol), KO*t*Bu (11.2 mg, 0.1 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (30 mg, 0.19 mmol). (Entry 4)

Alternatively, to an oven-dried pressure tube potassium metal (19.5 mg, 0.5 mmol), KO*t*Bu (11.2 mg, 0.1 mmol) and anhydrous benzene (2 mL) were added. The reaction was left at RT for 21h and then quenched and analysed as general procedure. No reaction occurred. (Entry 5)

Entry	**Reagents**	**Yields (mg)**		
		11	**546**	**547**
1[a]	K (1.5 mmol), KO*t*Bu (1.5 mmol)	122 mg	12 mg	3 mg
2	K (0.5 mmol), KO*t*Bu (0.5 mmol)	32 mg	-	-
3	K (0.1 mmol), KO*t*Bu (1.5 mmol)	1.0 mg	-	-
4	K (0.5 mmol), KO*t*Bu (0.1 mmol)	30 mg	-	-
5[b]	K (0.5 mmol), KO*t*Bu (0.5 mmol)	-	-	-

Table 34. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via NMR using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents. [a] Isolated yield.[b] Reaction performed at RT.

Variation from general procedure. Table 35.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), LiI (201 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. No reaction occurred. (Entry 1)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), NaI (225 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (15 mg, 0.09 mmol), **546** (6 mg, 0.04 mmol). (Entry 2)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KI (249 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (54 mg, 0.09 mmol), **546** (traces), **547** (traces). (Entry 3)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), RbI (318 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (42 mg, 0.27 mmol), **546** (41 mg, 0.26 mmol). (Entry 4)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), CsI (390 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (18 mg, 0.12 mmol), **546** (43 mg, 0.28 mmol), **547** (25 mg, 0.16 mmol). (Entry 5)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (122 mg, 0.79 mmol), **546** (12 mg, 0.07 mmol), **547** (3 mg, 0.02 mmol). (Entry 6)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), NaO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. No reaction occurred. (Entry 7)

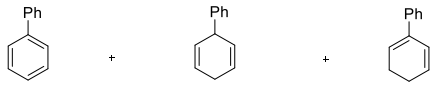
Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KBF_4 (189 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (96 mg, 0.62 mmol), **546** (11 mg, 0.07 mmol), **547** (5 mg, 0.03 mmol). (Entry 8)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), $NaBF_4$ (165 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **564** (5 mg, 0.03 mmol). (Entry 9)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KBr (79 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (47 mg, 0.30 mmol), **546** (17 mg, 0.11 mmol), **547** (5 mg, 0.03 mmol). (Entry 10)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KF (87 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (14 mg, 0.09 mmol), **546** (11 mg, 0.07 mmol), **547** (traces). (Entry 11)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), Me_4NCl (417 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. No reaction occurred. (Entry 12)



11 546 547

Entry	Reagents	Yields (mg)		
		11	**546**	**547**
1	K (1.5 mmol), LiI (1.5 mmol)	-	-	-
2	K (1.5 mmol), NaI (1.5 mmol)	15 mg	6 mg	-
3	K (1.5 mmol), KI (1.5 mmol)	54 mg	traces	traces
4	K (1.5 mmol), RbI (1.5 mmol)	42 mg	41 mg	-
5	K (1.5 mmol), CsI (1.5 mmol)	18 mg	43 mg	25 mg
6	K (1.5 mmol), KO*t*Bu (1.5 mmol)	122 mg	12 mg	3 mg
7	K (1.5 mmol), NaO*t*Bu (1.5 mmol)	-	-	-
8	K (1.5 mmol), KBF_4 (1.5 mmol)	96 mg	11 mg	5 mg
9	K (1.5 mmol), $NaBF_4$ (1.5 mmol)	-	5 mg	-
10	K (1.5 mmol), KBr (1.5 mmol)	47 mg	17 mg	5 mg
11	K (1.5 mmol), KF (1.5 mmol)	14 mg	11 mg	traces
12	K (1.5 mmol), Me_4NCl (1.5 mmol)	-	-	-

Table 35. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents

Variation from general procedure. Table 36.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), MgI_2 (417 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. No reaction occurred. (Entry 1)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), $MgBr_2$ (276 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. No reaction occurred. (Entry 1)

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), CaI_2 (441 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (44 mg, 0.29 mmol), **546** (traces), **547** (traces). (Entry 3)

Alternatively, to an oven-dried pressure tube potassium metal (19.5 mg, 0.5 mmol), SrI_2 (511 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (5 mg, 0.03 mmol). (Entry 4)

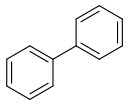
Alternatively, to an oven-dried pressure tube sodium metal (11.5 mg, 0.5 mmol), KO*t*Bu (56 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. No reaction occurred (Entry 5)

Entry	**Reagents**	**Yields (mg)**		
		11	**546**	**547**
1	K (1.5 mmol), MgI_2 (1.5 mmol)	-	-	-
2	K (1.5 mmol), $MgBr_2$ (1.5 mmol)	-	-	-
3	K (1.5 mmol), CaI_2 (1.5 mmol)	44 mg	traces	traces
4	K (0.5 mmol), SrI_2 (0.5 mmol)	5 mg	-	-
5	Na (0.5 mmol), KO*t*Bu (0.5 mmol)	-	-	-

Table 36. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents.

Some reactions only gave biphenyl as product, some others gave a mixture of biphenyl and dihydro-biphenyl as product.

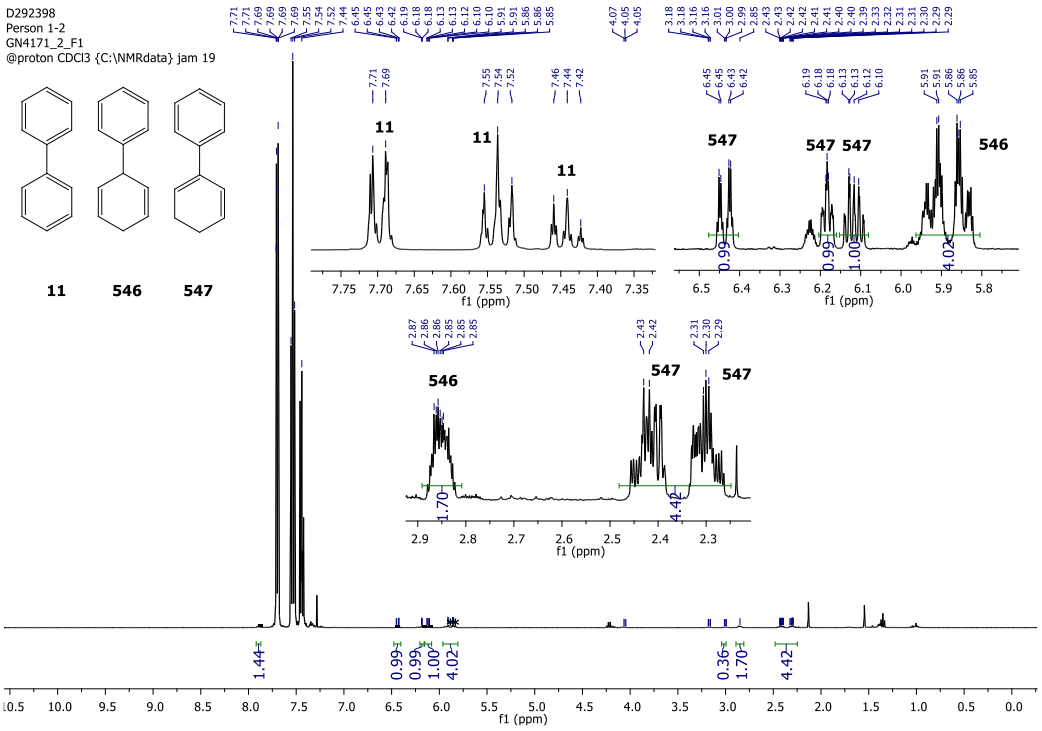
Biphenyl, **11**



1,1'-biphenyl
Chemical Formula: $C_{12}H_{10}$
Exact Mass: 154.0783

White solid. Mp: 64-67 °C (lit: 65-67 °C).[228] ν_{max} (neat, cm^{-1}) 3061, 3034, 1477, 1429, 1344, 1182, 1169, 902, 725, 692. ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.71 – 7.64 (4 H, m, Ar*H*), 7.55 – 7.48 (4 H, m, Ar*H*), 7.45 – 7.39 (2 H, m, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 140.8, 128.3, 126.8, 126.8. GC-MS (EI) *m/z* 154.1. Data were consistent with the literature.[236]

The mixture of dihydrobiphenyl was inseparable, nonetheless they are known in the literature: 1,4-dihydrobiphenyl, **546**, [237] and 3,4-dihydrobiphenyl **547**. [238]



Spectrum 34. Mixture of biphenyl and dihydrobiphenyls.

Mg calculation of products-general calculation

The quantity of each product was determined as the following formula (also see annotated example spectra below):

mg of compound = (NMR integral/ number of proton) x mmol of internal standard x MW (mg/mmol)

For the biphenyl product **11** the integration of the aromatic signal of the internal standard was set to 3. The integration of the aromatic signals of **11** at 7.64–7.59 ppm (4 H) was then measured and the following calculation gave the amount of **11** present:

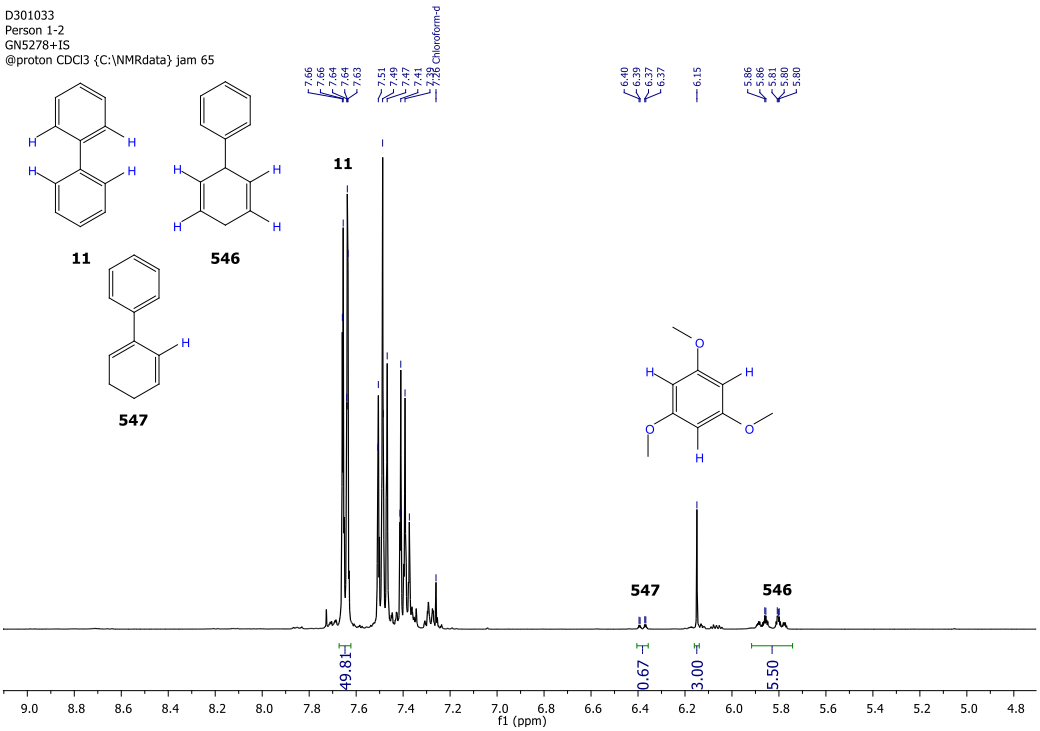
(49.81/4) x 0.05 mmol x 254 mg/mmol = 96 mg

For 1,4-dihydro-biphenyl, **546**, the integration of aromatic signal of the internal standard in the ^{1}H-NMR spectrum was set to 3 units. The integration of the aromatic protons of **546** (5.86 ppm) was then measured and the following calculation gave the amount of **546** present:

(5.50/4) x 0.05 mmol x 256 mg/mmol= 18 mg

For 3,4-dihydro-1,1'-biphenyl **547** the integration of aromatic signal of the internal standard in the ^{1}H-NMR spectrum was set to 3 units. The integration of the aromatic proton of **547** (6.41 ppm) was then measured and the following calculation gave the amount of **547** present:

0.67 x 0.05 mmol x 256 mg/mmol= 8.5 mg



Spectrum 35. Spectrum example for yield calculation.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and anhydrous toluene (5 mL) were added. No reaction occurred.

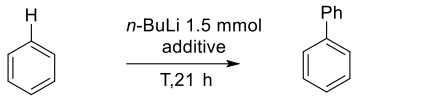
Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol) and anhydrous toluene (5 mL) were added. Phenol (56 mg, 0.6 mmol, 40%) was detected at the end of the reaction.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol), anhydrous benzene (2.5 mL) and anhydrous THF (2.5 mL) were added. No reaction occurred.

Alternatively, to an oven-dried pressure tube potassium metal (58.5 mg, 1.5 mmol), KO*t*Bu (168 mg, 1.5 mmol), anhydrous benzene (0.1 mL) and anhydrous THF (4.9 mL) were added. No reaction occurred.

5.B5.2 Reactions with *n*-BuLi and benzene-d_5

Reactions with *n*-BuLi



1,1'-biphenyl
Chemical Formula: $C_{12}H_{10}$
Exact Mass: 154.0783

11

General reaction procedure: To an oven-dried pressure tube, an additive (KO*t*Bu or KI or NaO*t*Bu) and anhydrous benzene were added in a glovebox. The tube was sealed with suba-seal rubber septum and transferred in a fumehood where *n*-BuLi (1.5 mmol) was syringed in the tube under nitrogen. The reaction was then stirred for 21 h at a desired temperature. After cooling to 0 °C, the reaction was quenched carefully with IPA/water (20 mL), the pH was adjusted to neutral by using HCl 5% and the organic fraction was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the crude product. The calculations of the yields reactions *via* internal standard 1,3,5-trimethoxybenzene (^{1}H-NMR internal standard) were performed as follows: 1,3,5-trimethoxybenzene (8.4 mg, 0.050 mmol, 10 mol%) was added as a solid to the reaction mixture. $CDCl_3$ (~1 mL) was added and the solution stirred for 5 min. A portion of the solution was taken and diluted for NMR analysis and yield calculation.

Table 37

Alternatively, to an oven-dried pressure tube anhydrous benzene (2 mL) was added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at rt for 21h and then quenched and worked up as in the general reaction procedure. No reaction was observed (Entry 1).

Alternatively, to an oven-dried pressure tube KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (2 mL) was added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75

mL) was then added. The reaction was allowed to stir at rt for 21h and then quenched and worked up as in the general reaction procedure. No reaction was observed (Entry 2).

Alternatively, to an oven-dried pressure tube anhydrous benzene (2 mL) was added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 110 °C for 21h and then quenched and worked up as in the general reaction procedure. Trace amounts of biphenyl **11** were found (Entry 3).

Alternatively, to an oven-dried pressure tube KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 110 °C for 21h and then quenched and worked up as in the general reaction procedure. Trace amounts of biphenyl **11** were found (Entry 4).

Alternatively, to an oven-dried pressure tube anhydrous benzene (2 mL) was added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 130 °C for 21h and then quenched and worked up as in the general reaction procedure. Biphenyl (6 mg, 0.04 mmol) was found at the end of the reaction (Entry 5).

Alternatively, to an oven-dried pressure tube KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 130 °C for 21h and then quenched and worked up as in the general reaction procedure. Biphenyl (100 mg, 0.65 mmol) was found at the end of the reaction (Entry 6).

Alternatively, to an oven-dried pressure tube KO*t*Bu (168 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 130 °C for 21h and then quenched

and worked up as in the general reaction procedure. Biphenyl (100 mg, 0.65 mmol) was found at the end of the reaction (Entry 6).

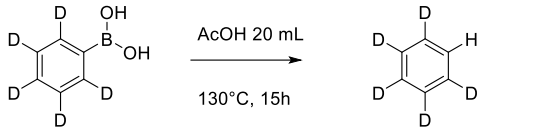
Alternatively, to an oven-dried pressure tube KI (249 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 130 °C for 21h and then quenched and worked up as in the general reaction procedure. Biphenyl (5 mg, 0.03 mmol) was found at the end of the reaction (Entry 7).

Alternatively, to an oven-dried pressure tube NaO*t*Bu (144 mg, 1.5 mmol) and anhydrous benzene (2 mL) were added and the tube sealed with suba-seal rubber septum in a glovebox. The tube was then transferred in the fumehood and *n*BuLi (1.5 mmol, 2M in hexane, 0.75 mL) was then added. The reaction was allowed to stir at 130 °C for 21h and then quenched and worked up as in the general reaction procedure. Biphenyl (39 mg, 0.25 mmol) was found at the end of the reaction (Entry 8).

Entry	**Additive (1.5 mmol)**	**Temperature (°C)**	**Yields (mg)**		
			11	**546**	**547**
1	-	RT	-	-	-
2	KO*t*Bu	RT	-	-	-
3	-	110 °C	traces	-	-
4	KO*t*Bu	110 °C	traces	-	-
5	-	130 °C	6 mg	-	-
6	KO*t*Bu	130 °C	100 mg	-	-
7	KI	130 °C	5 mg	-	-
8	NaO*t*Bu	130 °C	39 mg	-	-

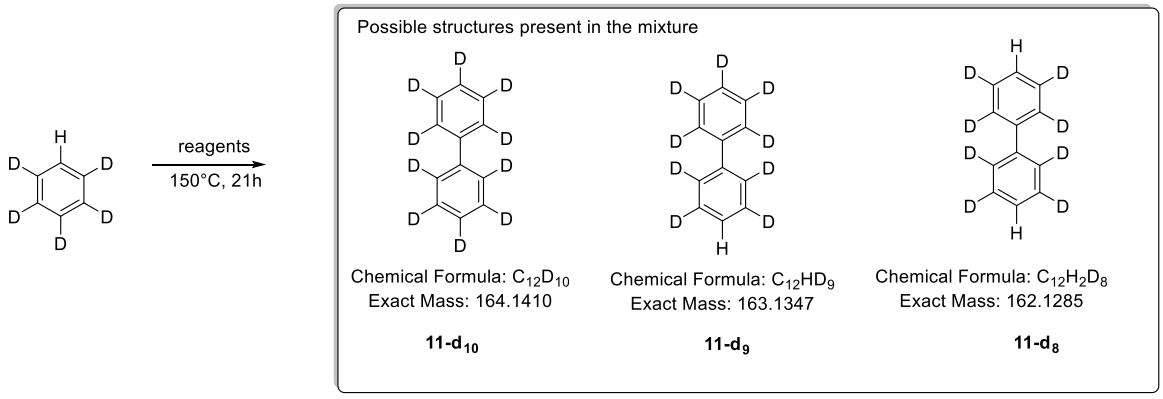
Table 37. Reaction of benzene + *n*BuLi in absence or presence of additives.

Preparation of benzene-d$_5$



553 **254**

Phenylboronic acid-d$_5$ **553** (2540 mg, 20 mmol) was added in a 25 mL pressure tube with AcOH (10 mL). The reaction was left at 130 °C overnight. After 15h the the residue was distilled using a vigreaux column (10 cm long, 120°C, 1 atm), giving rise to 1.0 g of product benzene-d$_5$ (1000 mg, 12.04 mmol, yield 24.1 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 7.39 (1 H, s, Ar*H*). ^{13}C-NMR (101 MHz, $CDCl_3$) δ ppm 128.3, 128.1, 128.0, 127.8, 127.7. ^{2}H-NMR (61 MHz, $CHCl_3$) 6.38 (5 D, s, ArD). GC-MS (EI) *m/z* 83.1.

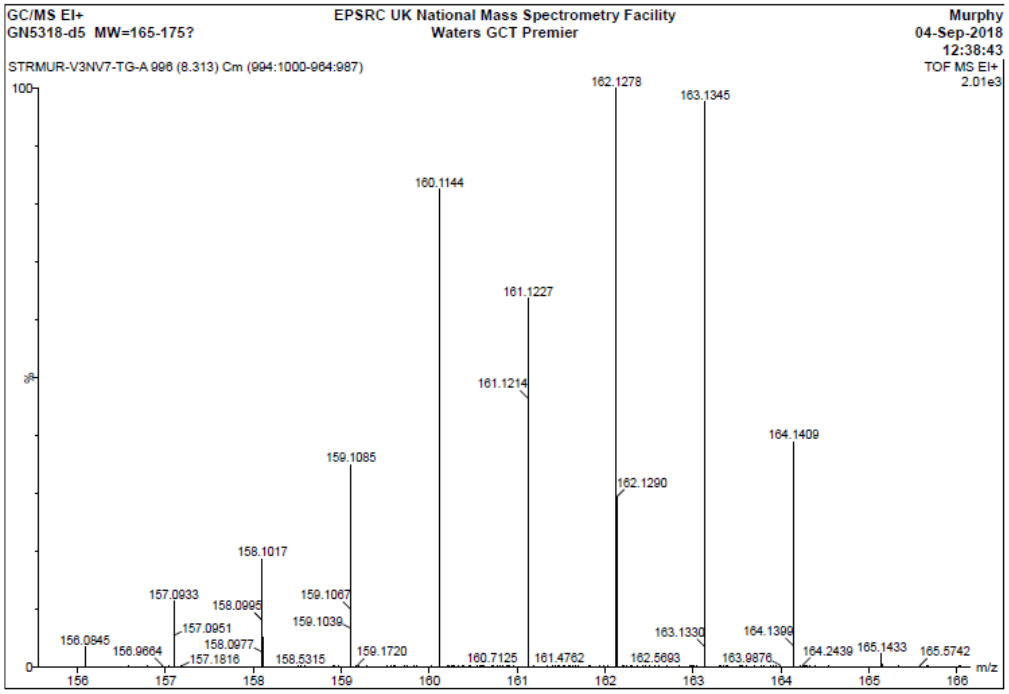


To an oven-dried pressure tube the potassium metal (58.5 mg, 15 mmol), and anhydrous benzene-d$_5$ were added in a glovebox. The tube was sealed and transferred and stirred at 150 ^{o}C for 21 h in a fumehood. After cooling to 0 °C, the reaction was quenched carefully with IPA/water (20 mL), the pH was adjusted to neutral by using HCl 5% and the organic fraction was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the crude product (only few mg were obtained). The sample was analysed via HRMS and a mixture of **11-dmix**, **534-dmix** and **546-mix**. Analysing the TOF MS EI$^+$ (HRMS) of the mixture **11-mix**, a 1 : 2.5 : 2.5 ratio was observed between the products **11-d$_{10}$** : **11-d$_9$** : **11-d$_8$** (Spectrum 33).

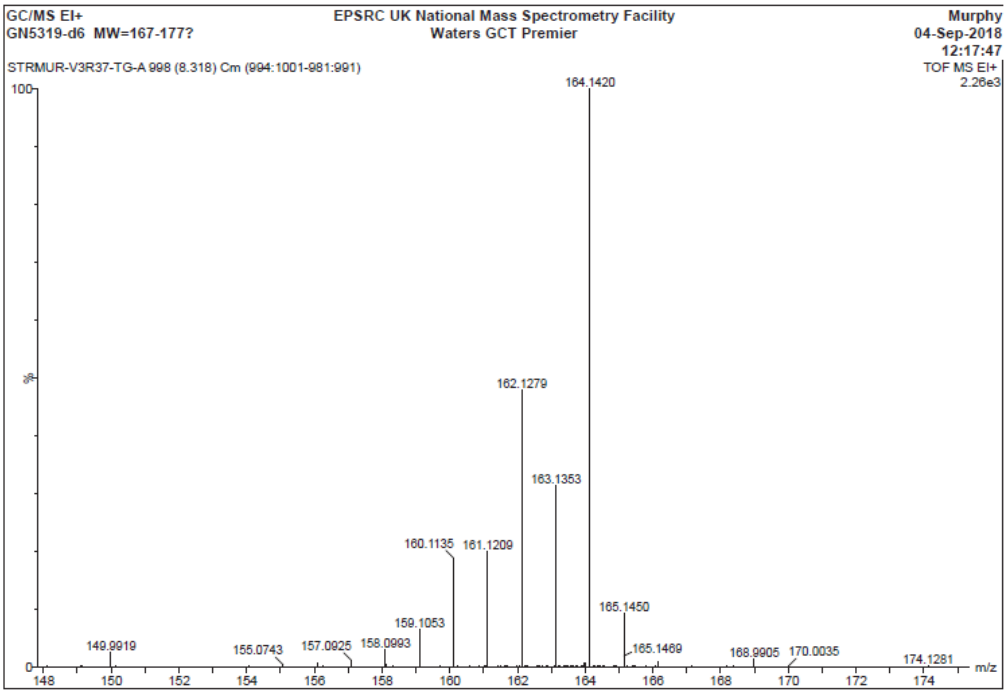
Compound	Mass		Mass (%)	Ratio calculated	Ratio predicted	
	Theoretical	Found			Radical	Ionic
11-d10	164.1410	1641409	40	1	1	1
11-d9	163.1347	163.1345	97	2.5	10	5
11-d8	132.1285	132.1278	100	2.5	25	-

Table 38. Outcome of the reaction with benzene-d_5.

Alternatively, To an oven-dried pressure tube the potassium metal (58.5 mg, 15 mmol), and anhydrous benzene-d_6 were added in a glovebox. Analysing the TOF MS EI$^+$ (HRMS) of the mixture **11-mix**, a 3.3 : 1 : 1.7 ratio was observed between the products **11-d$_{10}$** : **11-d$_9$** : **11-d$_8$** (Spectrum 34).



Spectrum 36. TOF MS EI$^+$ (HRMS) of the mixture **11-d$_{10}$: 11-d$_9$: 11-d$_8$**, deriving from the reaction with benzene-d_5.



Spectrum 37. TOF MS EI$^+$ (HRMS) of the mixture **11-d$_{10}$: 11-d$_9$: 11-d$_8$**, deriving from the reaction with benzene-d$_6$.

5.B5.3 Reactions with KH and benzene

1,1'-biphenyl
Chemical Formula: $C_{12}H_{10}$
Exact Mass: 154.0783

11

1,4-dihydro-1,1'-biphenyl
Chemical Formula: $C_{12}H_{12}$
Exact Mass: 156.0939

546

3,4-dihydro-1,1'-biphenyl
Chemical Formula: $C_{12}H_{12}$
Exact Mass: 156.0939

547

General reaction procedure: To an oven-dried pressure tube the metalhydride (potassium or sodium hydride), a possible additive and anhydrous benzene were added in a glovebox. The tube was sealed and transferred in a fumehood. The reaction was stirred at 150 ^{o}C. After 21h the reaction was cooled to 0 °C, it was quenched carefully with IPA/water (20 mL), the pH was adjusted to neutral by using HCl 5% and the organic fraction was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the crude product. The calculations of the yields

reactions *via* internal standard 1,3,5-trimethoxybenzene (^{1}H-NMR internal standard) were performed as general procedure.

Variation from general procedure. Table 39.

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. Traces amounts of biphenyl were detected. (Entry 1)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), potassium metal (58.5 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (51 mg, 0.33 mmol), **546** (12 mg, 0.07 mmol), **547** (16 mg, 0.10 mmol). (Entry 2)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), potassium metal (19.5 mg, 0.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (35 mg, 0.0.23 mmol). (Entry 3)

Alternatively, to an oven-dried pressure tube KH (20 mg, 0.5 mmol), KO*t*Bu (56 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (47 mg, 0.30 mmol). (Entry 4)

Alternatively, to an oven-dried pressure tube KH (20 mg, 0.5 mmol), KO*t*Bu (56 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The reaction was performed at 130 °C for 18h. The results are reported. **11** (17 mg, 0.11 mmol). (Entry 5)

Alternatively, to an oven-dried pressure tube KH (20 mg, 0.5 mmol), NaO*t*Bu (48 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (11 mg, 0.07 mmol). (Entry 6)

Alternatively, to an oven-dried pressure tube NaH (12 mg, 0.5 mmol), NaO*t*Bu (48 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. No products occurred. (Entry 7)

Alternatively, to an oven-dried pressure tube NaH (12 mg, 0.5 mmol), KO*t*Bu (56 mg, 0.5 mmol) and anhydrous benzene (2 mL) were added. The results are reported. **11** (21 mg, 0.14 mmol). (Entry 8)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), Me_4NCl (417 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. Traces amounts of biphenyl were detected. (Entry 9)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), $NaBF_4$ (165 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (27 mg, 0.18 mmol). (Entry 10)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), KBF_4 (189 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (36 mg, 0.23 mmol). (Entry 11)

Entry	Reagents	Yields (mg)		
		11	**546**	**547**
1	KH (1.5 mmol)	traces	-	-
2	KH (1.5 mmol), K (1.5 mmol)	51 mg	12 mg	16 mg
3	KH (1.5 mmol), K (0.5 mmol)	35 mg	3 mg	traces
4	KH (0.5 mmol), KO*t*Bu (0.5 mmol)	34 mg	-	-
5[a]	KH (0.5 mmol), KO*t*Bu (0.5 mmol)	17 mg	-	-
6	KH (0.5 mmol), NaO*t*Bu (0.5 mmol)	11 mg	-	-
7	NaH (0.5 mmol), NaO*t*Bu (0.5 mmol)	-	-	-
8	NaH (0.5 mmol), KO*t*Bu (0.5 mmol)	21 mg	-	-
9	KH (1.5 mmol), Me_4NCl (1.5 mmol)	traces	-	-
10	KH (1.5 mmol), $NaBF_4$ (1.5 mmol)	27 mg	-	-
11	KH (1.5 mmol), KBF_4 (1.5 mmol)	36 mg	-	-
12	KH (1.5 mmol), KF (1.5 mmol)	27 mg	-	-
13	KH (1.5 mmol), LiI (1.5 mmol)	23 mg	traces	traces

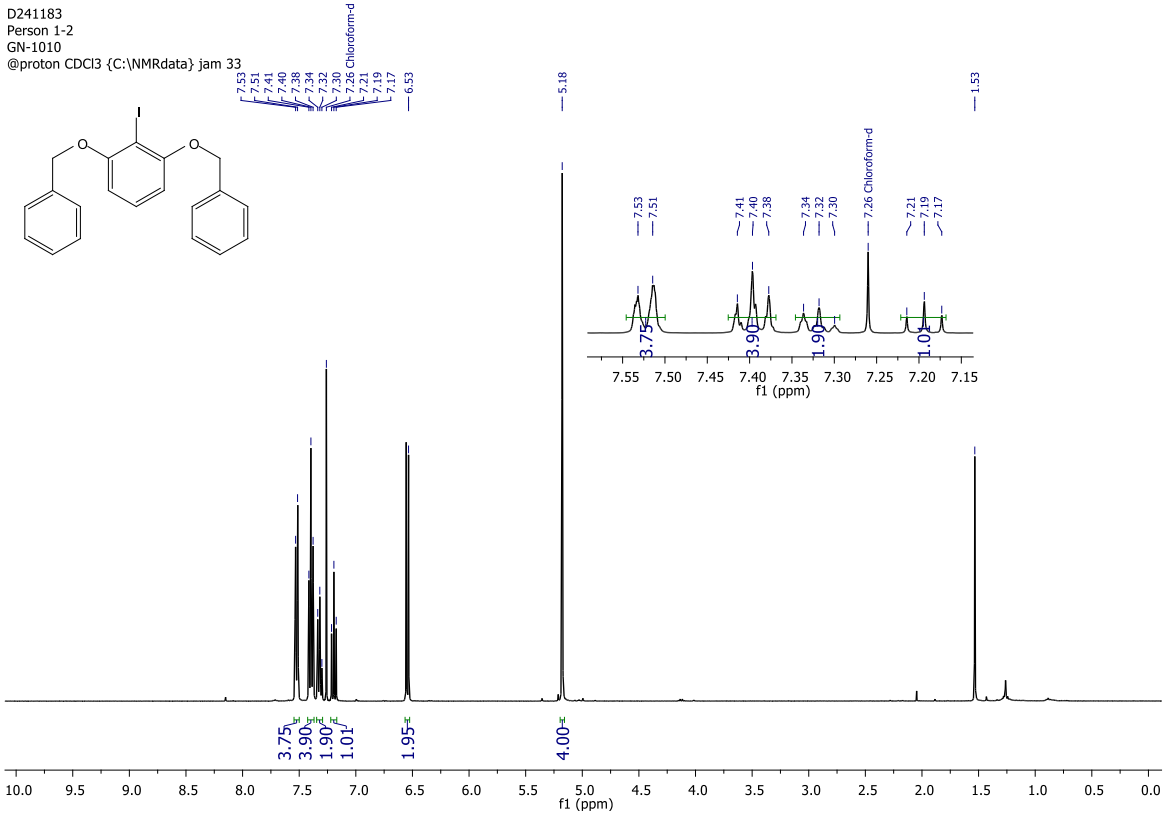
Table 39. Unless otherwise stated, all the reactions were performed at 150°C for 21h and yields (mg) were calculated via internal standard using trimethoxybenzene as internal standard (traces refers to < 1 mg). 5 mL of benzene were used with 1.5 mmol of reagents, 2 mL of benzene were used with 0.5 mmol of reagents. [a] Reaction performed at 130 °C for 18h.

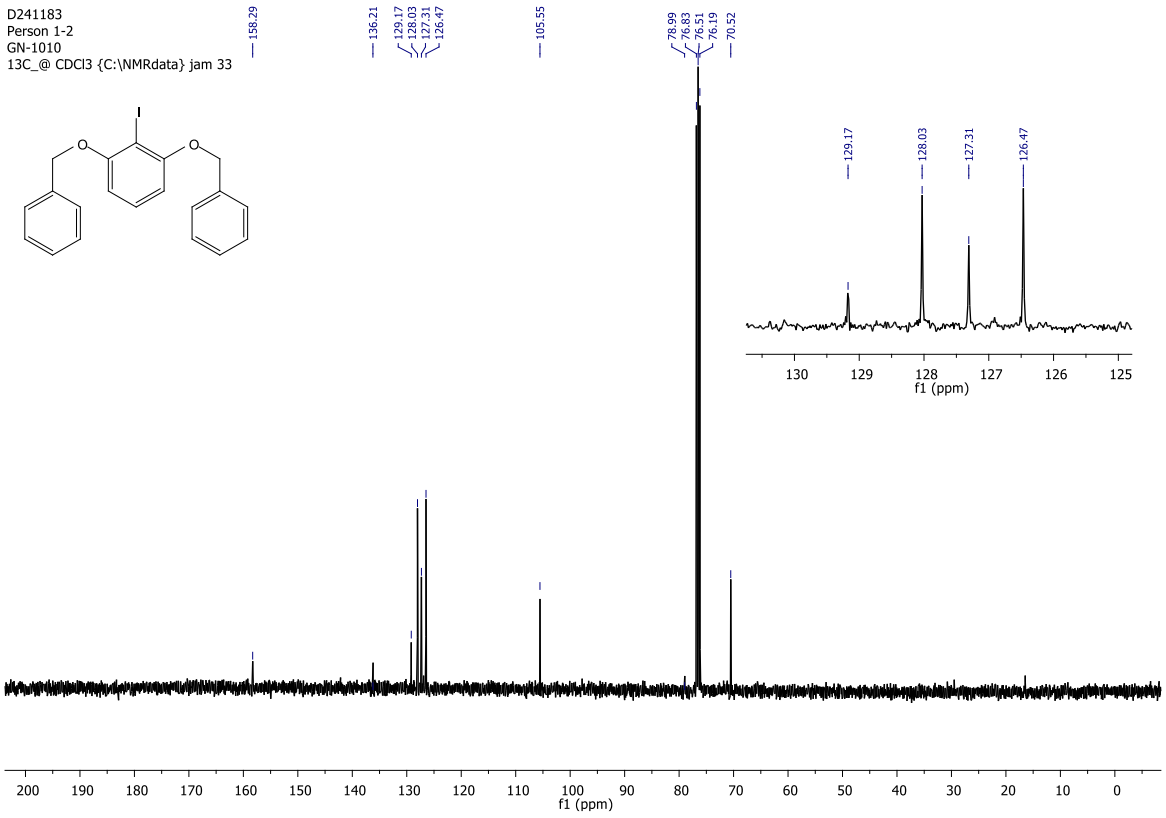
Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), KF (87 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (27 mg, 0.18 mmol). (Entry 12)

Alternatively, to an oven-dried pressure tube KH (60 mg, 1.5 mmol), LiI (201 mg, 1.5 mmol) and anhydrous benzene (5 mL) were added. The results are reported. **11** (23 mg, 0.18 mmol), traces amounts of **546** and **547** were also detected. (Entry 13)

6 SPECTRA

2,6-Dibenzyloxy-1-iodobenzene, 290

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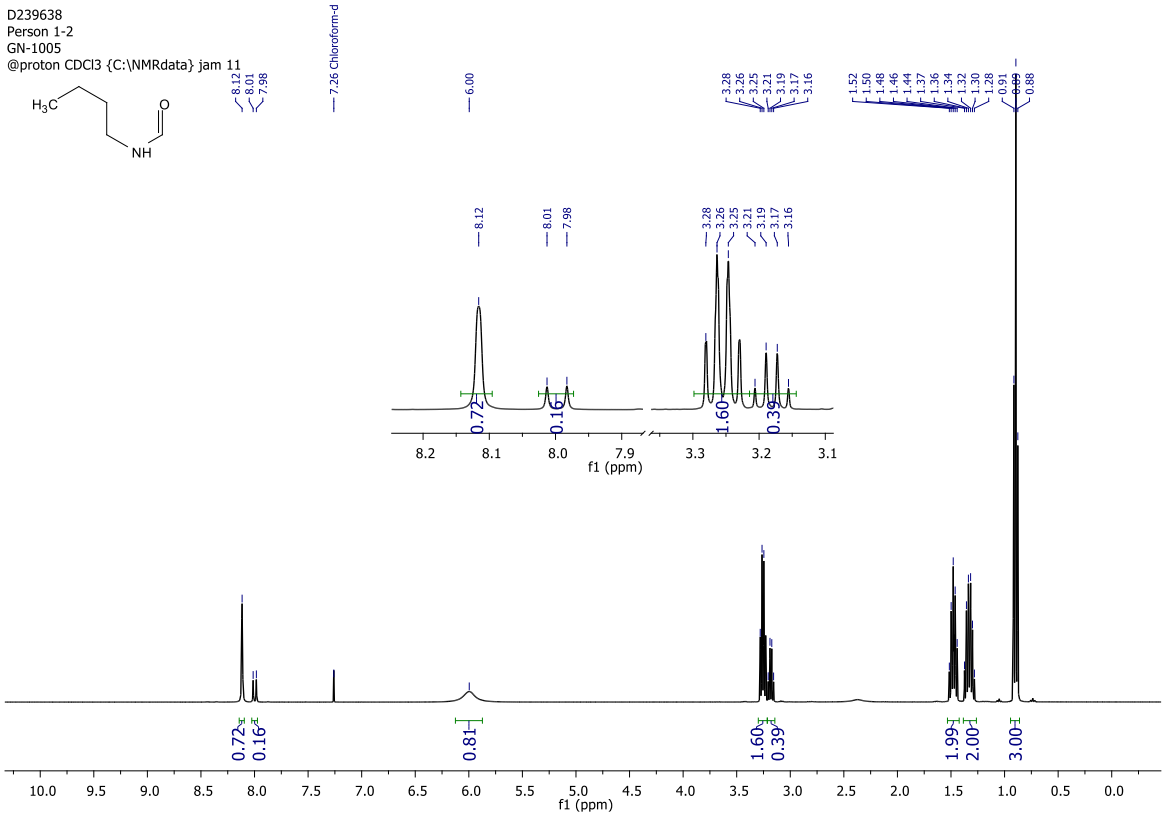
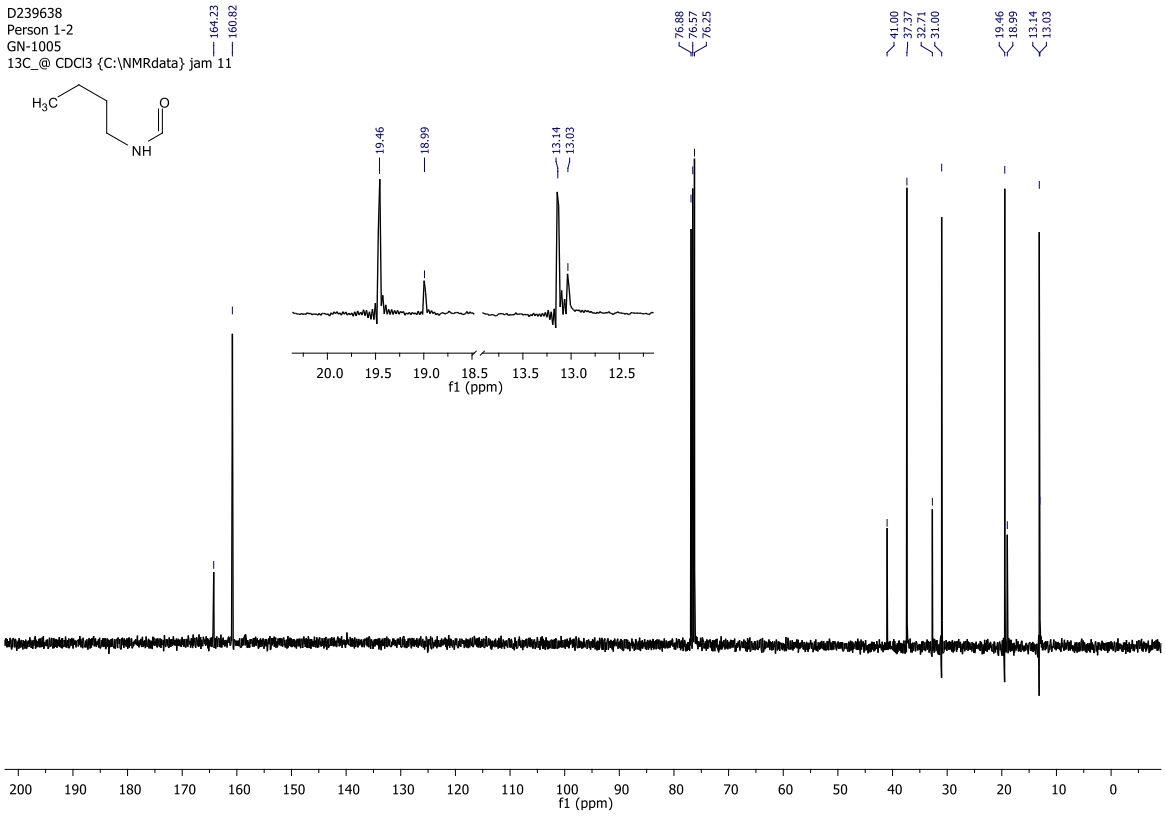
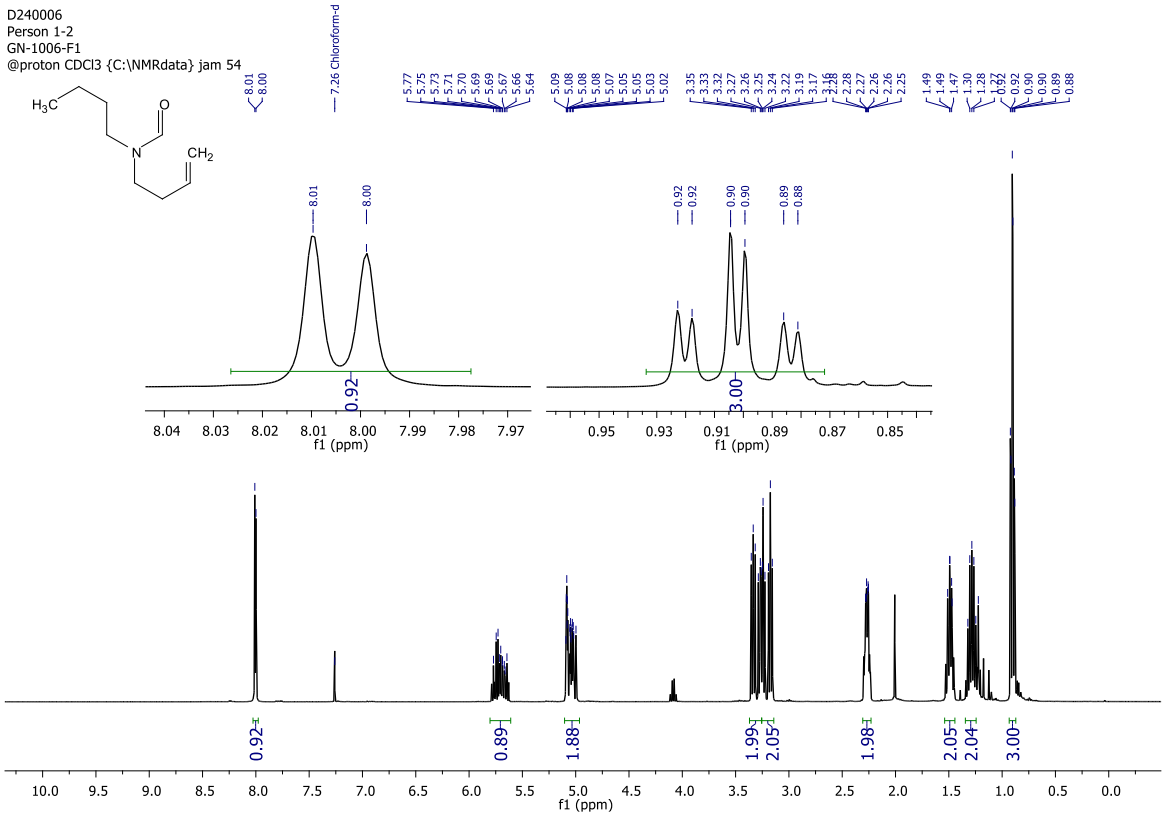
136.21
129.17
128.03
127.31
126.47
105.55
78.99
76.83
76.51
76.19
70.52
I
O
O
f1 (ppm)
f1 (ppm)

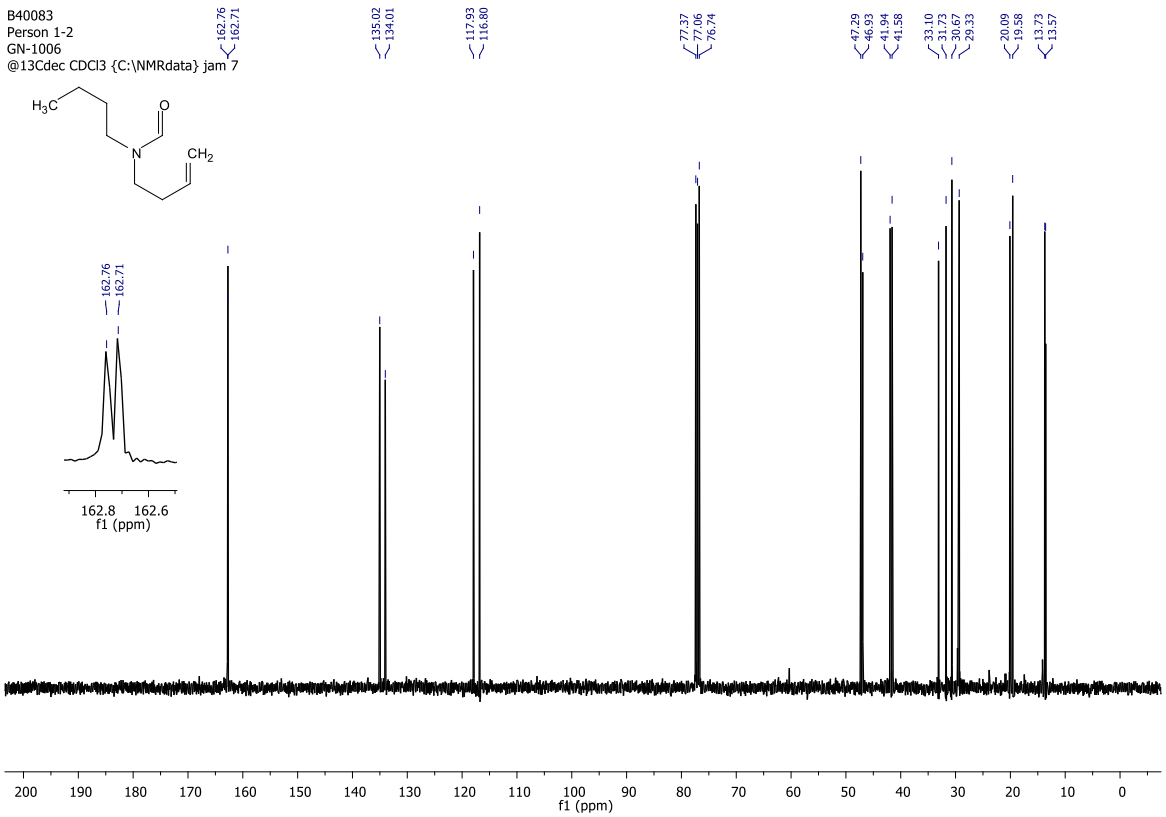
n-Butylformamide, 296



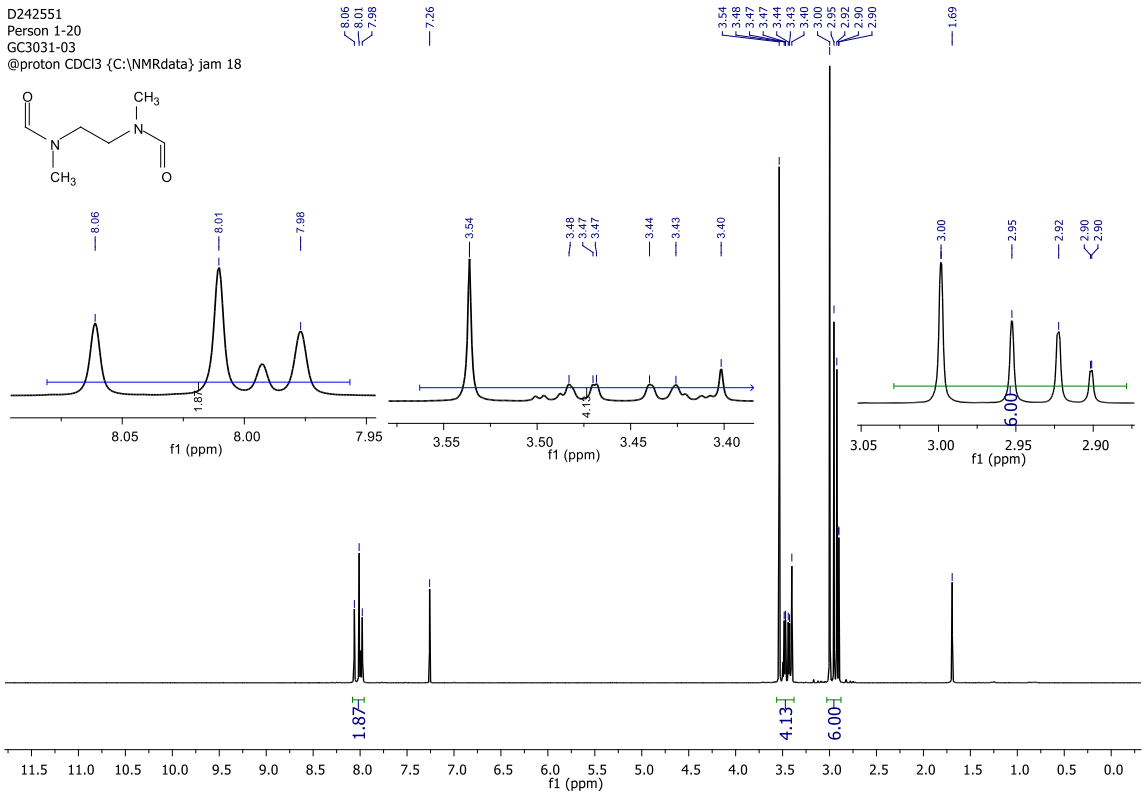


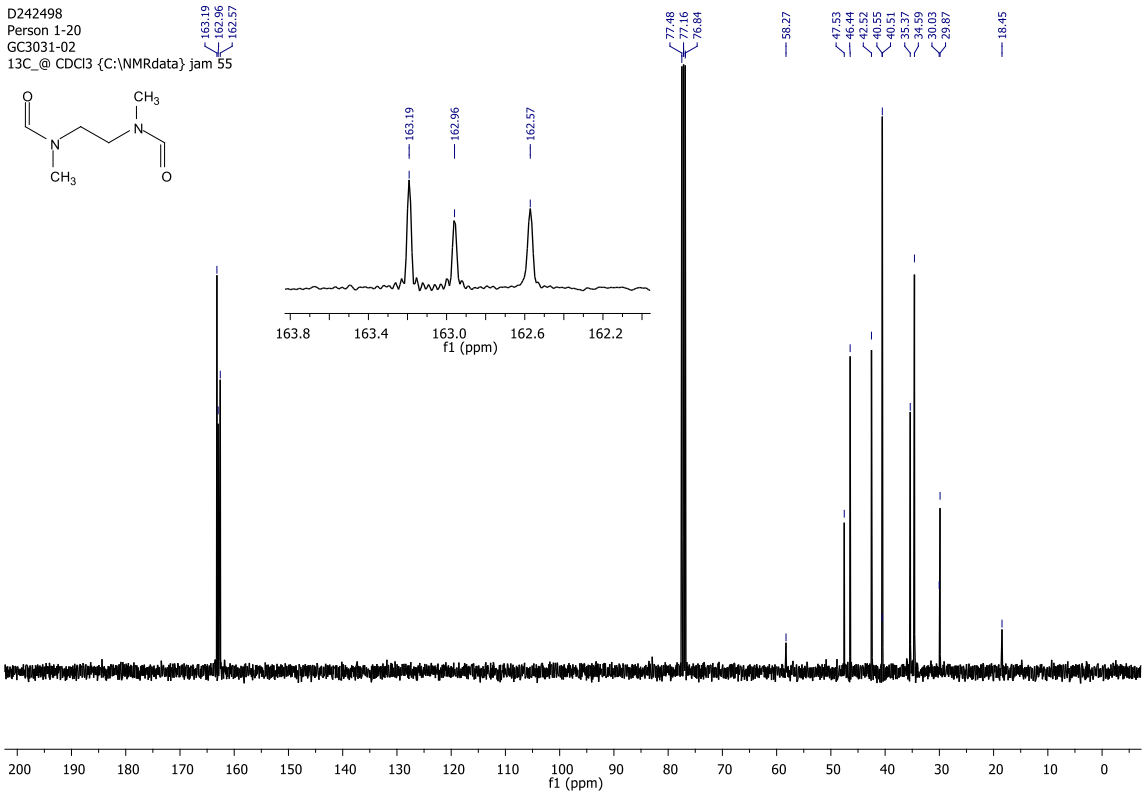
N-But-3-enyl-*N*-butylformamide, 284



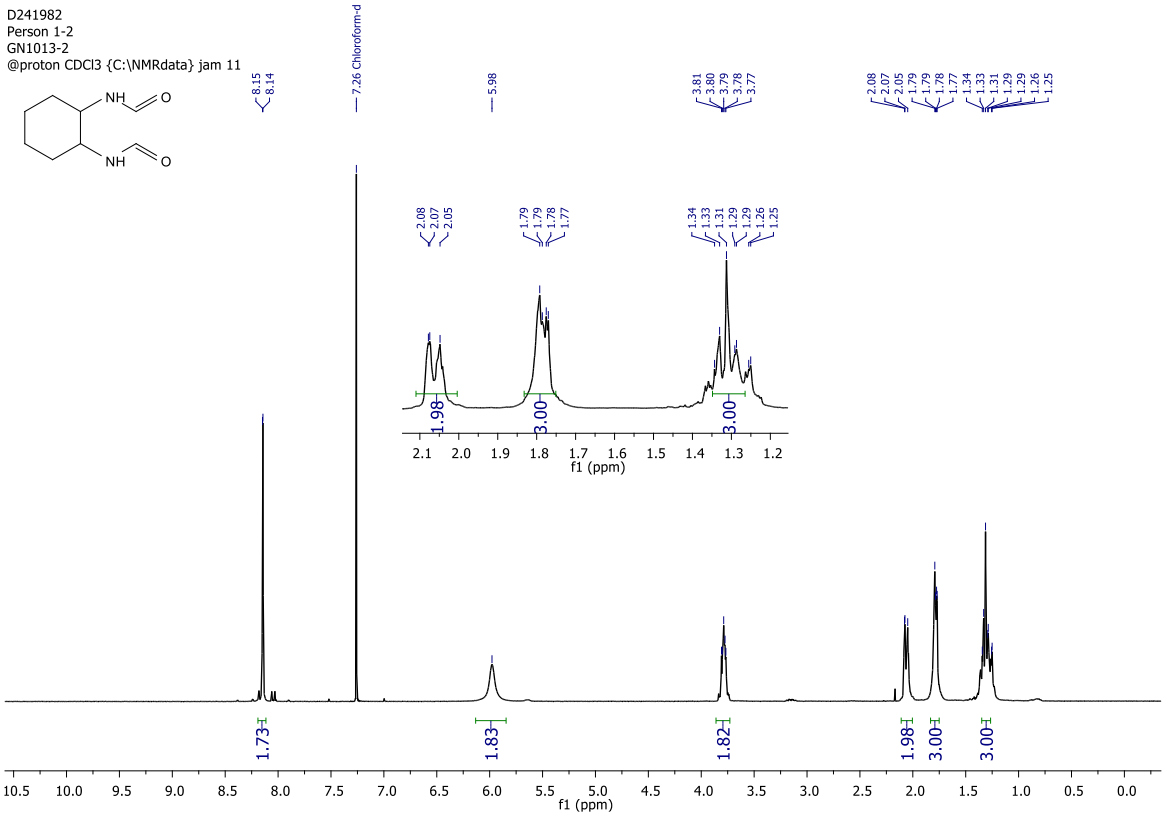


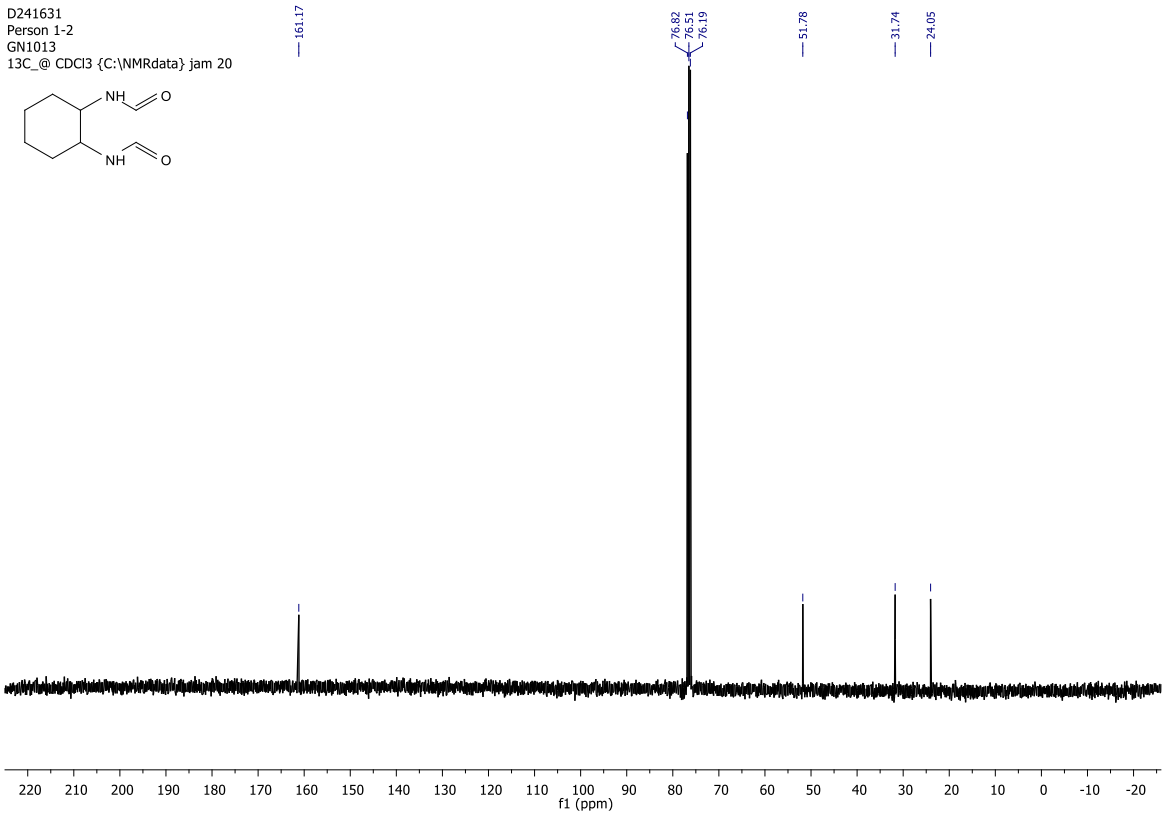
N,*N*'-Diformyl-*N*,*N*'-dimethylethylene-1,2-diamine, 238





N,*N*’-[(±)-*trans*-Cyclohexane-1,2-diyl]diformamide, 299





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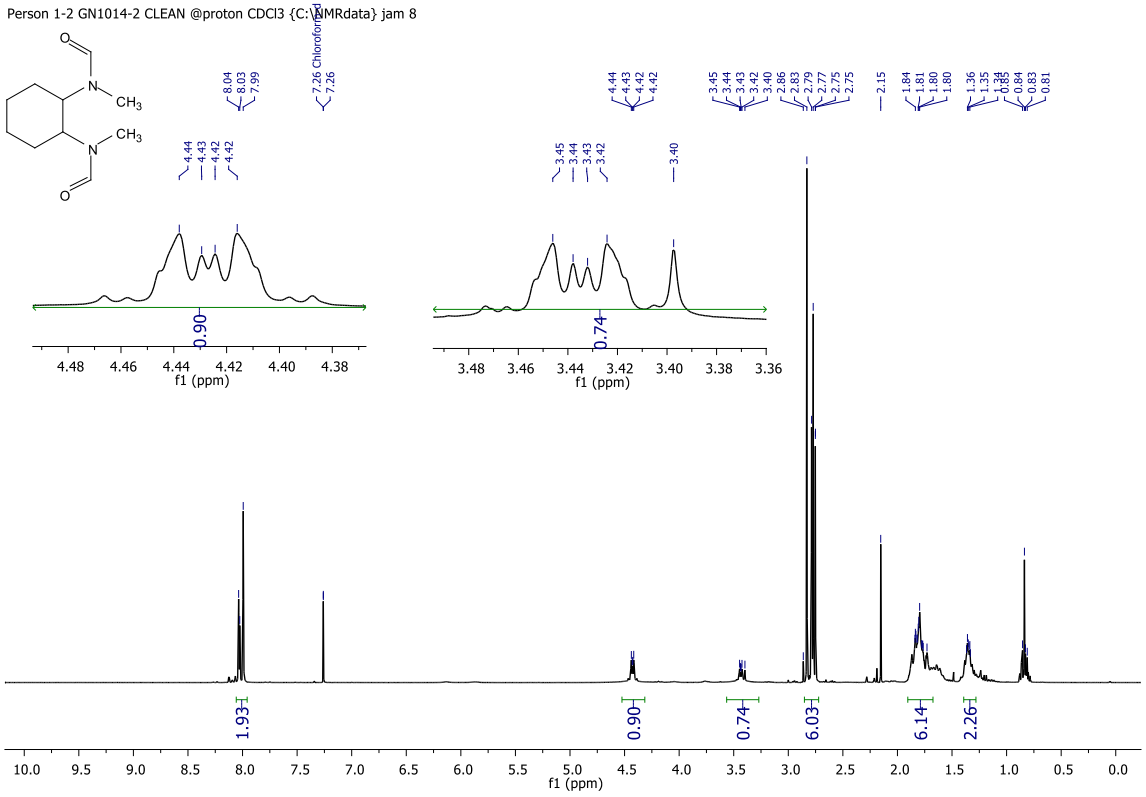
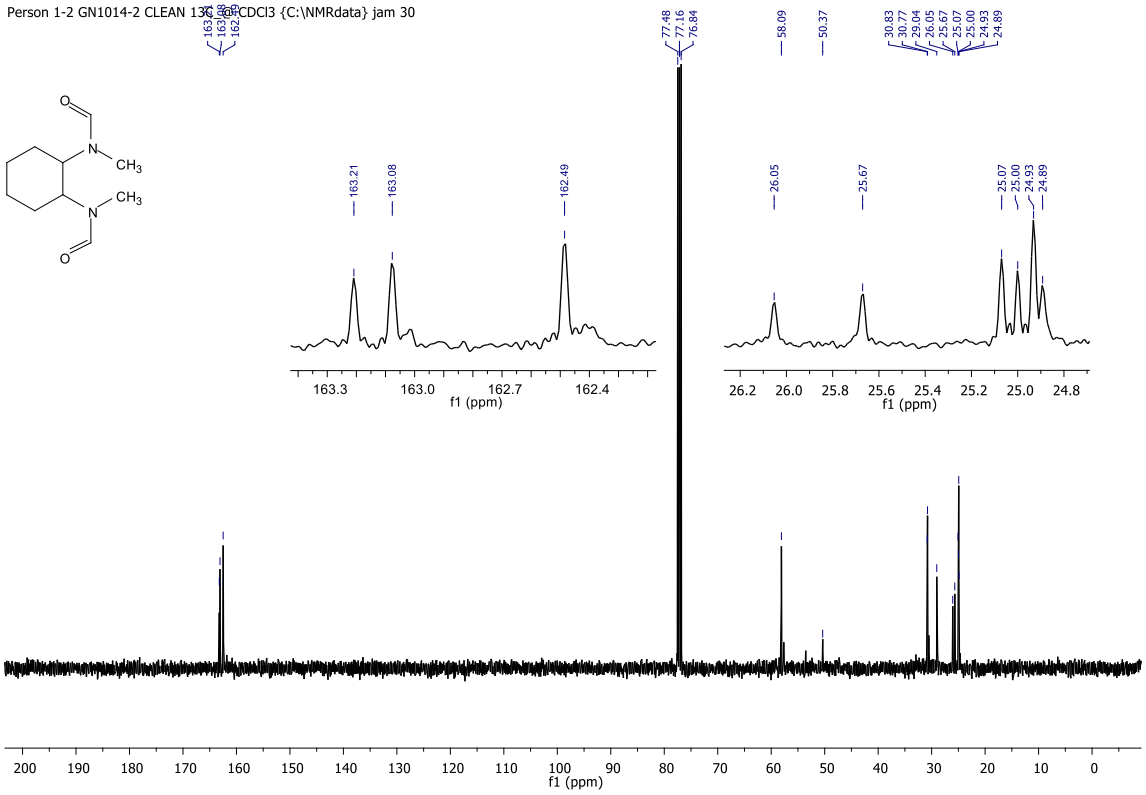
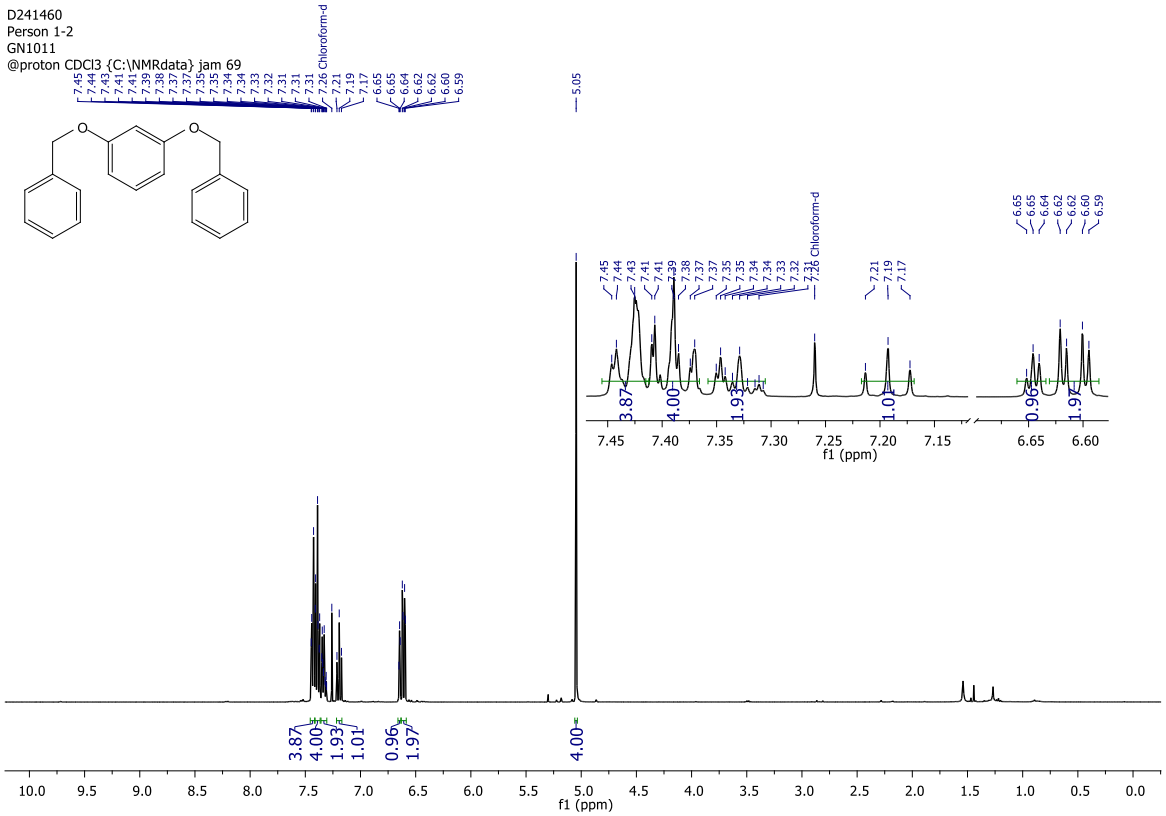
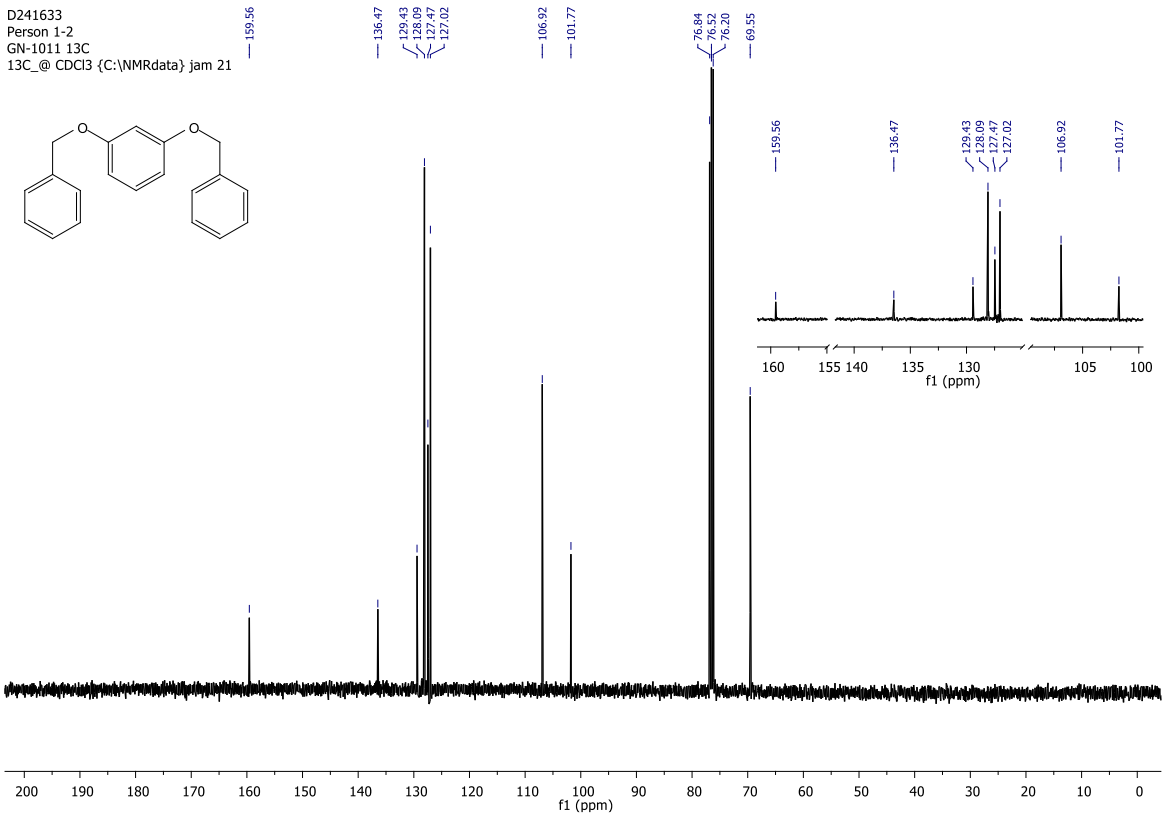


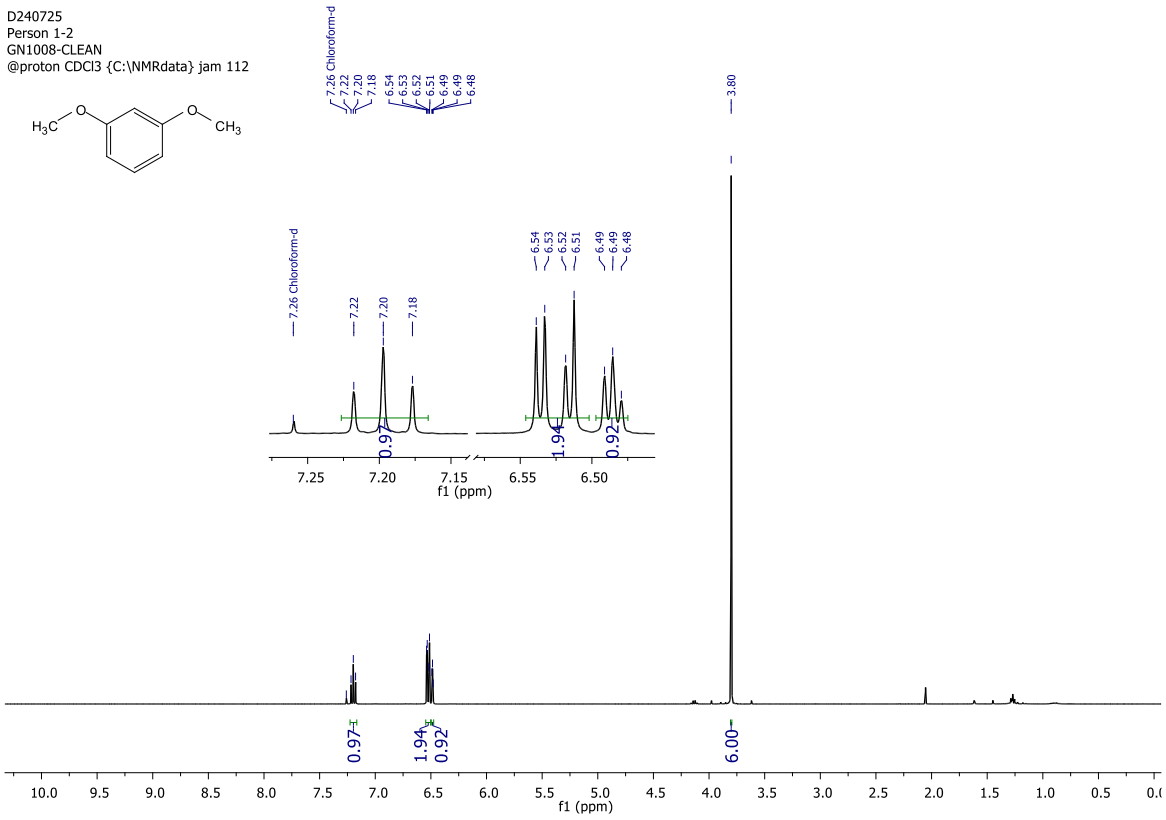


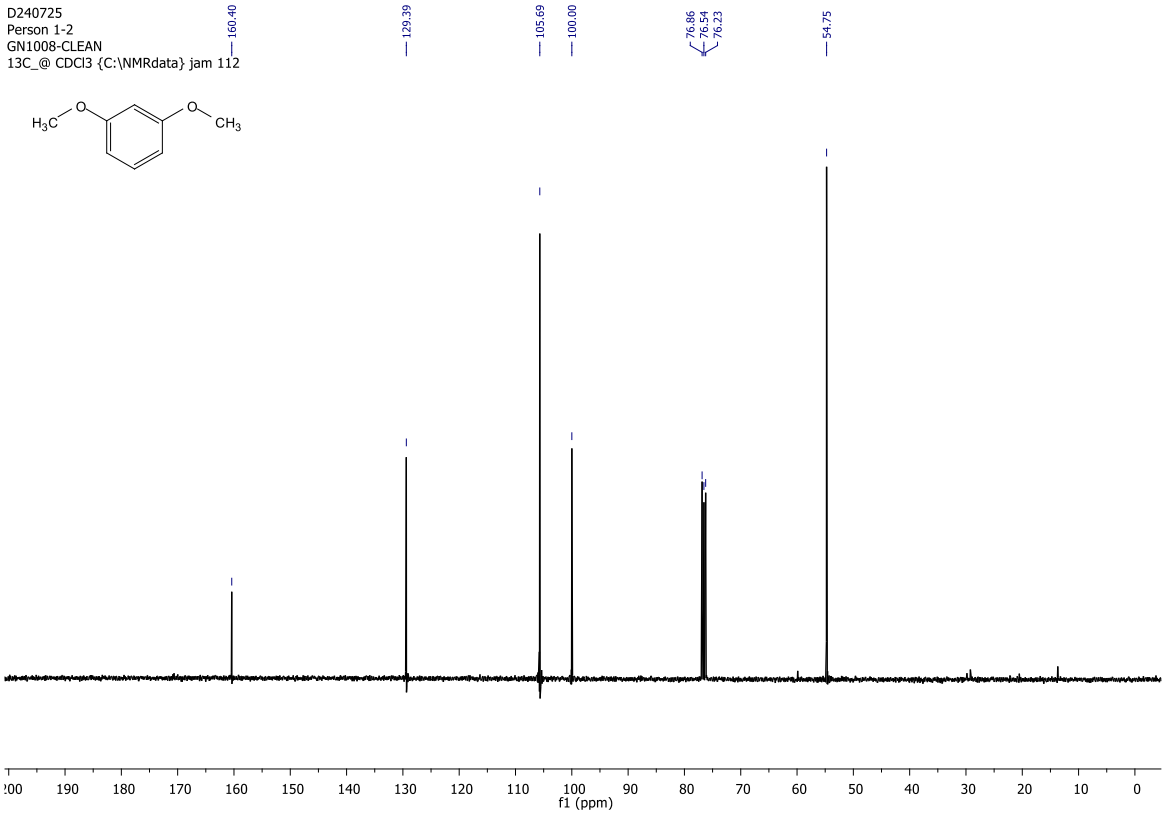
1,3-Bis(benzyloxy)benzene, 291



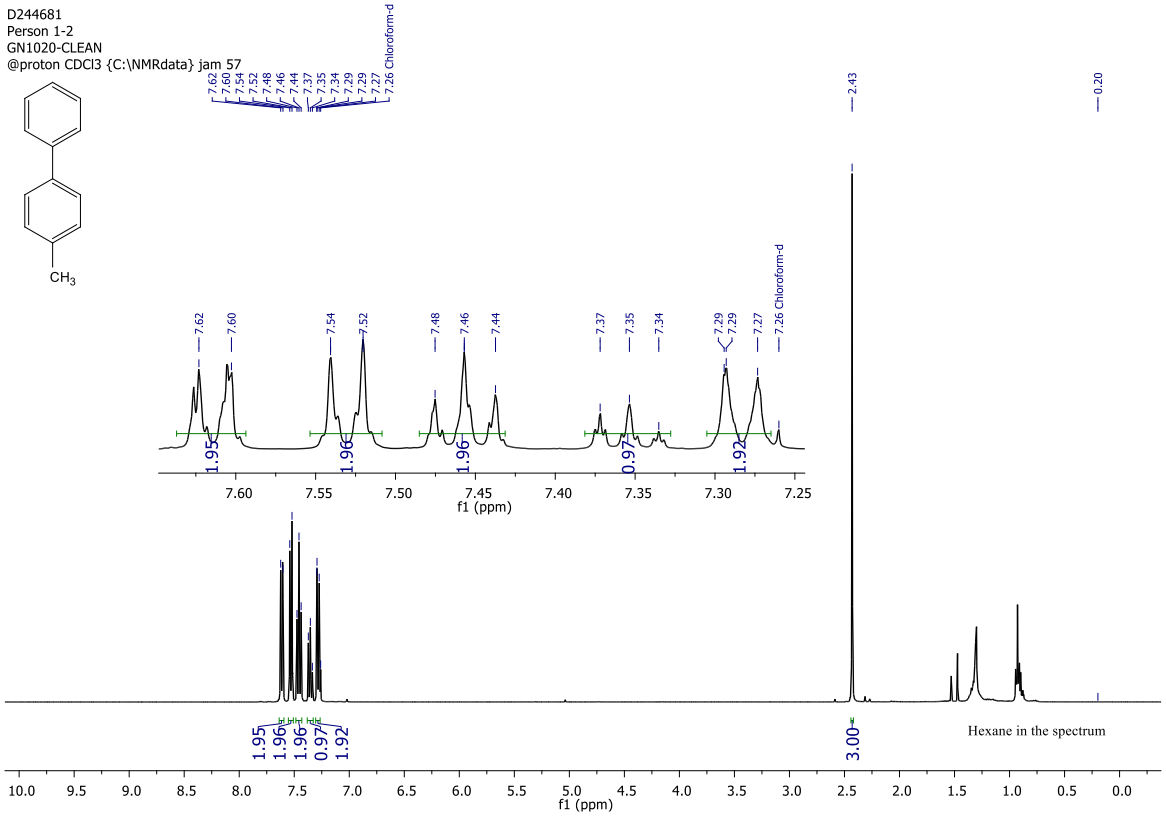


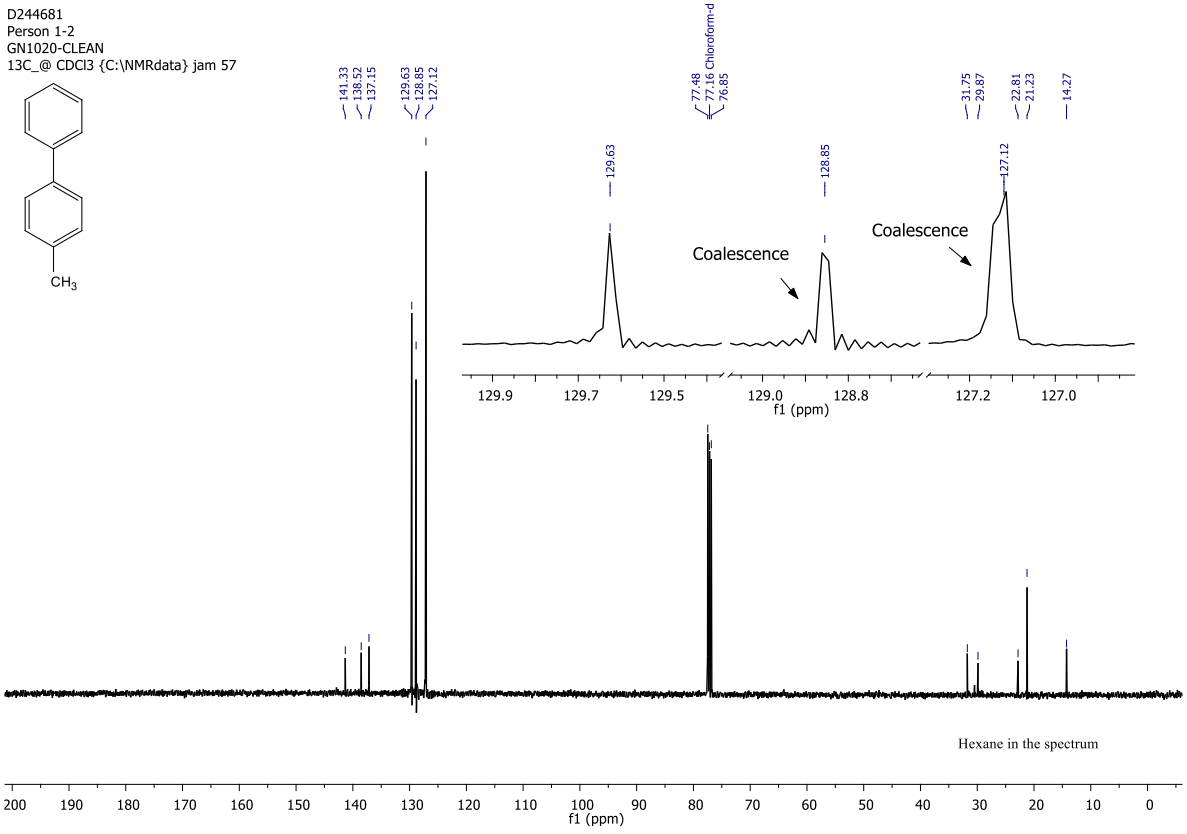
1,3-Dimethoxybenzene, 293



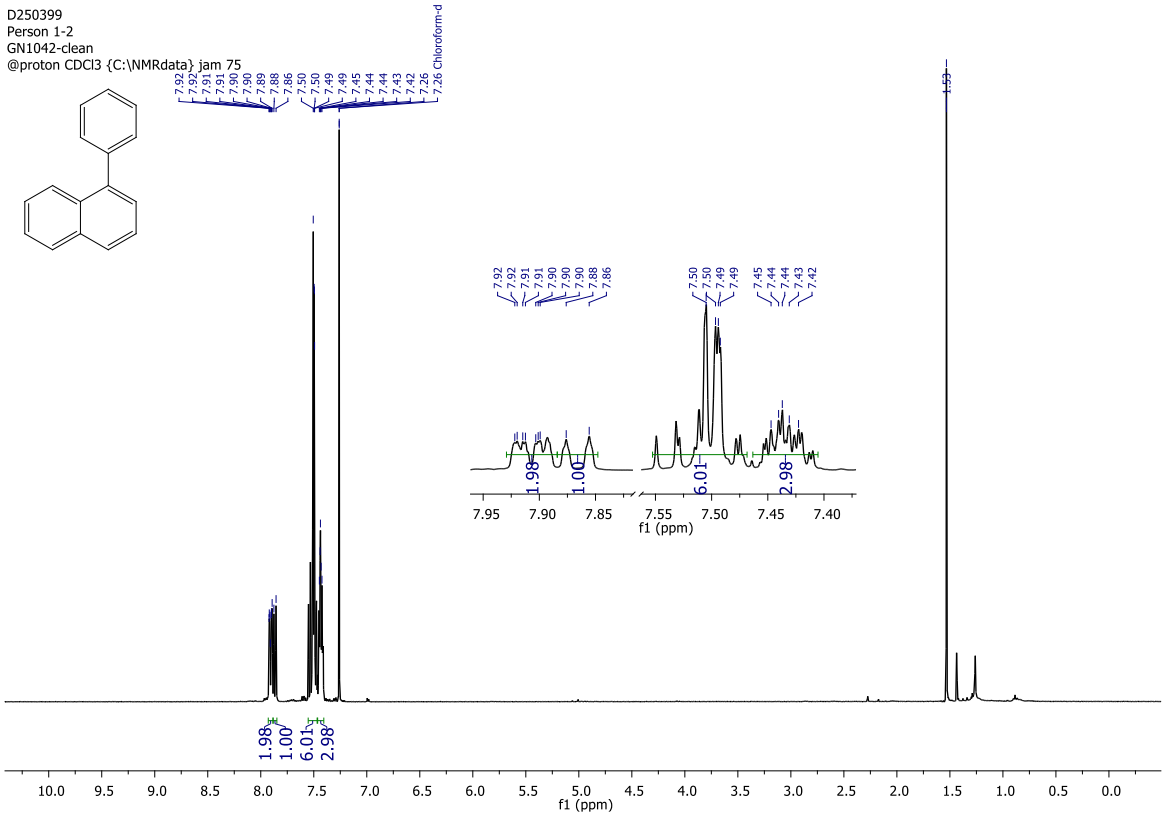


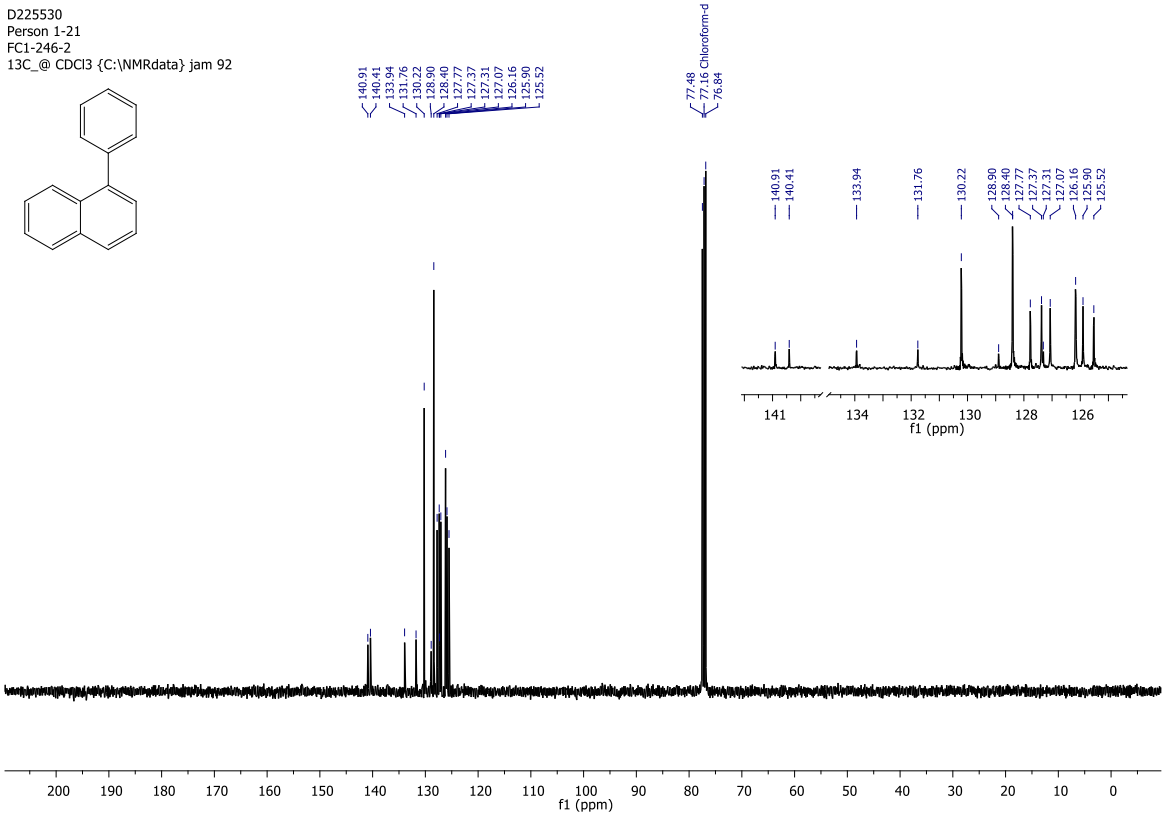
4-methyl-1,1'-biphenyl, **123**



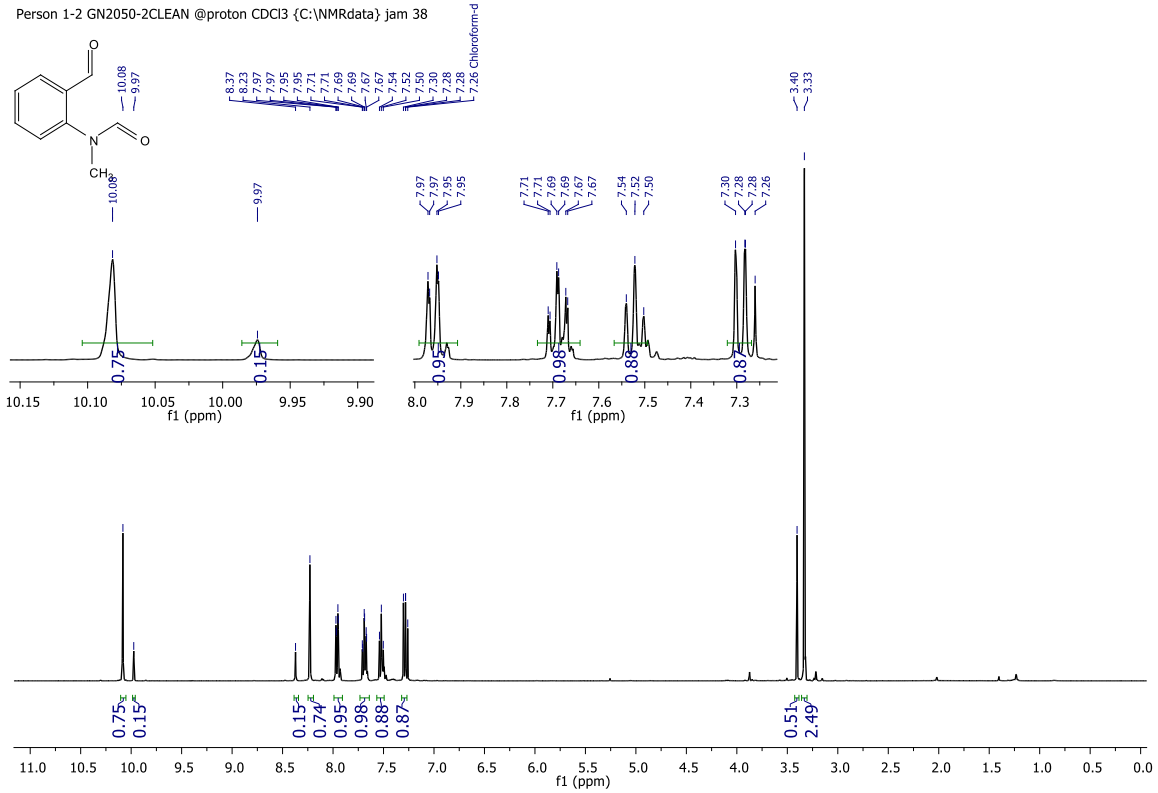


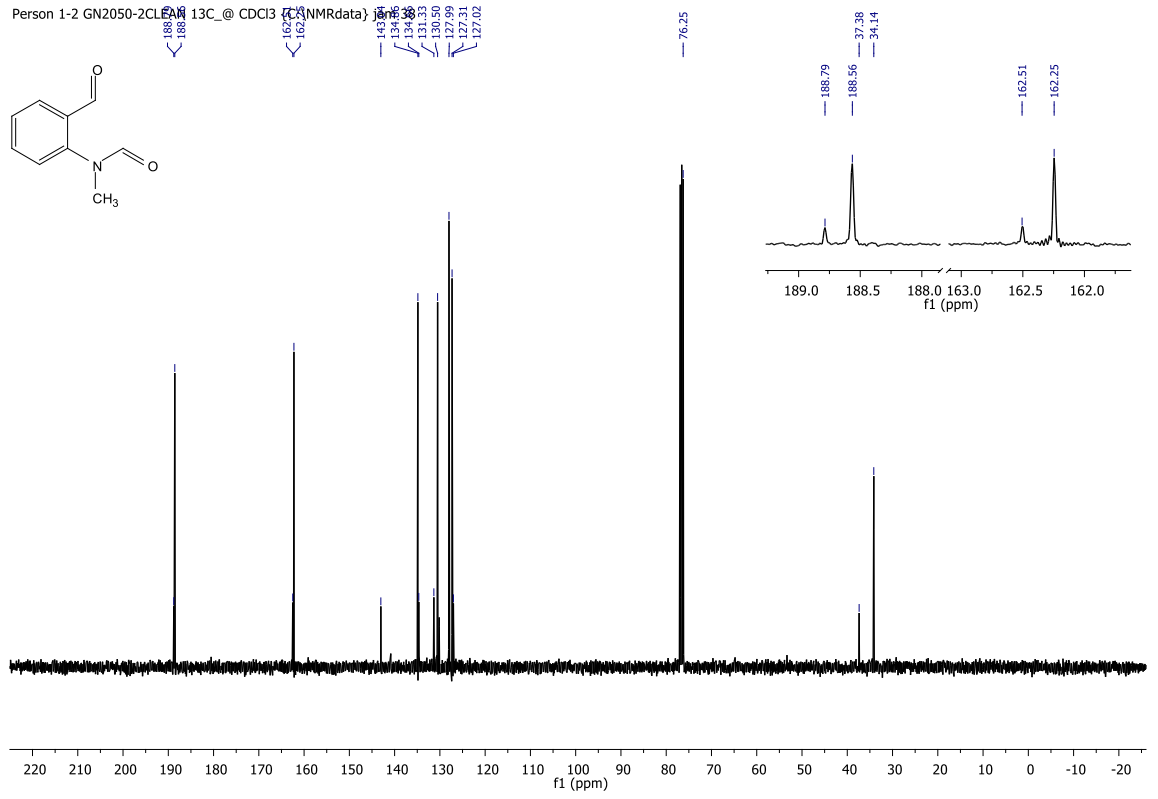
1-phenylnaphthalene, **311**



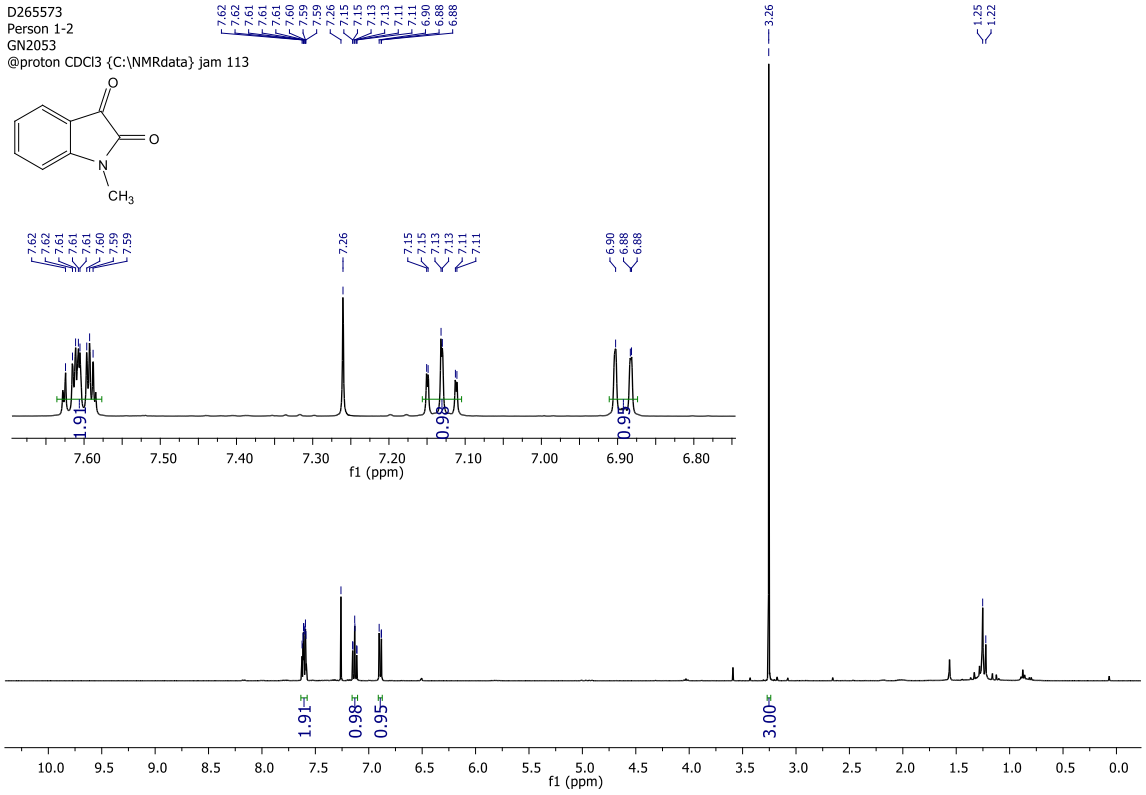


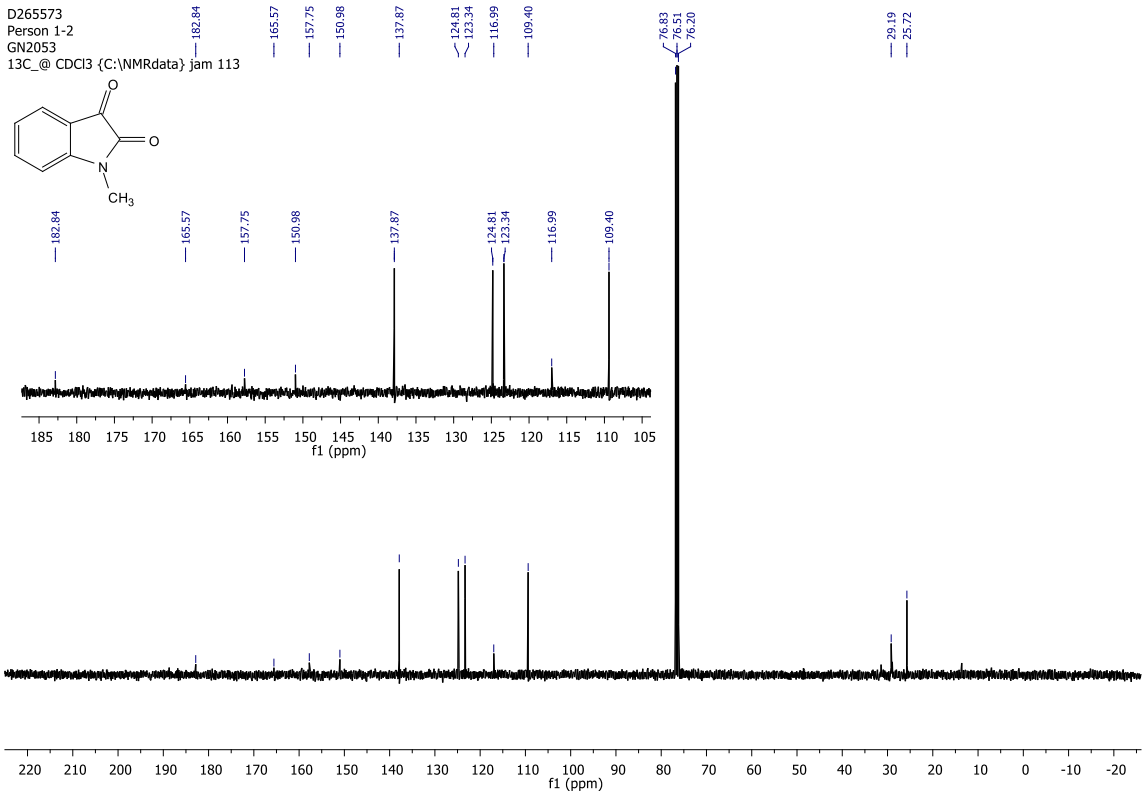
N-(2-formylphenyl)-N-methylformamide, **7**



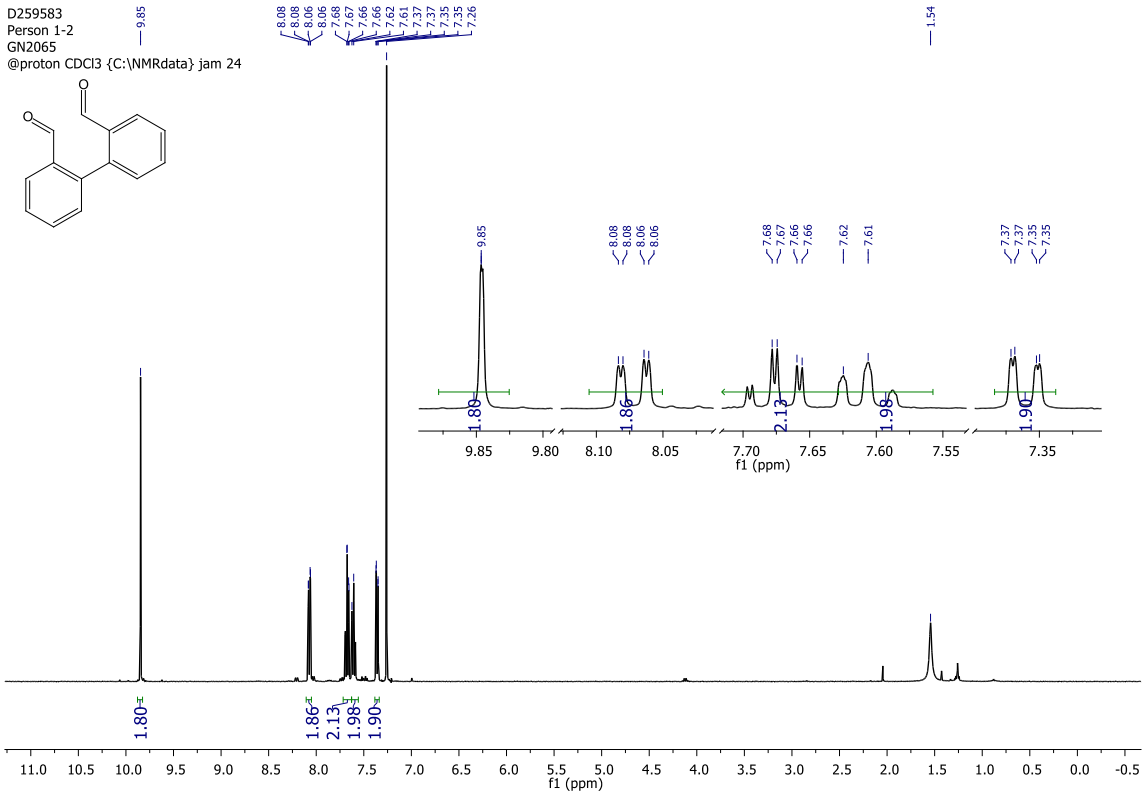


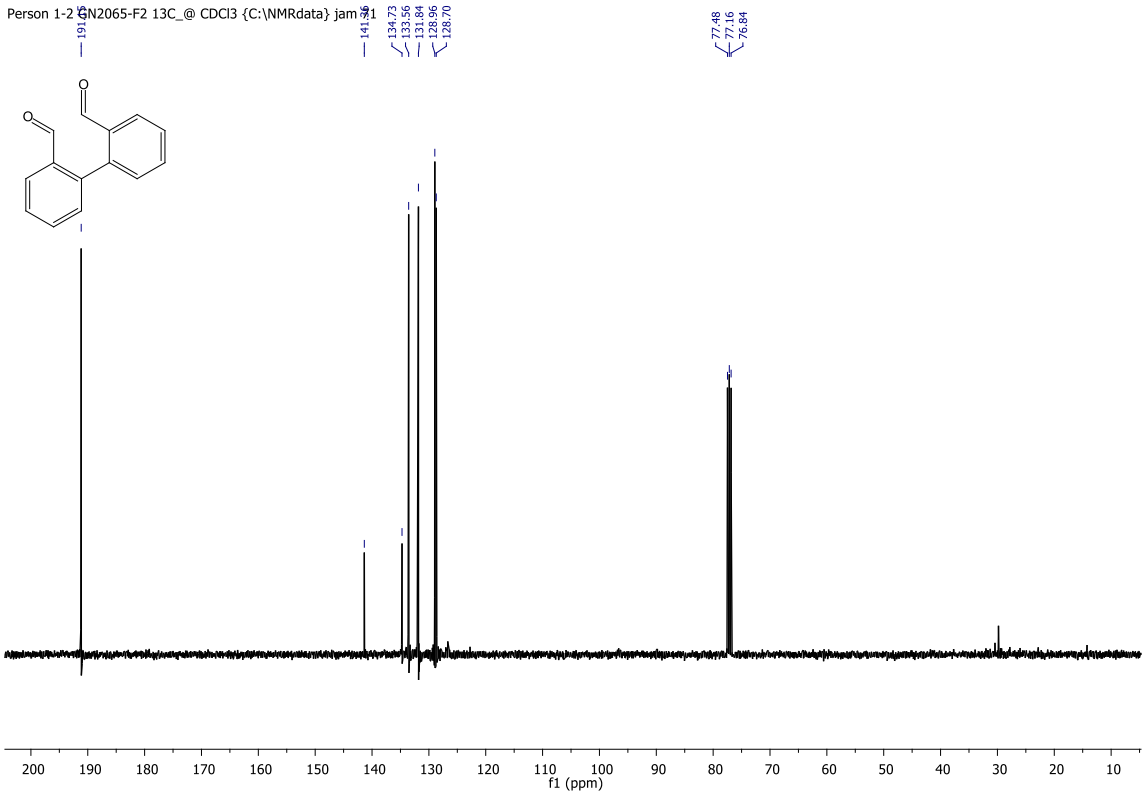
N-methylisatin, **8**



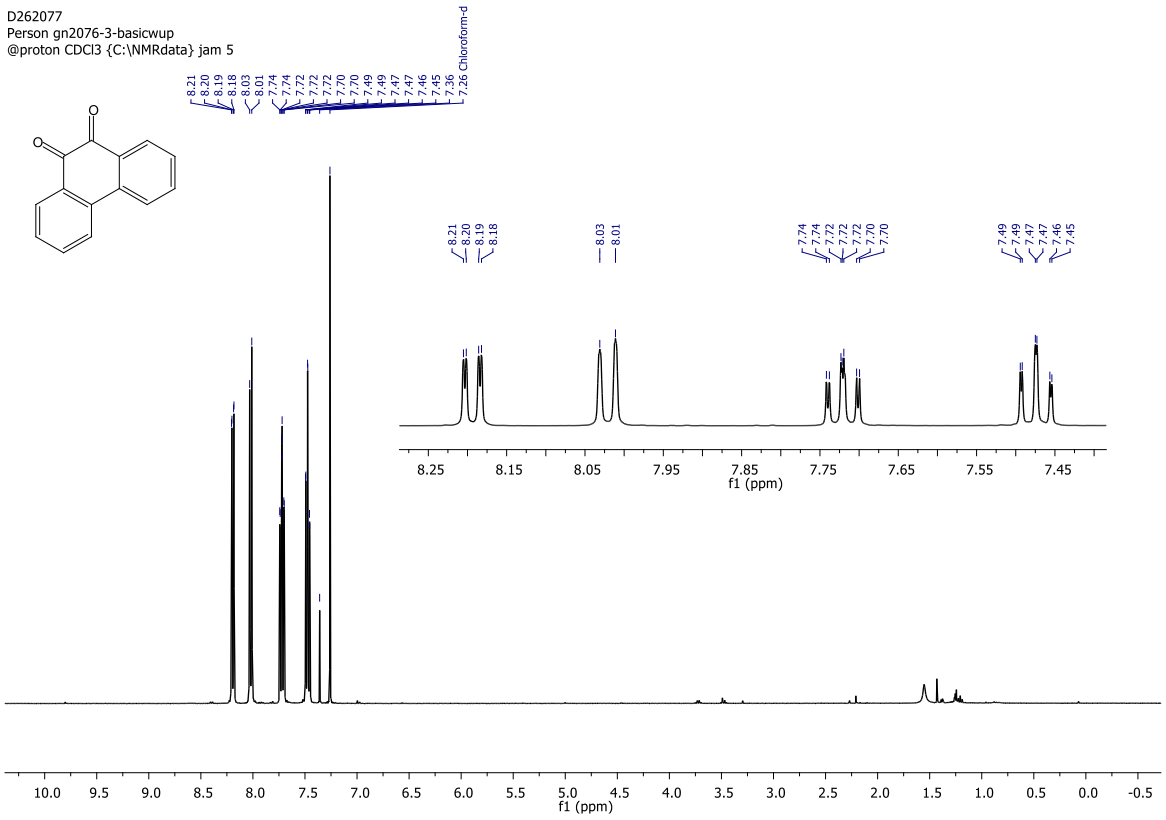


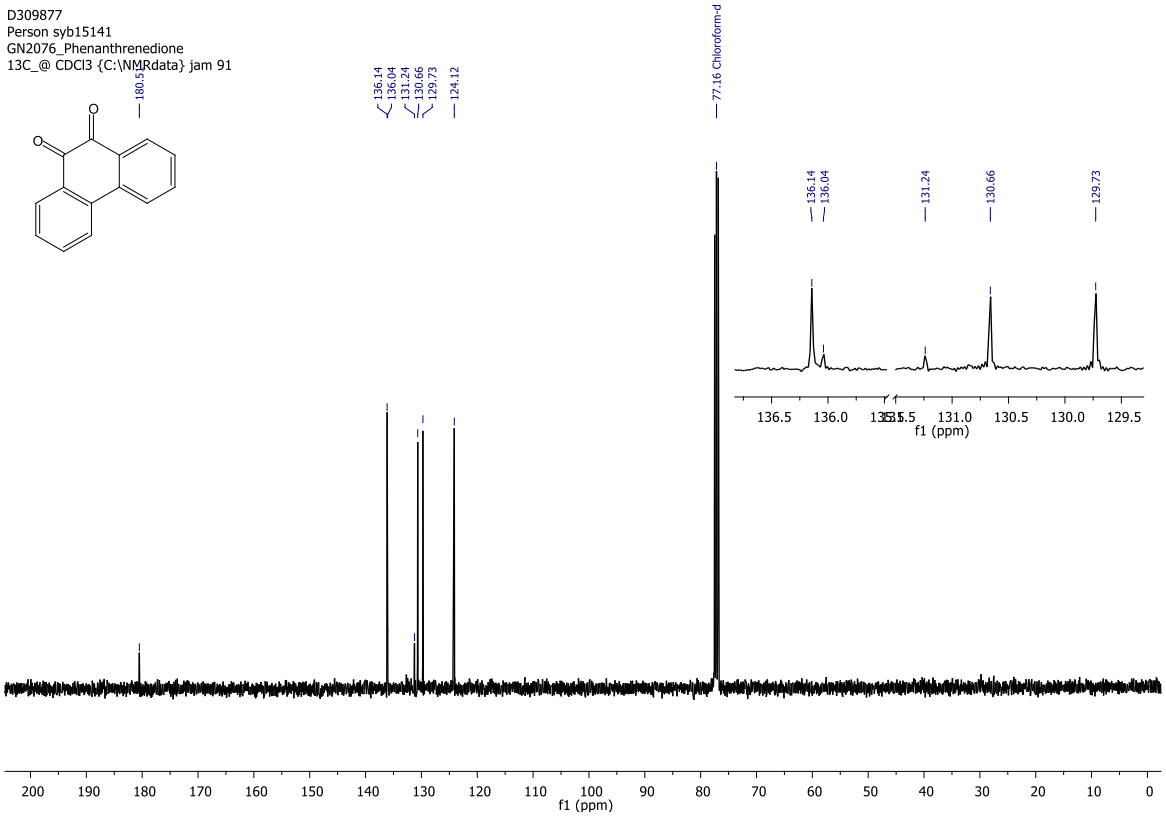
[1,1'-Biphenyl]-2,2'-dicarbaldehyde, **5**



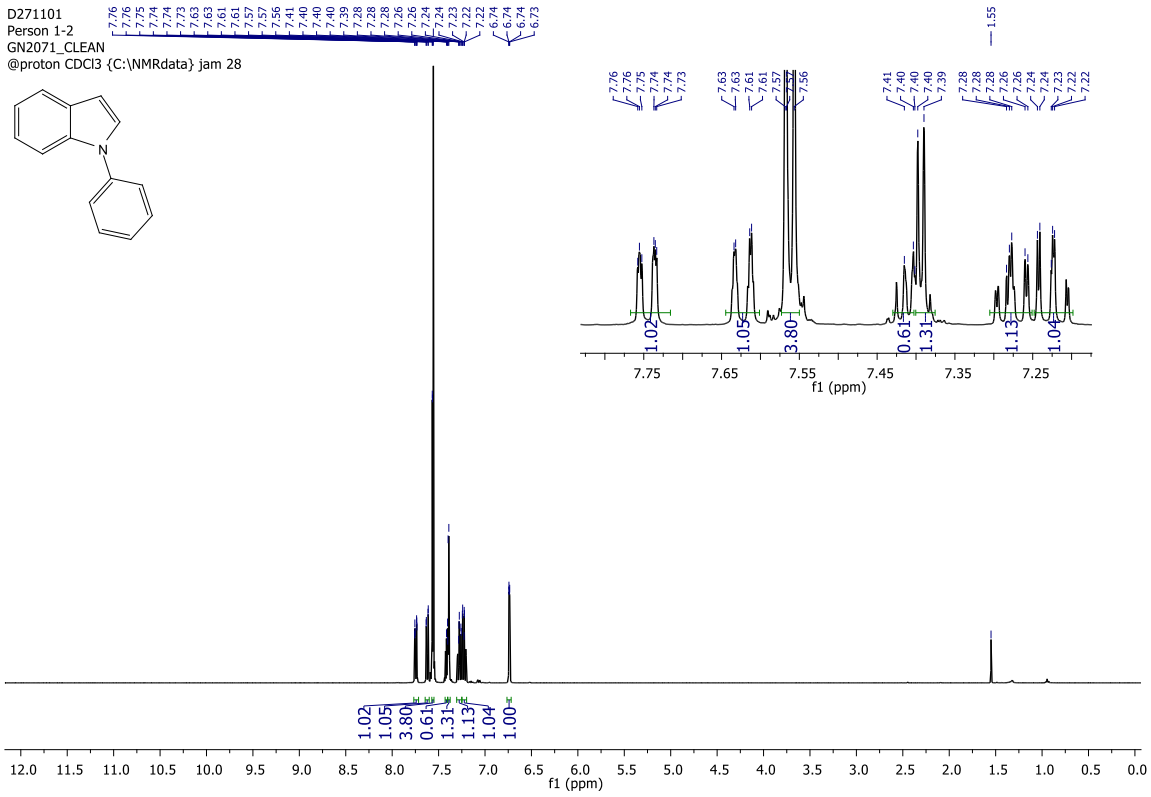


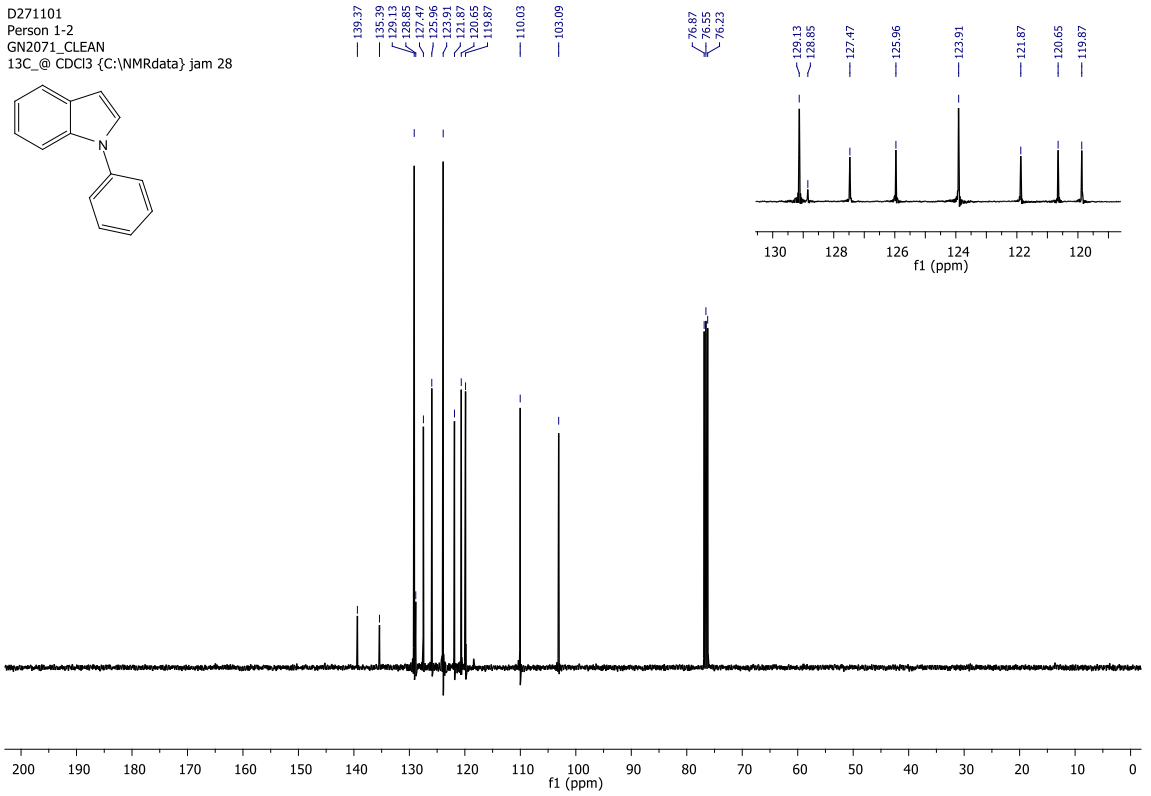
Phenanthrene-9,10-dione, **6**



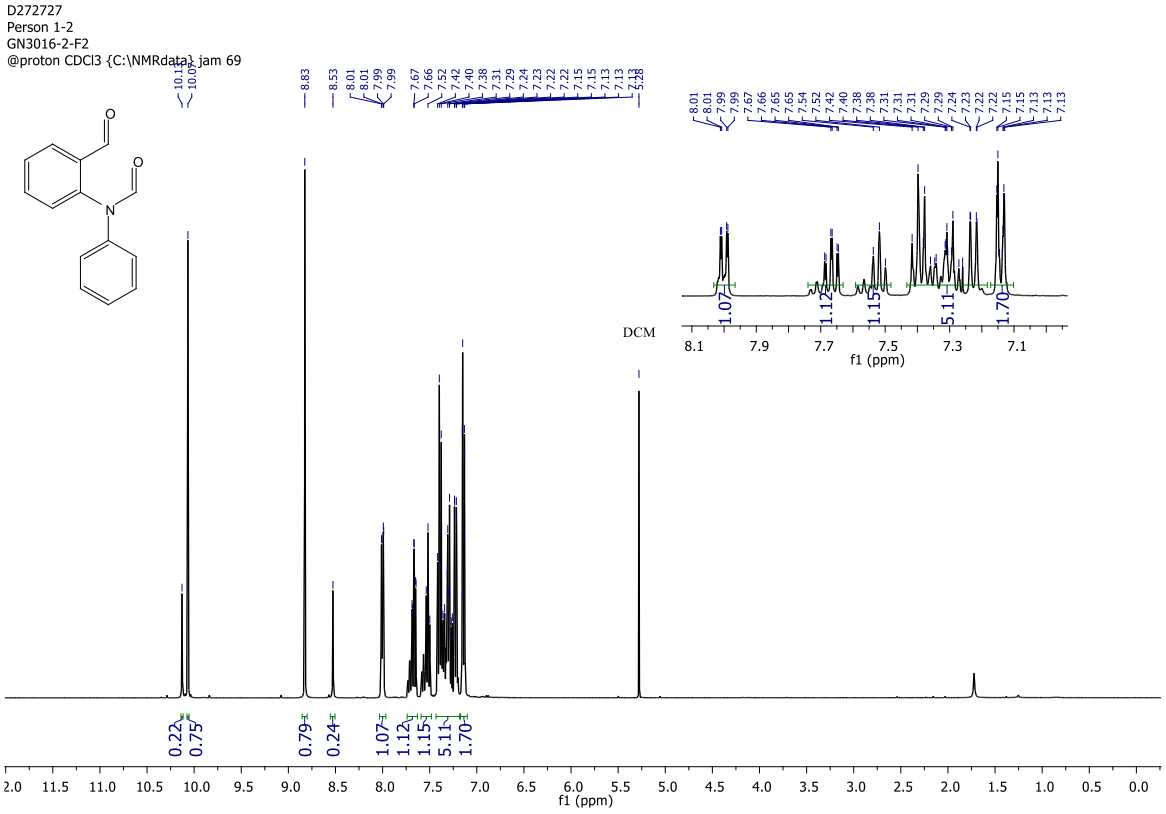


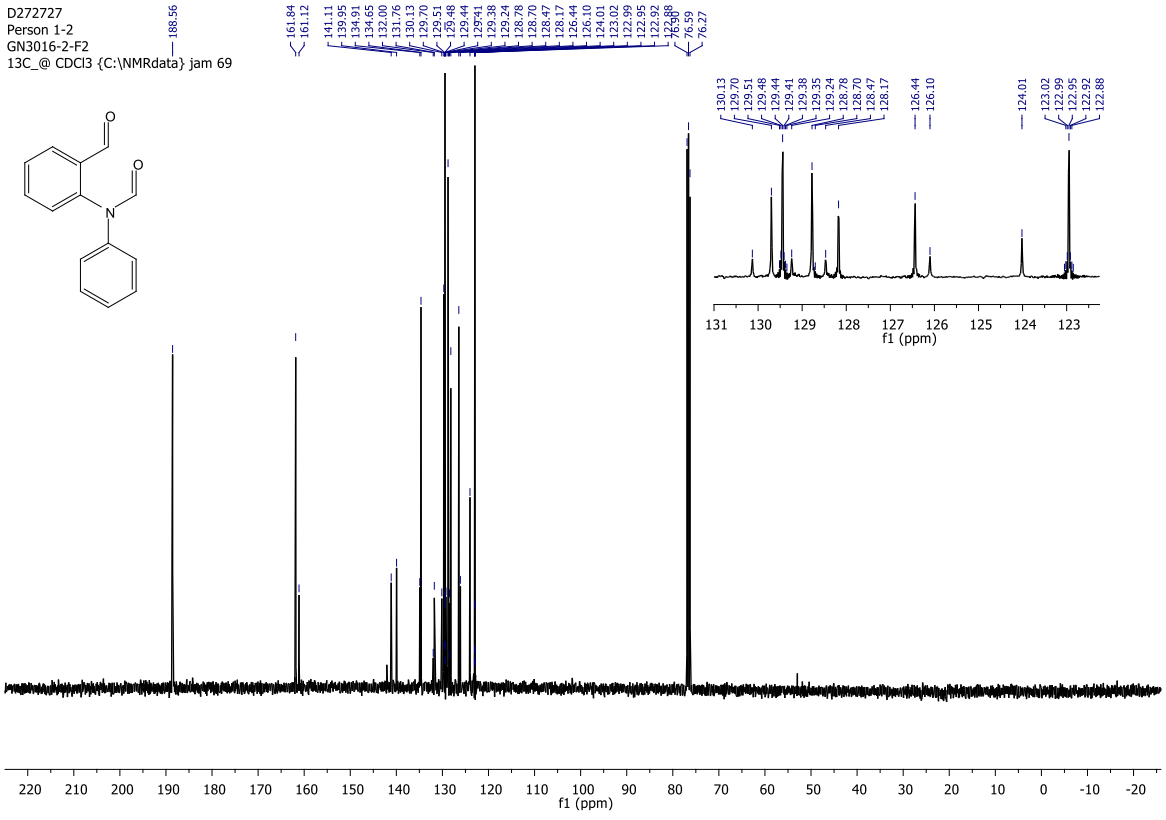
1-phenyl-1H-indole, **382**



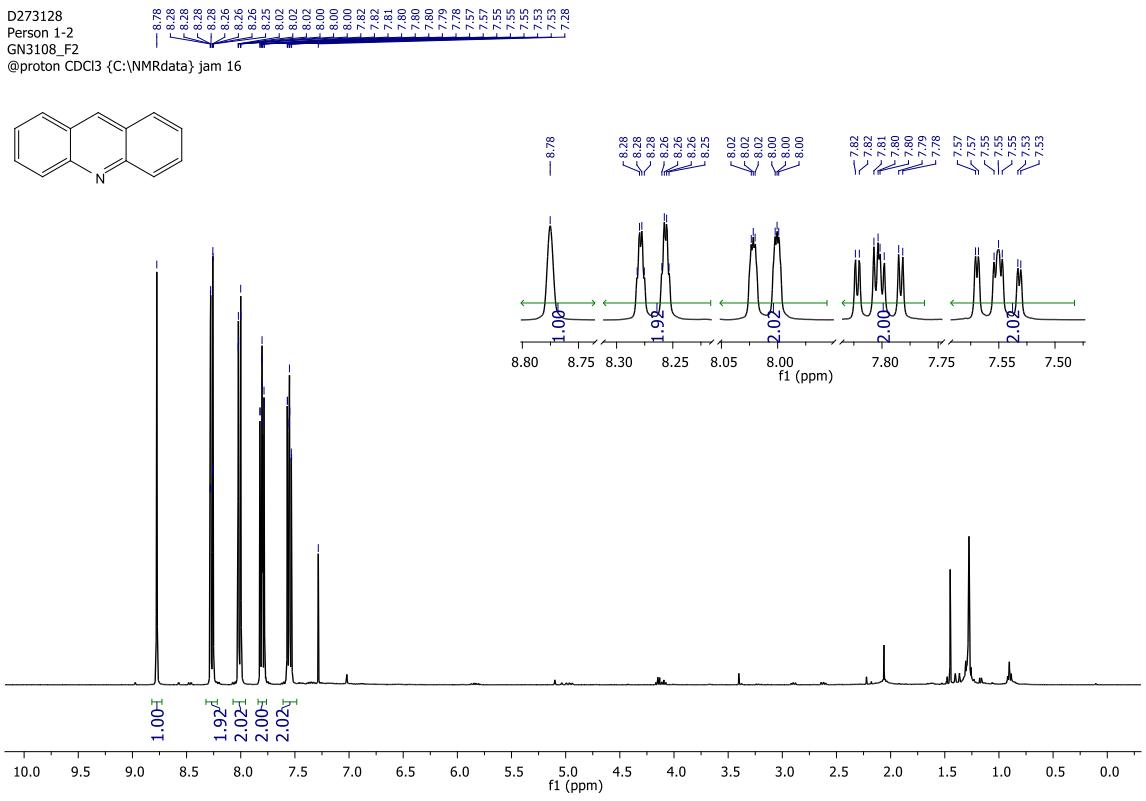


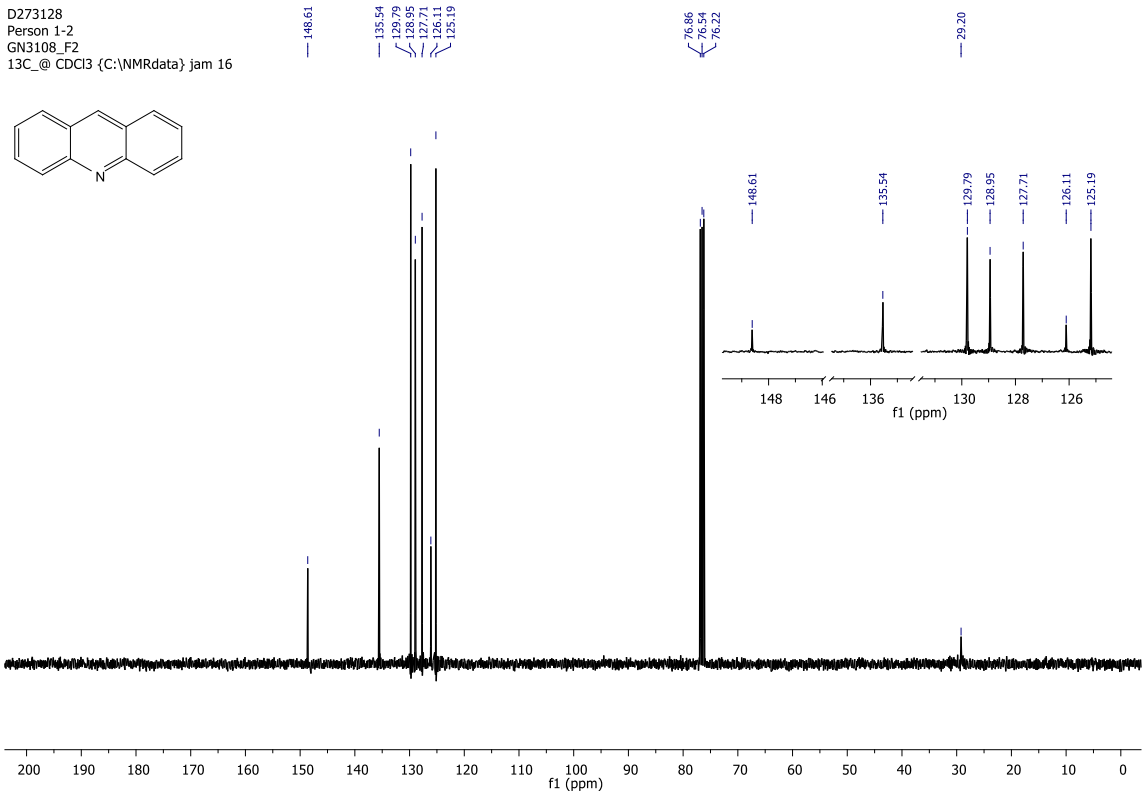
N-(2-formylphenyl)-N-phenylformamide, **383**



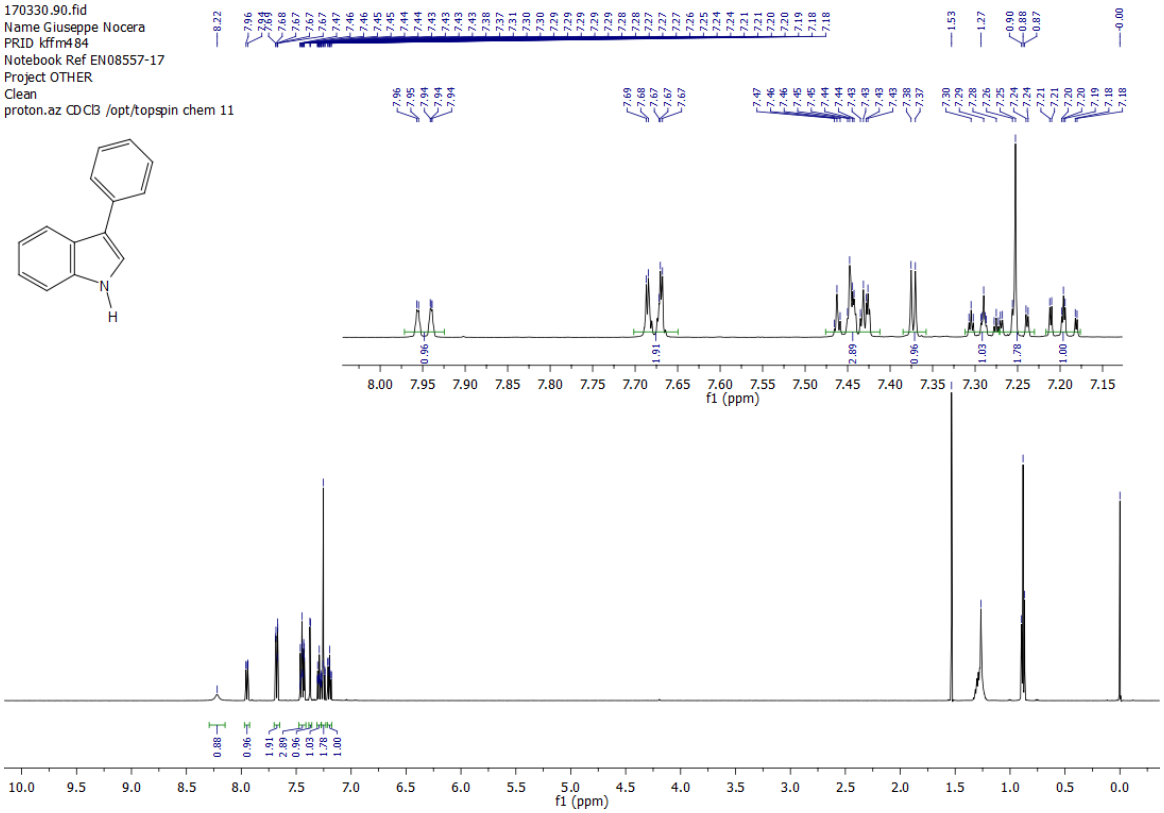


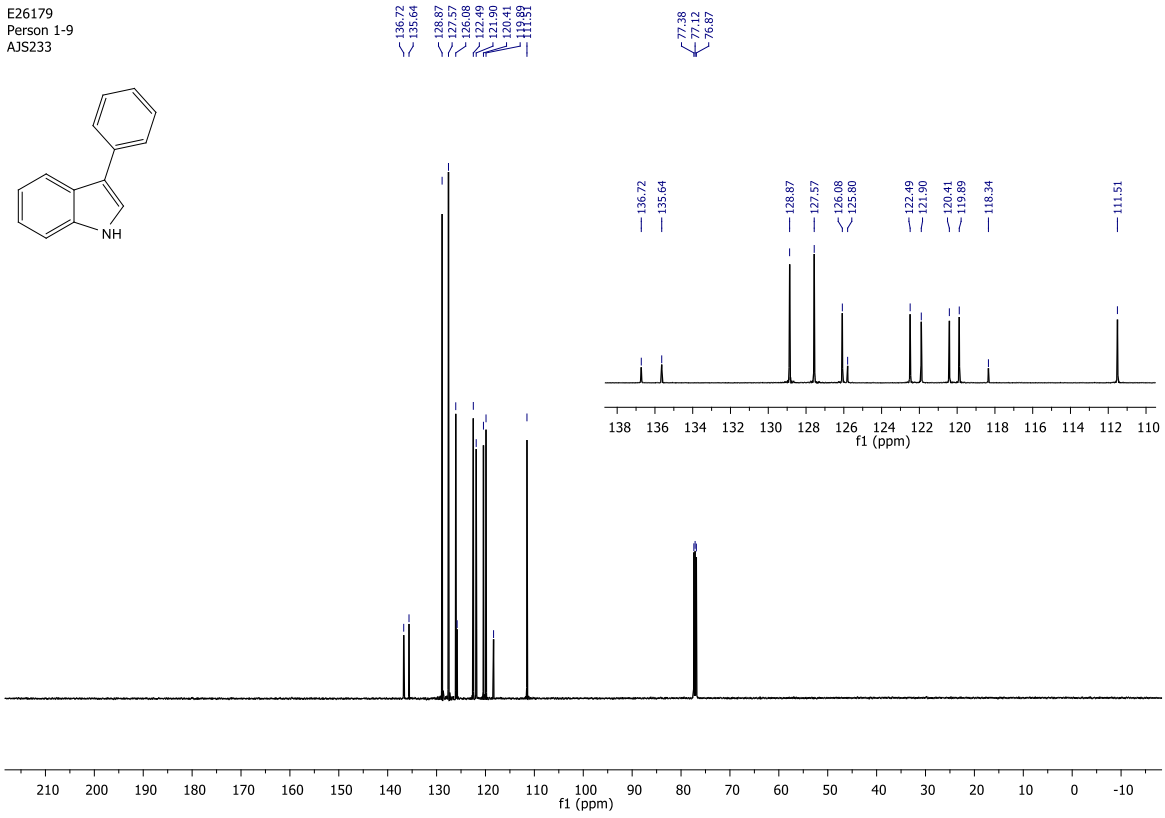
Acridine, **384**



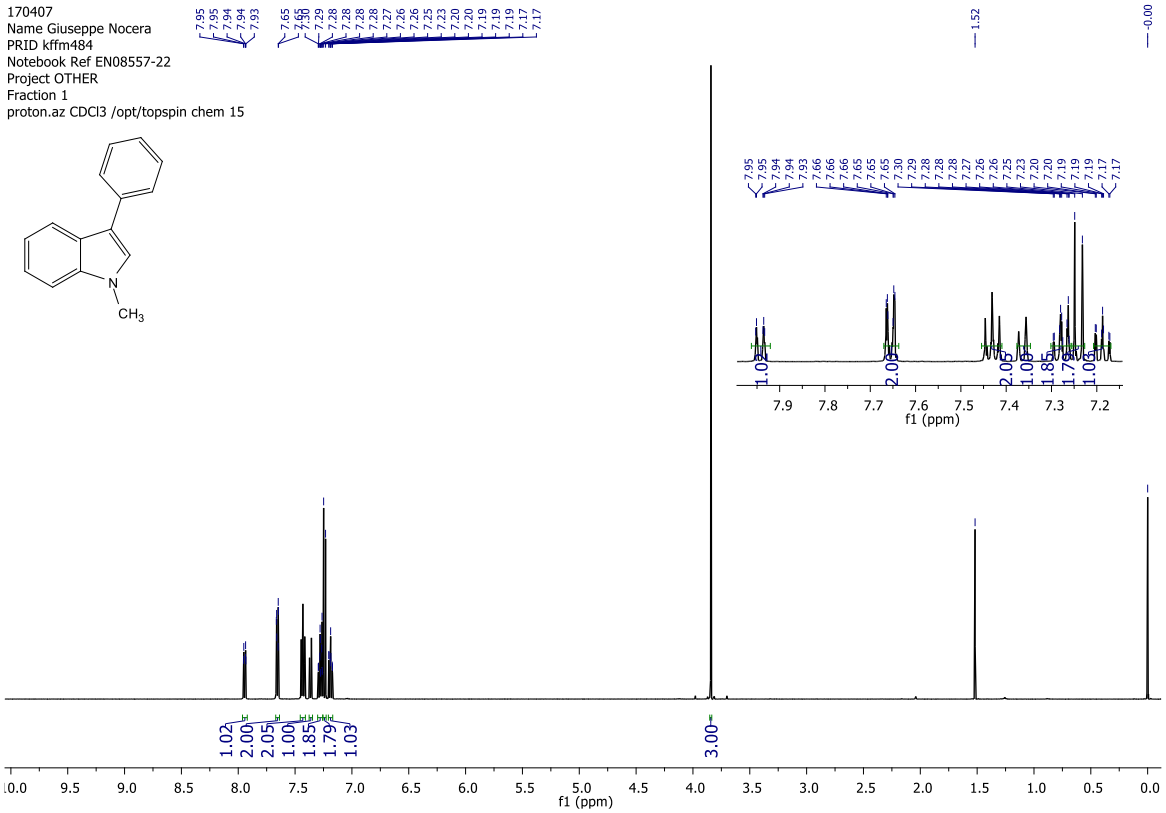


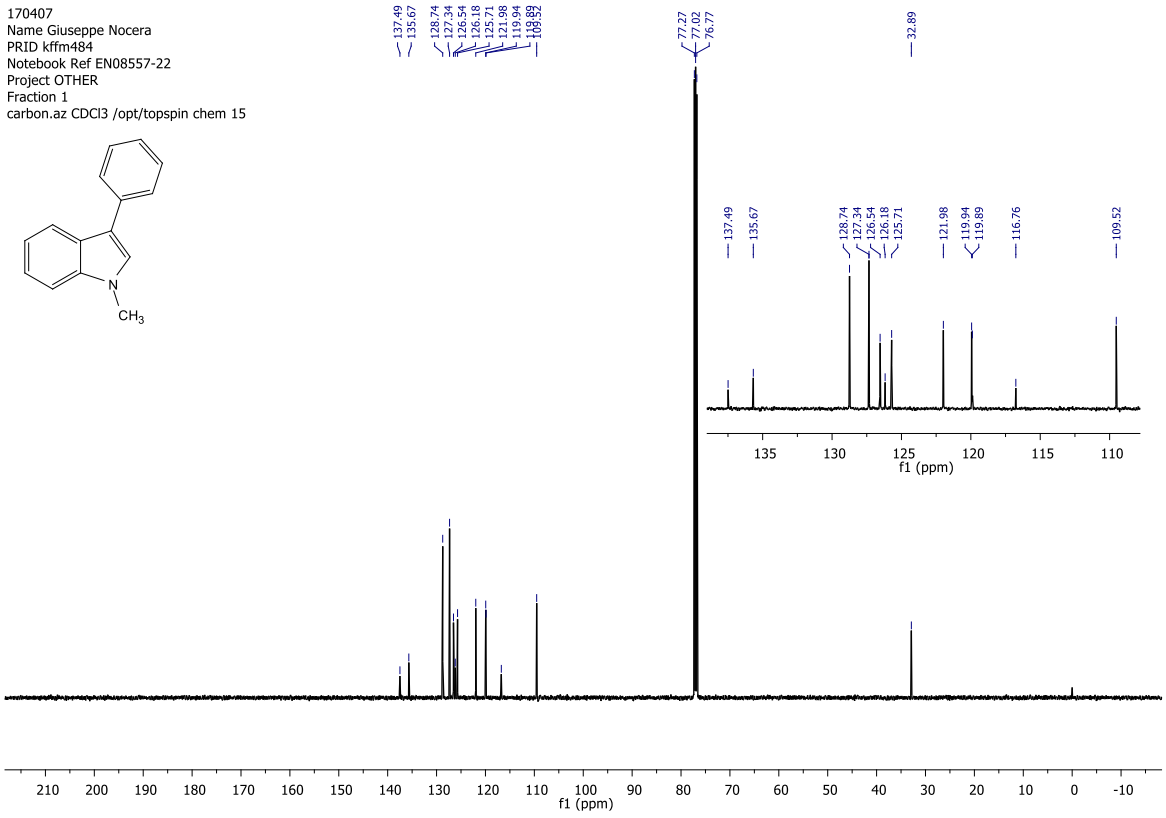
3-phenyl-1H-indole, **392**



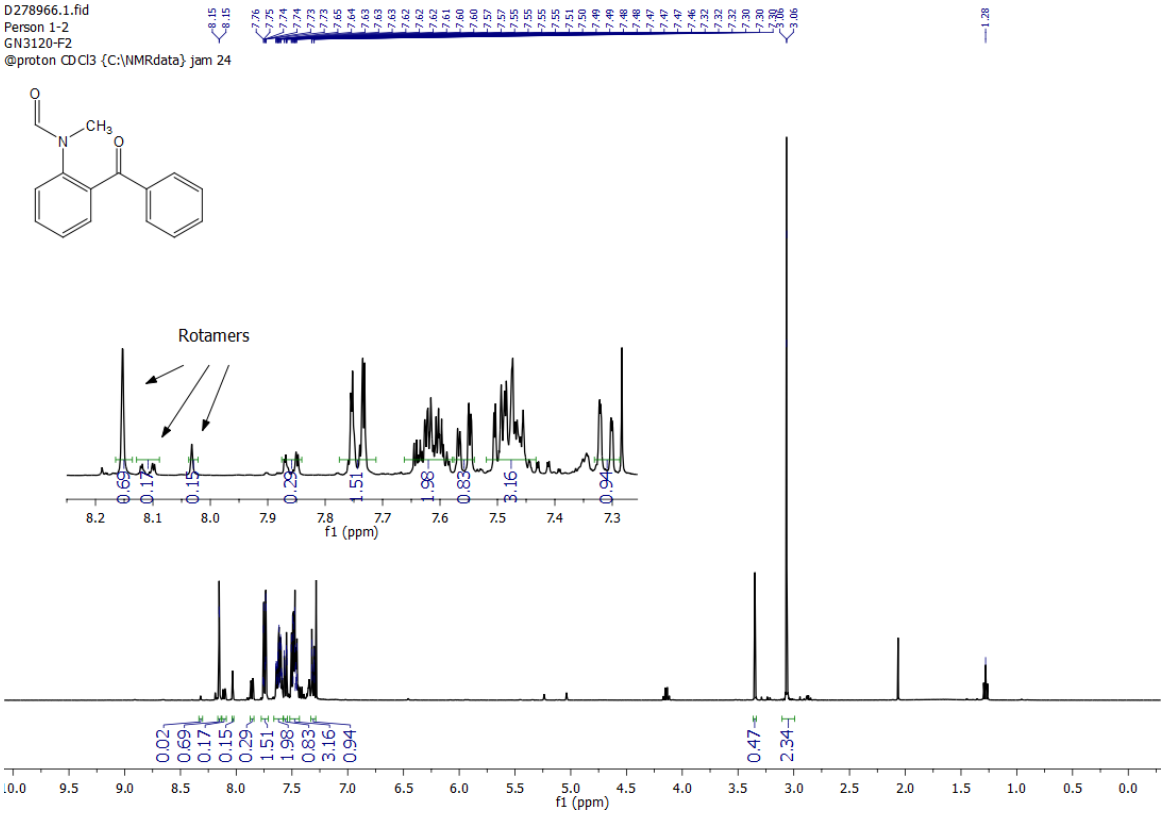


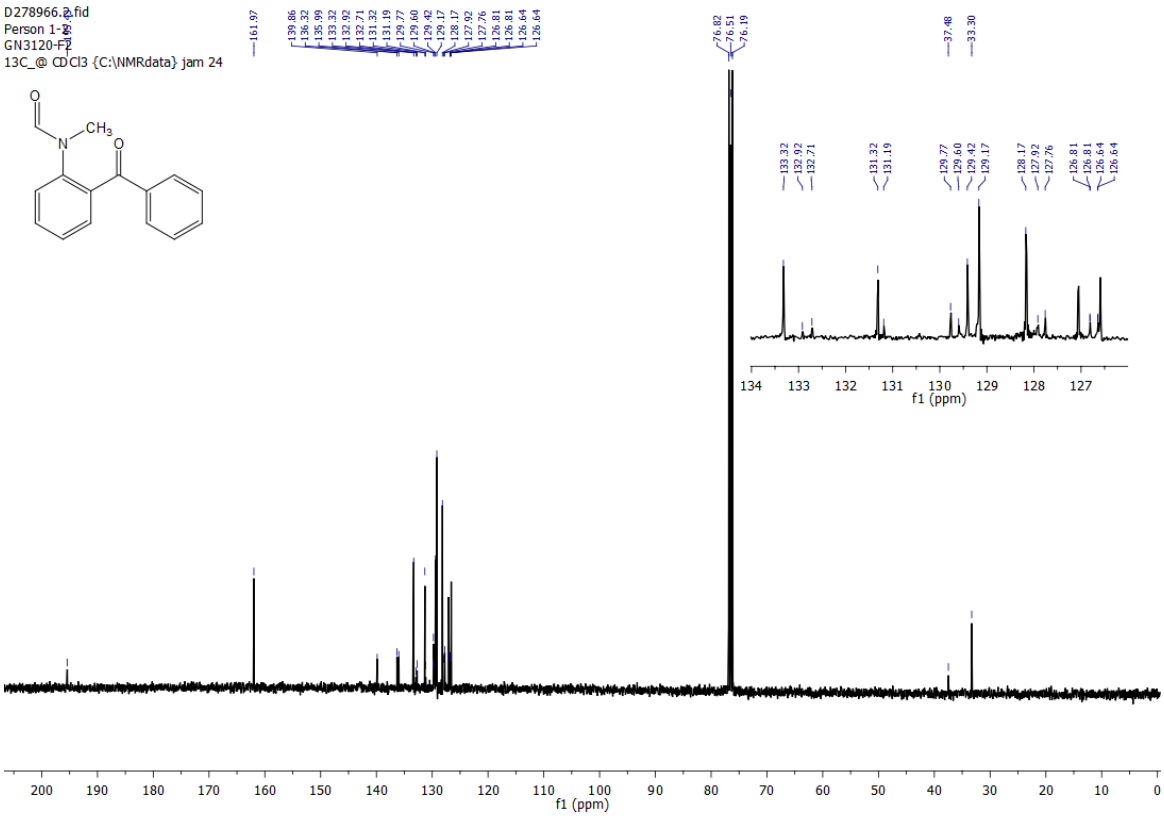
1-methyl-3-phenyl-1H-indole, **393**



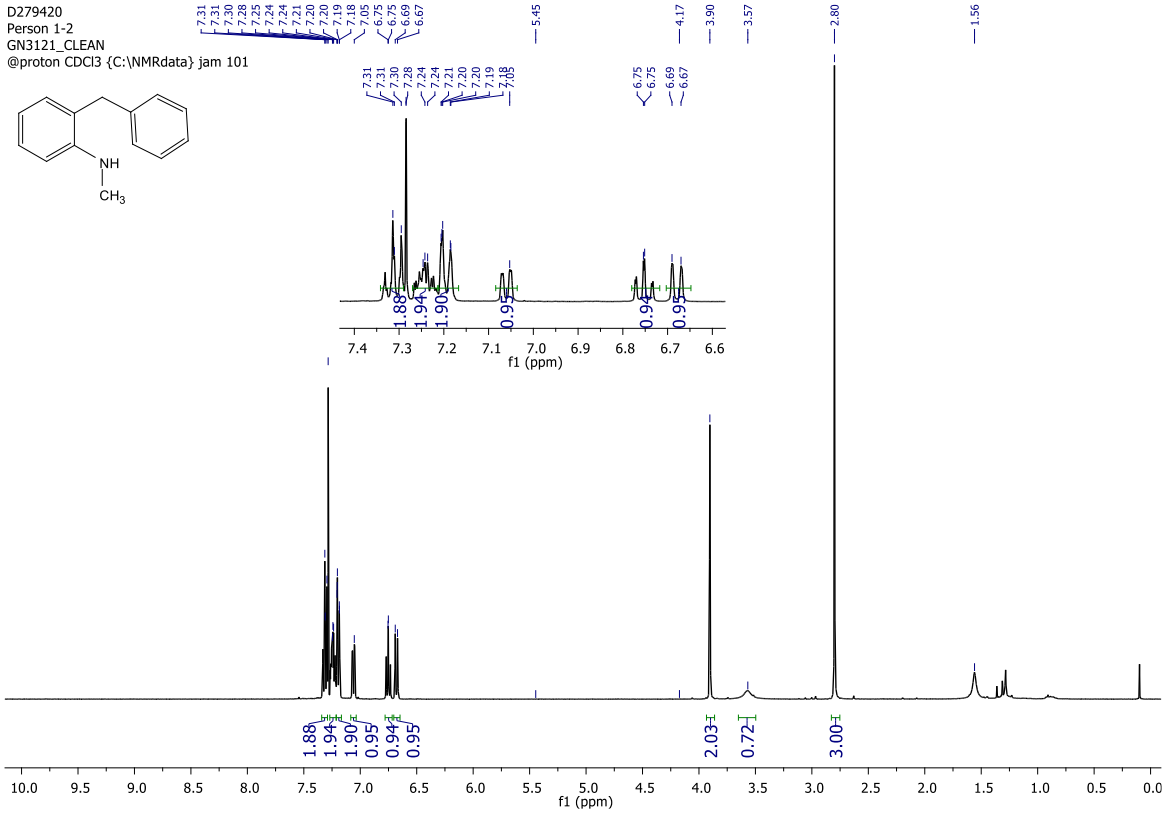


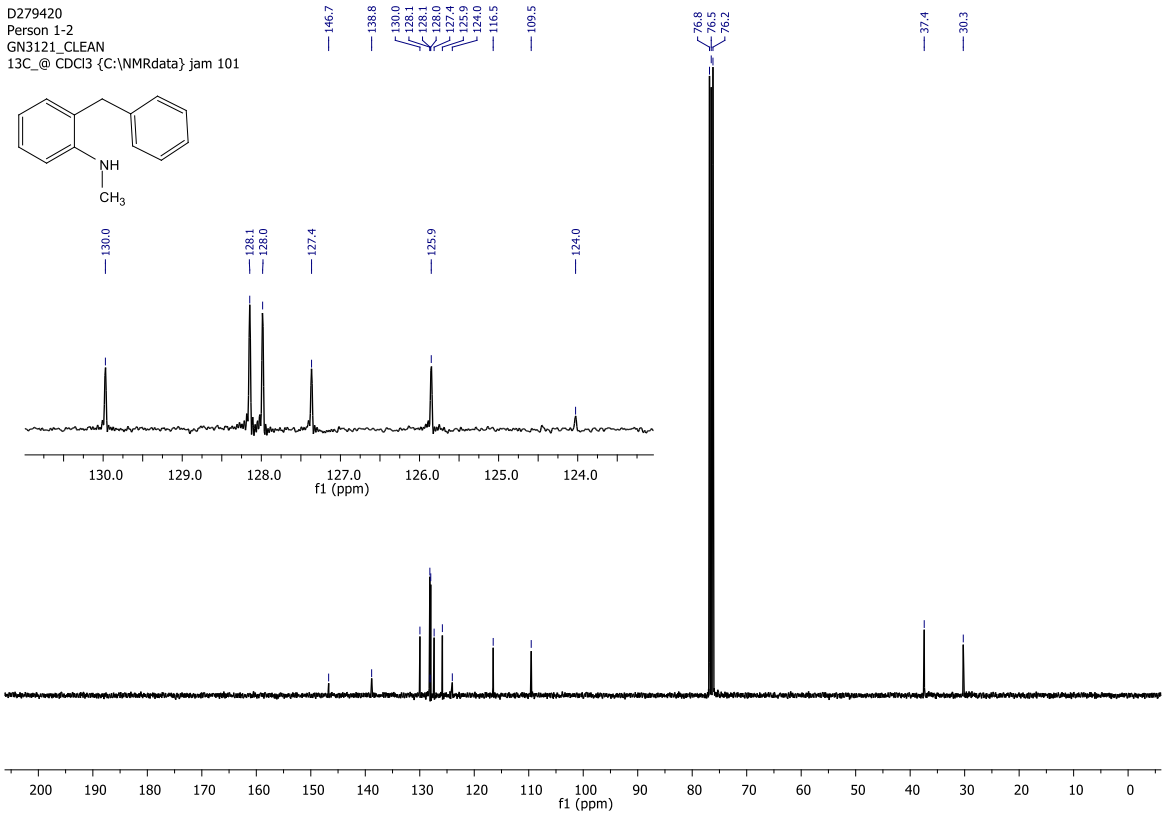
N-(2-benzoylphenyl)-N-methylformamide, **394**



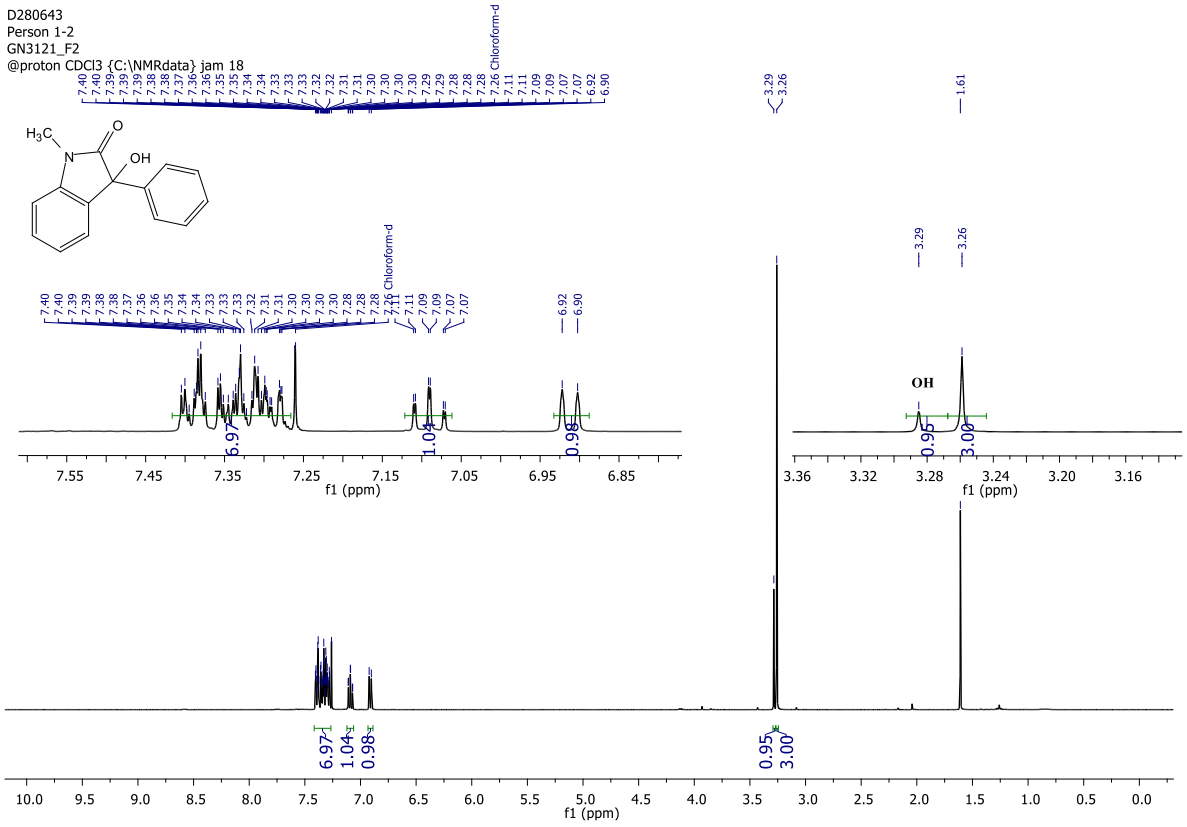


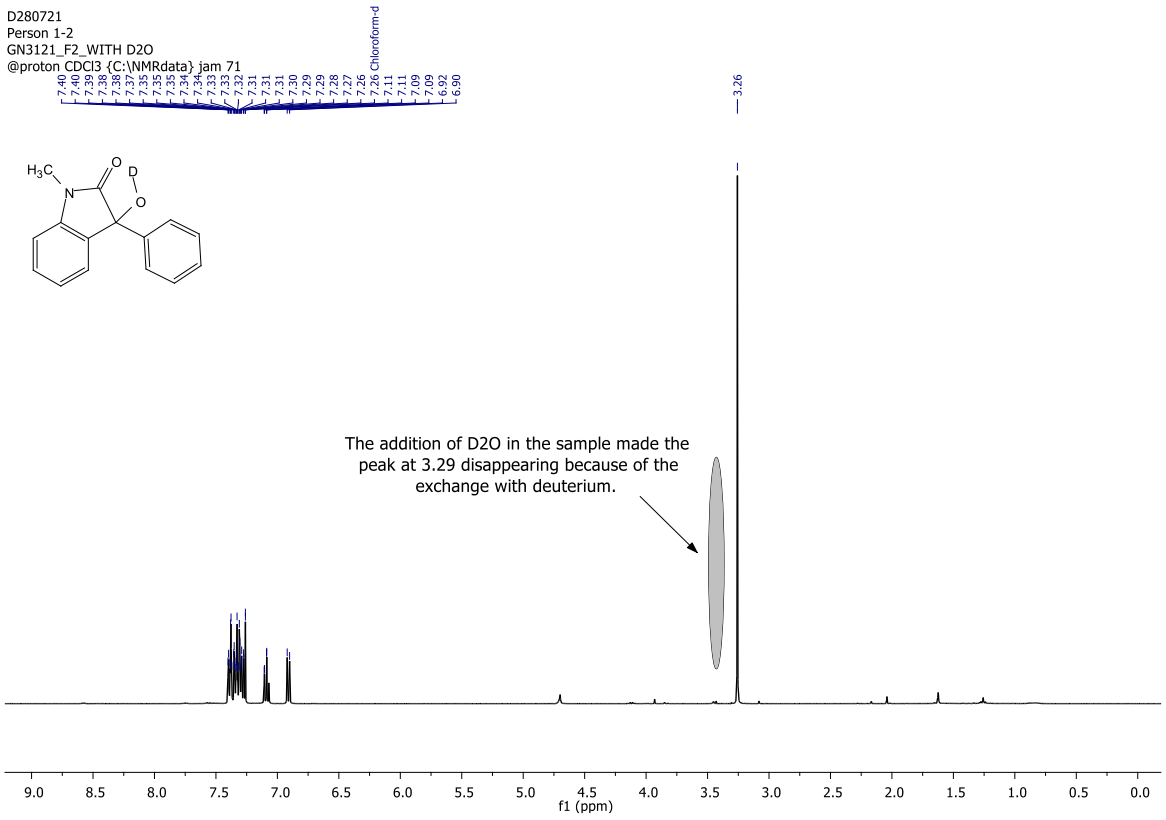
2-benzyl-N-methylaniline, **396**

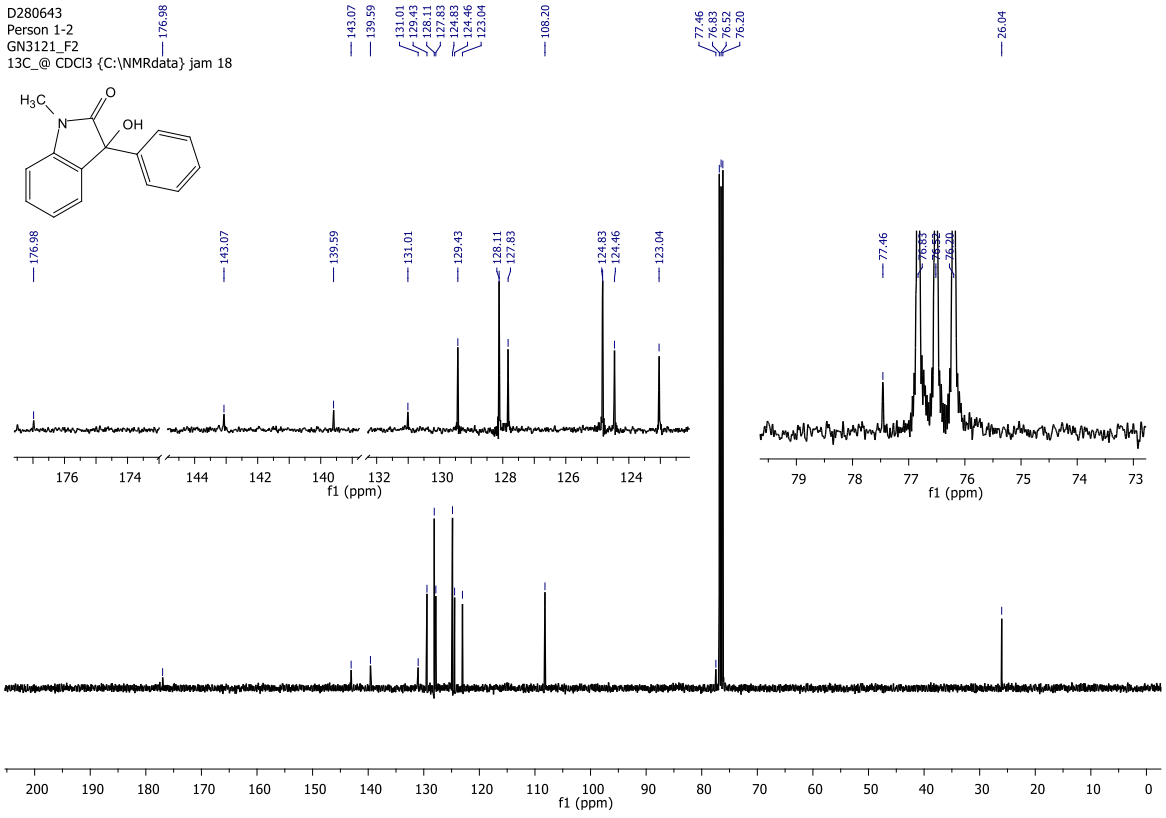




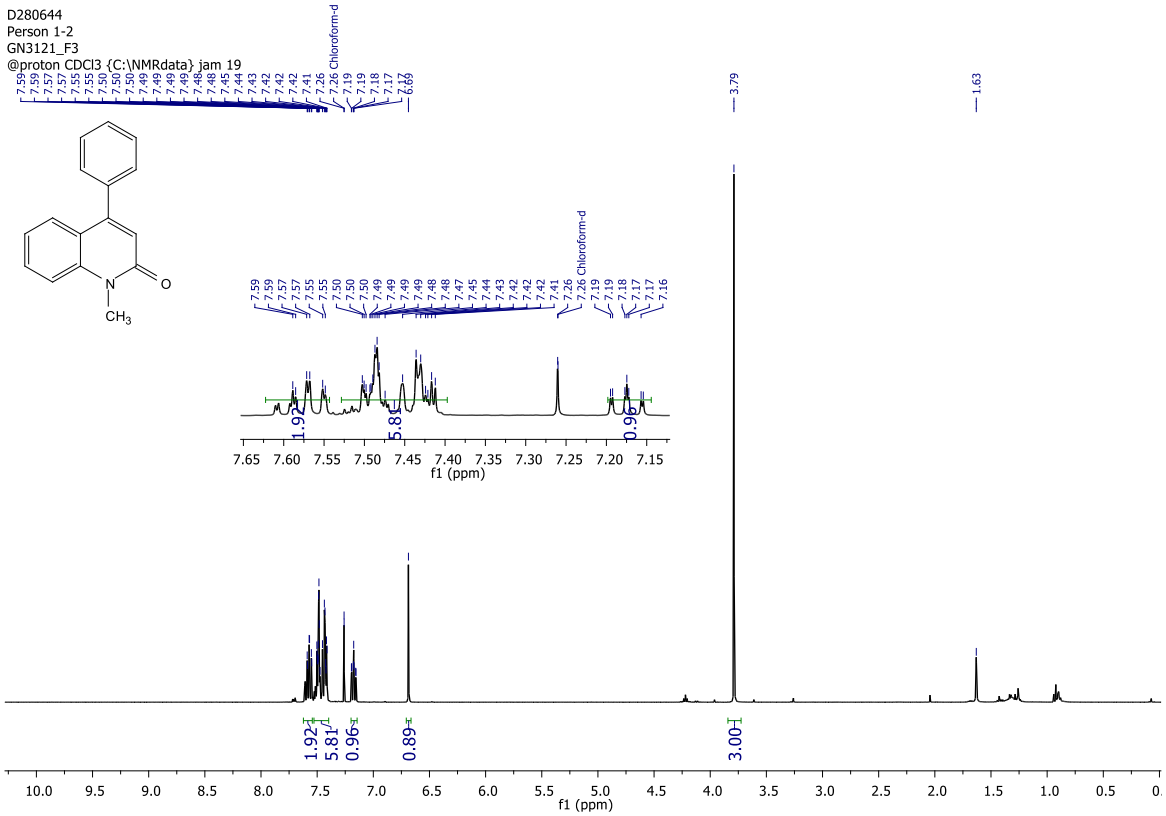
3-hydroxy-1-methyl-3-phenylindolin-2-one, **395**

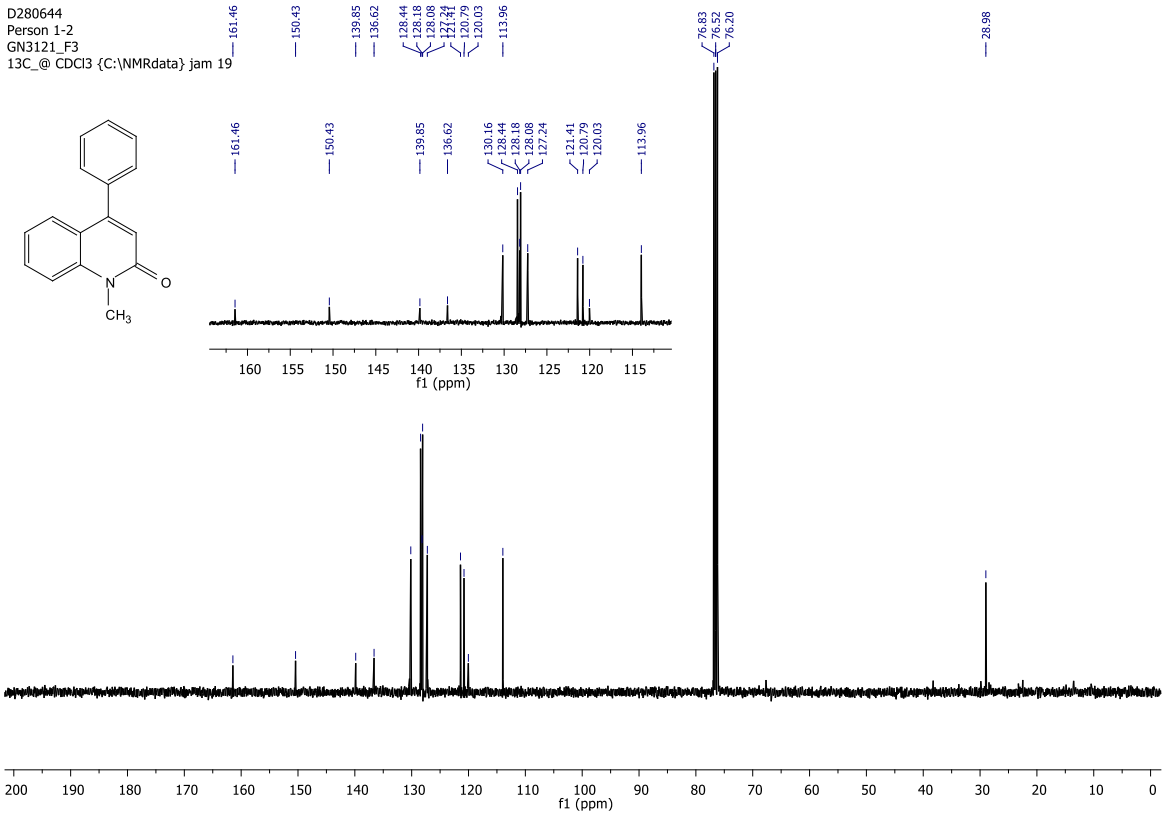



D280721
Person 1-2
GN3121_F2_WITH D2O
@proton CDCl3 {C:\NMRdata} jam 71
Chloroform-d
3.26
The addition of D2O in the sample made the peak at 3.29 disappearing because of the exchange with deuterium.
f1 (ppm)

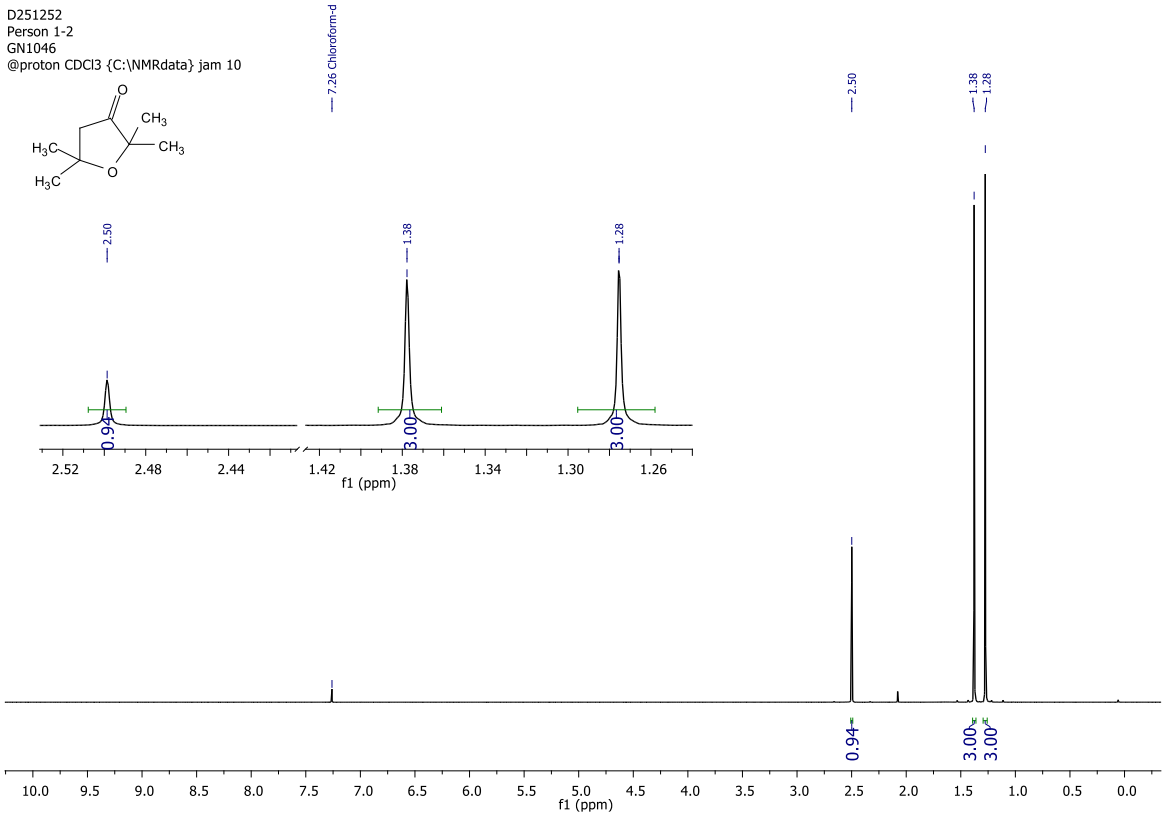

D280643
Person 1-2
GN3121_F2
13C_@ CDCl3 {C:\NMRdata} jam 18
176.98
143.07
139.59
131.01
129.43
128.11
127.83
124.83
124.46
123.04
108.20
77.46
76.83
76.52
76.20
26.04
f1 (ppm)

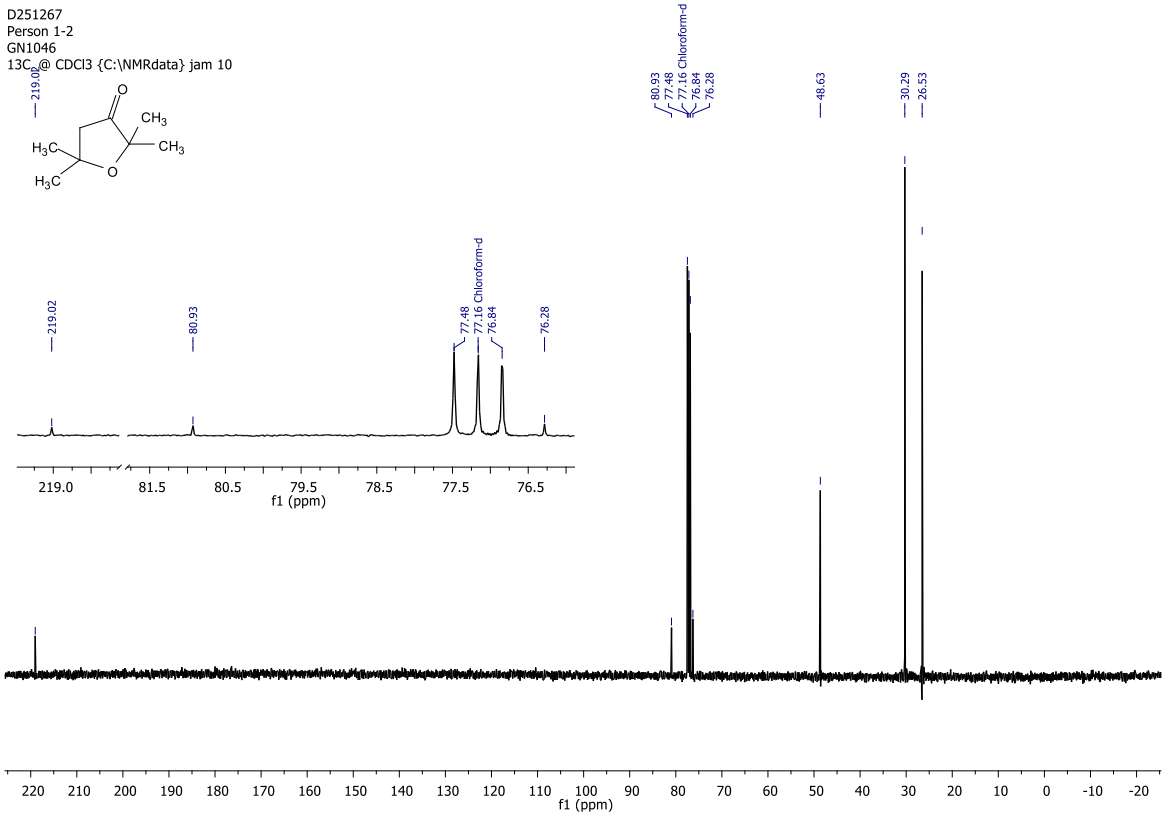
1-methyl-4-phenylquinolin-2(1H)-one, **397**



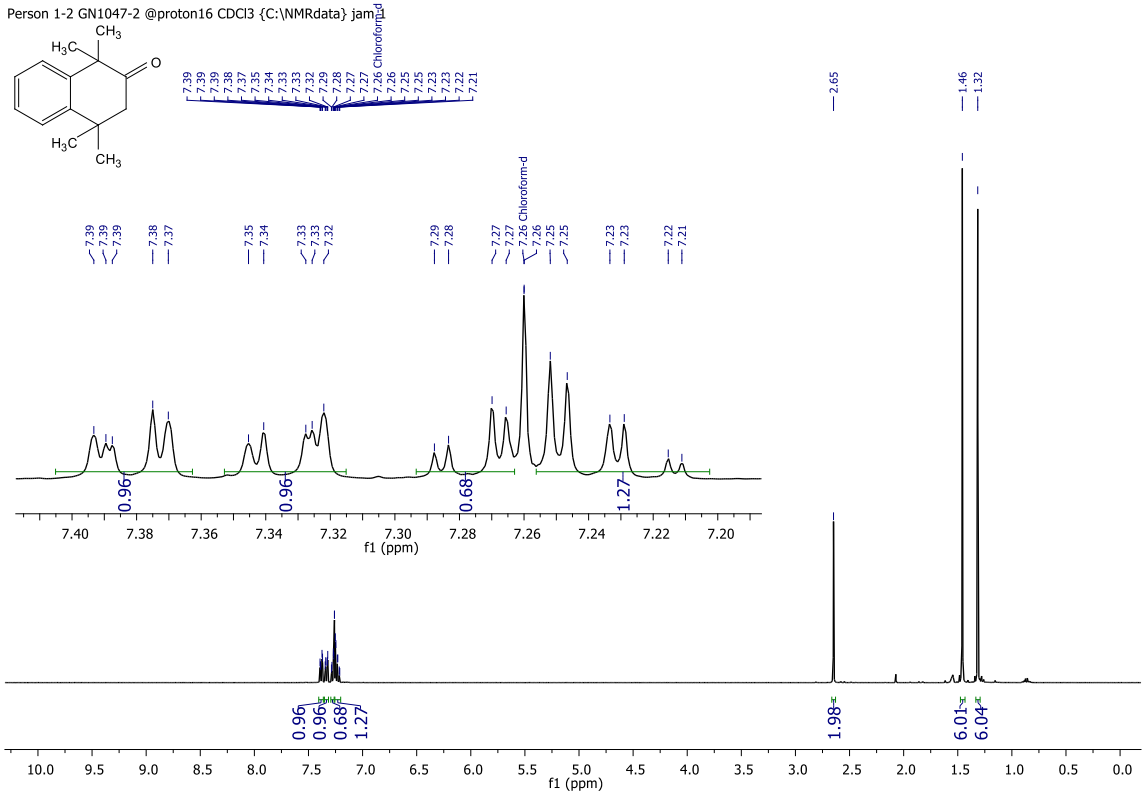


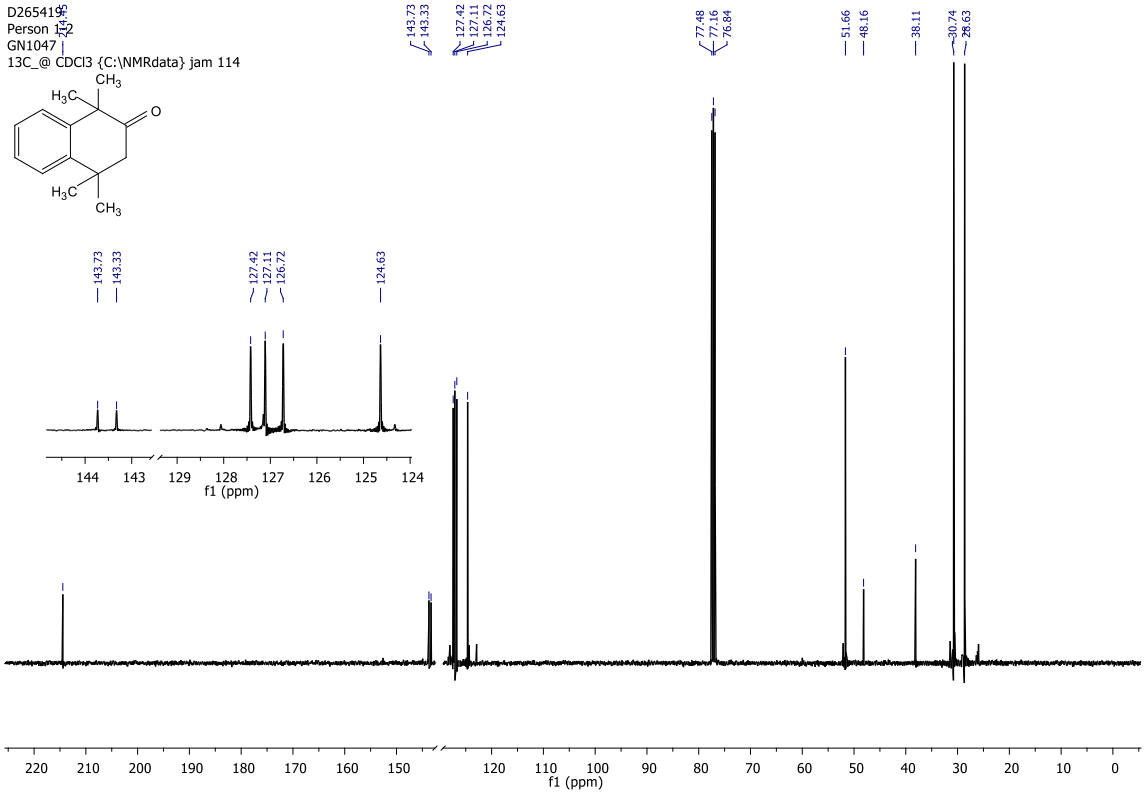
2,2,5,5-Tetramethyltetrahydro-3-oxofuran, **411**



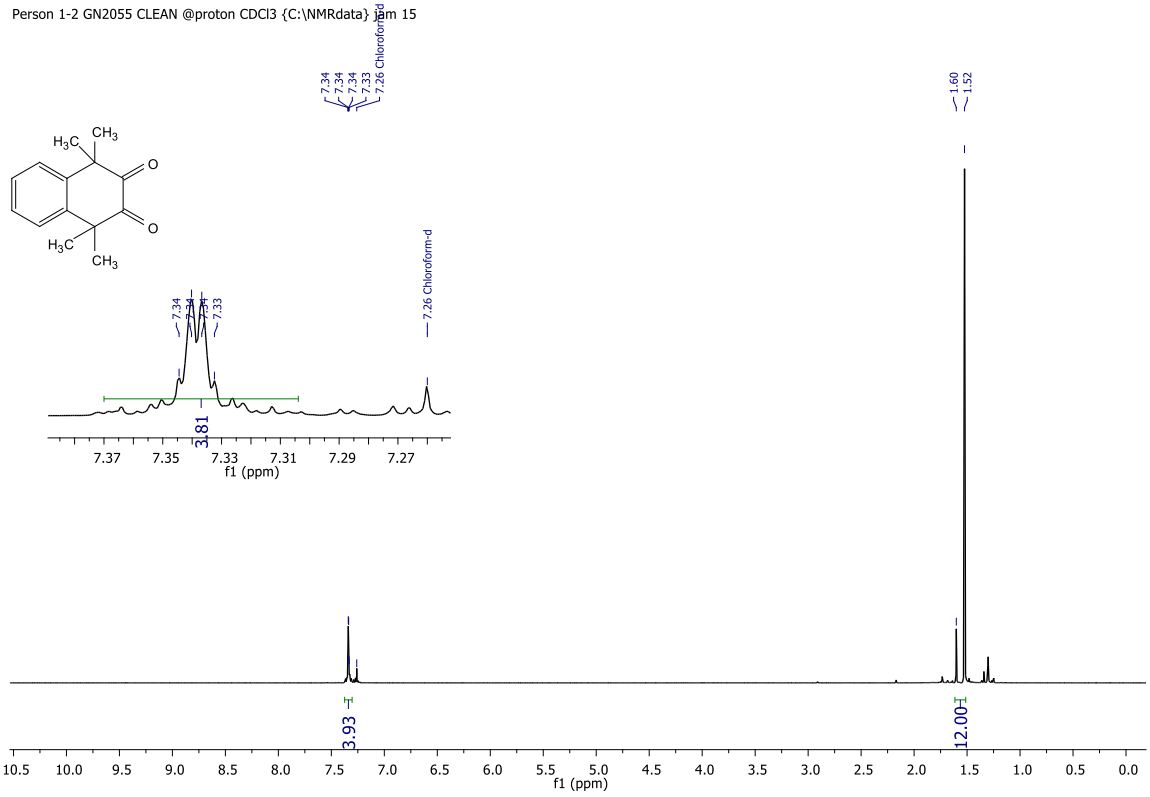


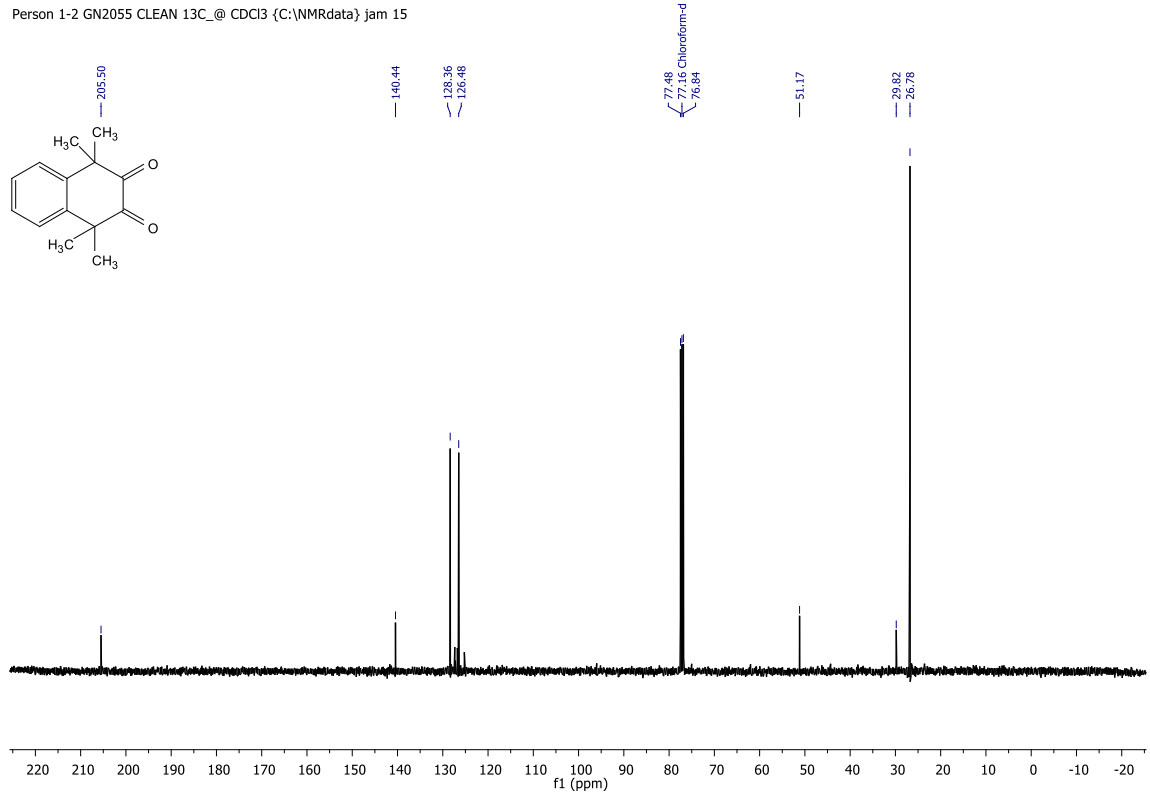
1,1,4,4-Tetramethyl-2-tetralon, **412**



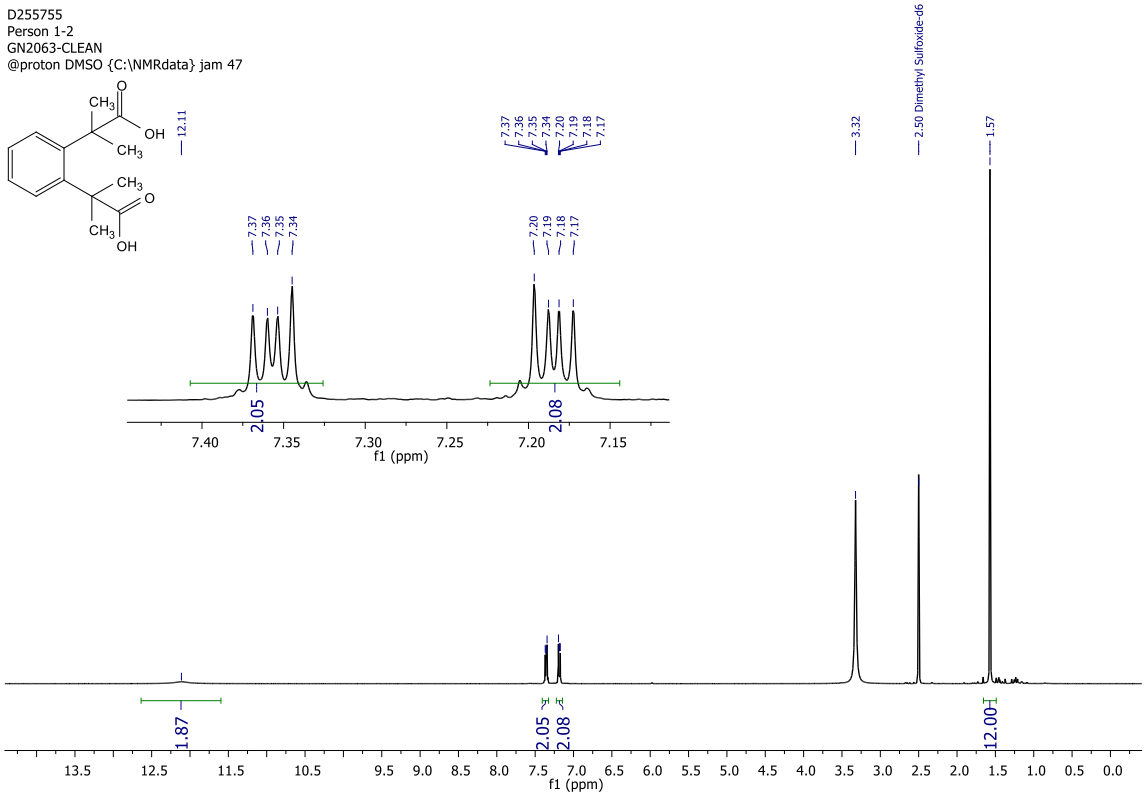


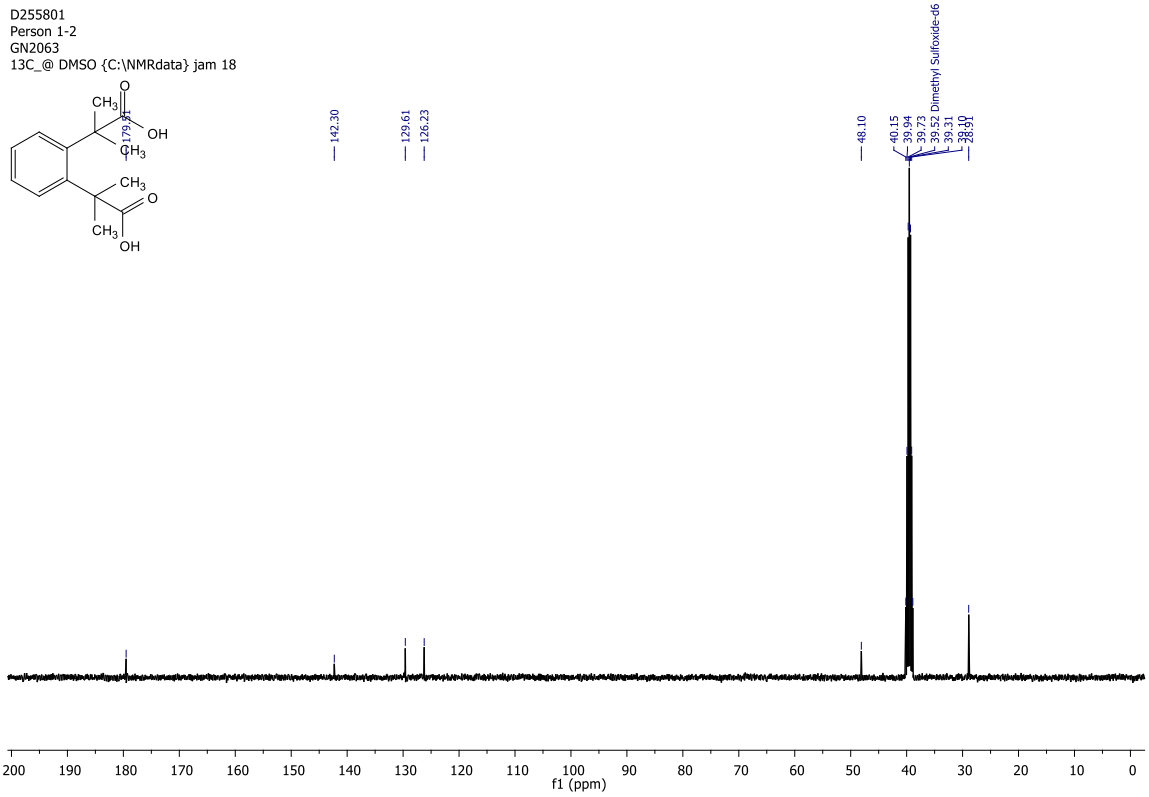
1,1,4,4-Tetramethyltetralin-2,3-dione: **413**



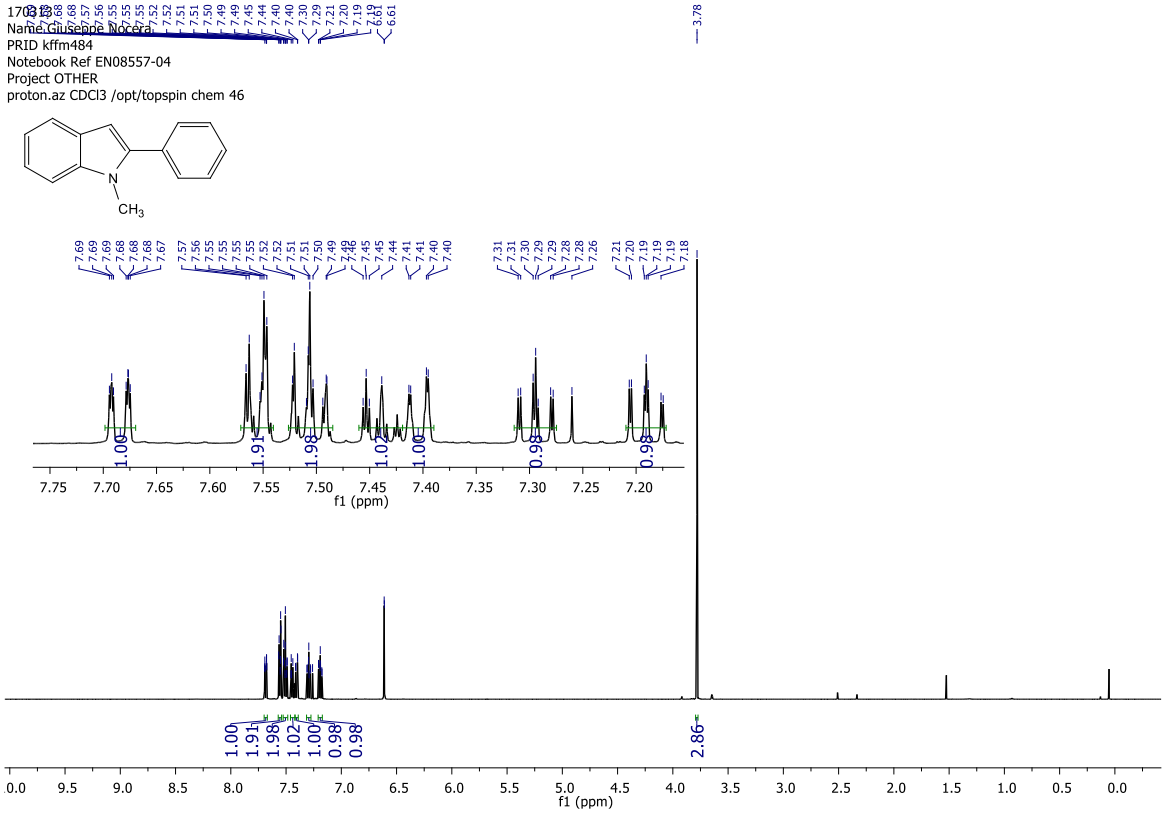


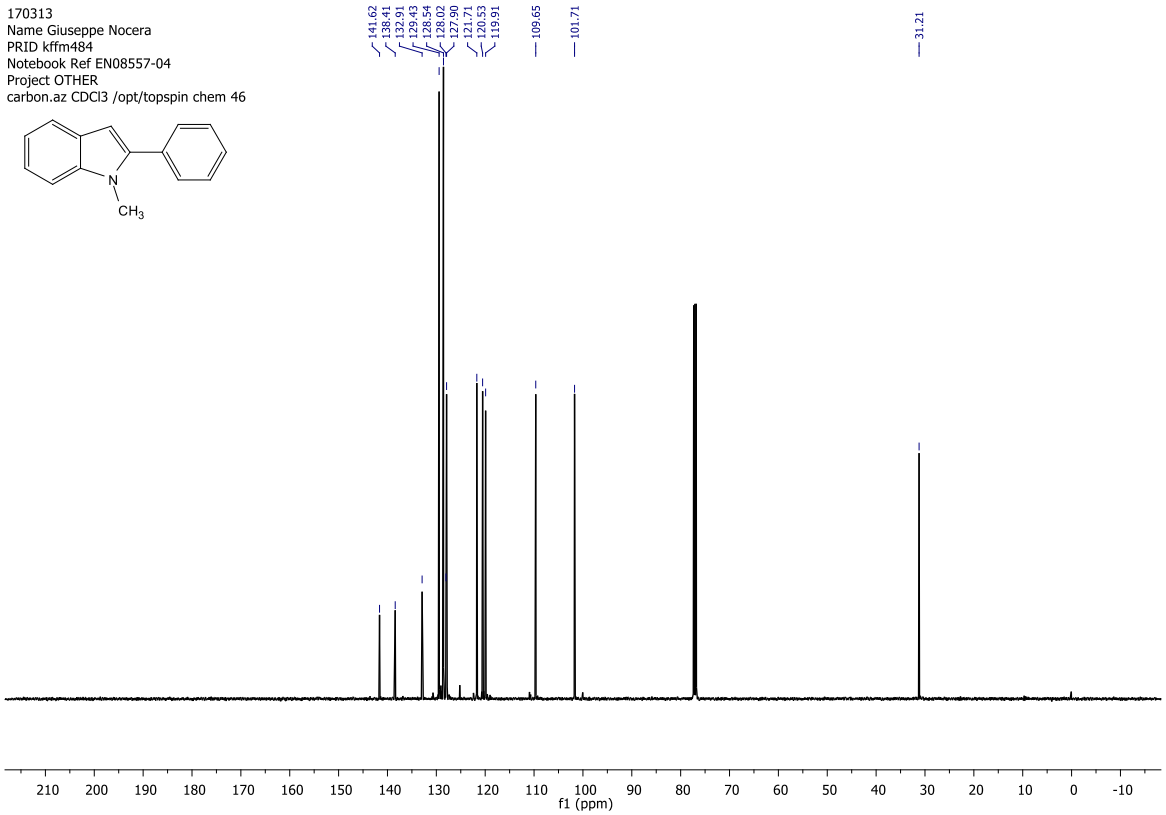
2,2'-(1,2-Phenylene)bis(2-methylpropanoic acid), **414**



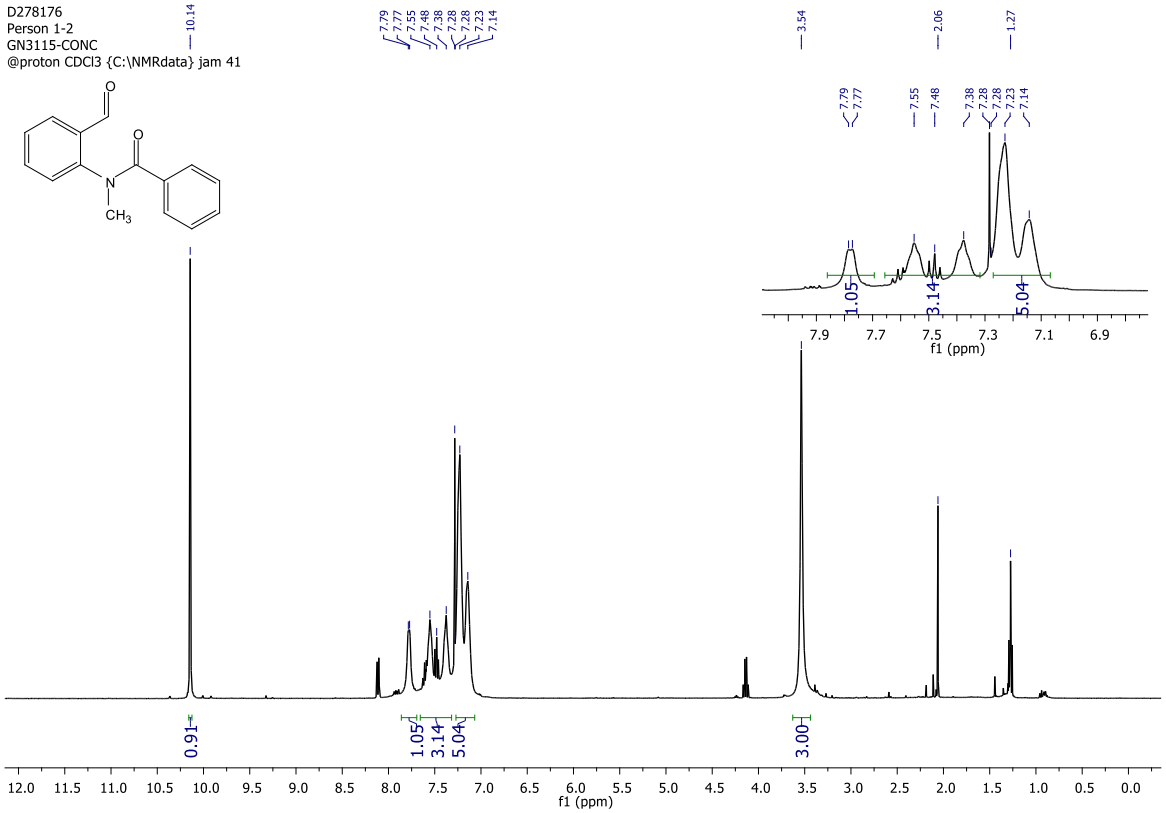


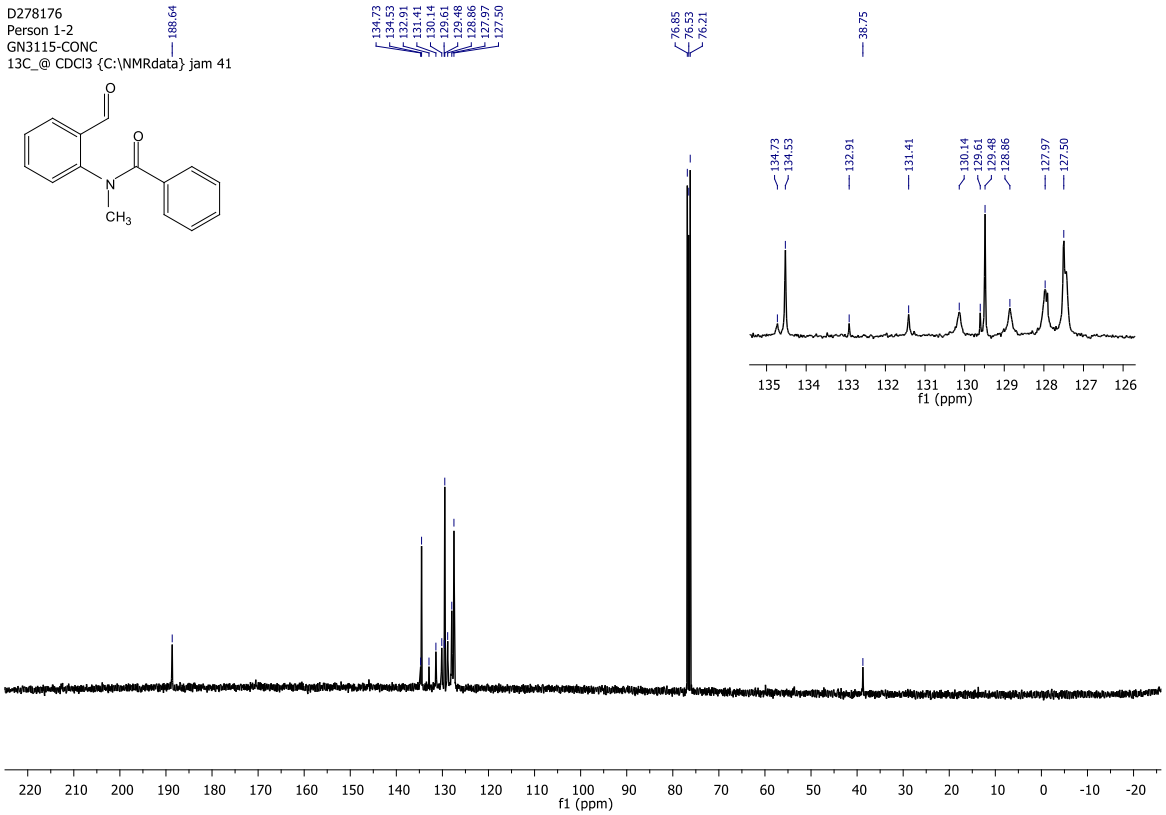
1-methyl-2-phenyl-1H-indole. **417**



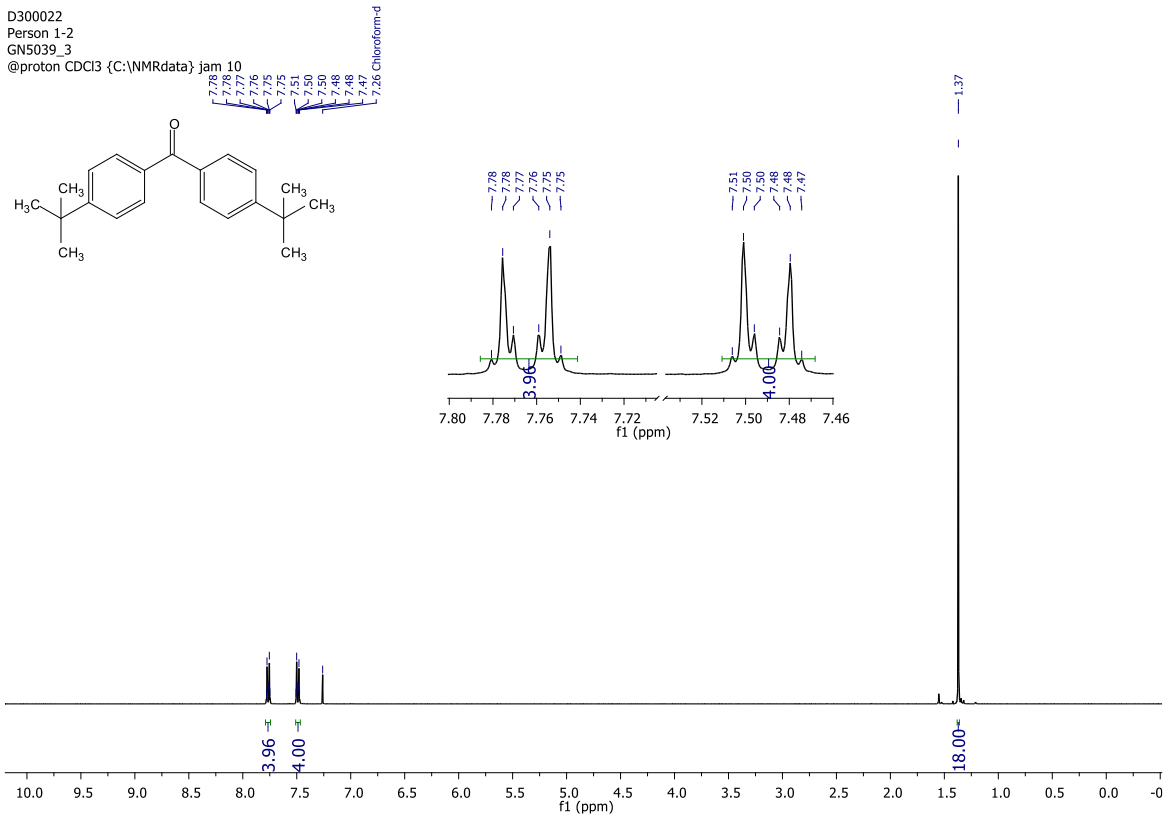


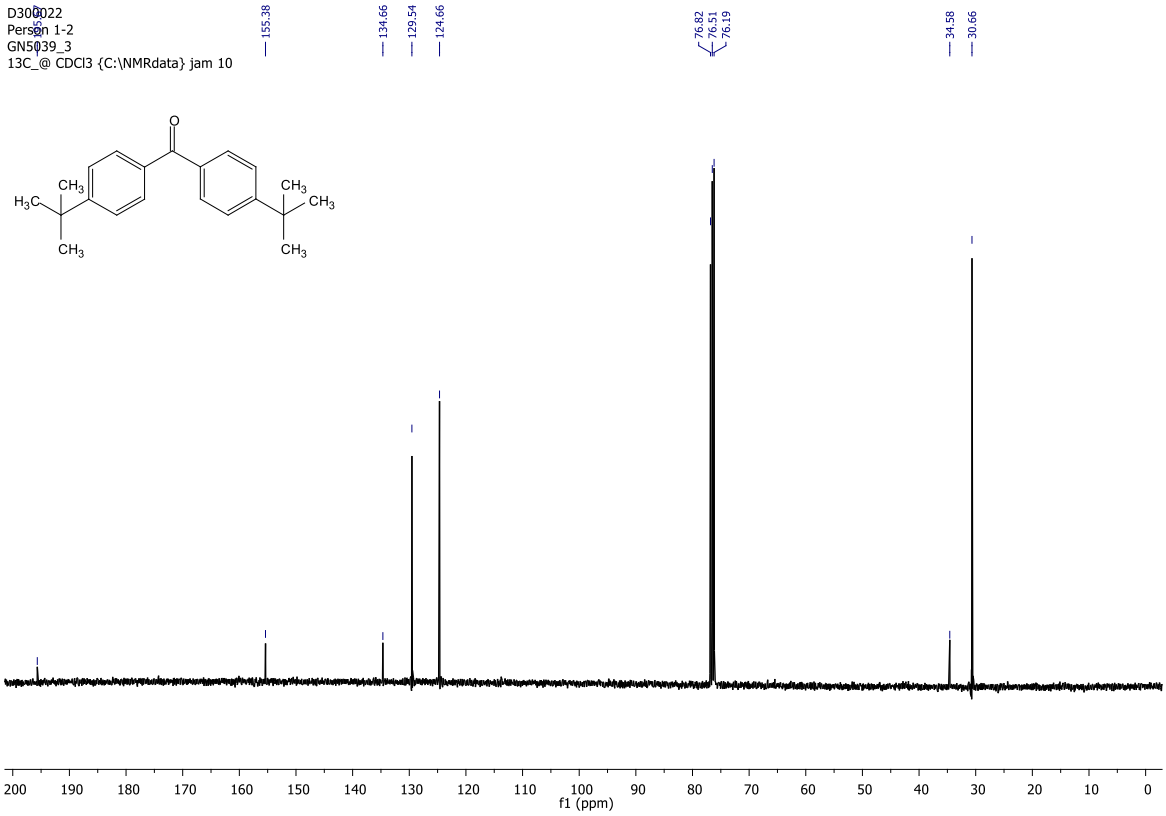
N-(2-formylphenyl)-N-methylbenzamide, **418**



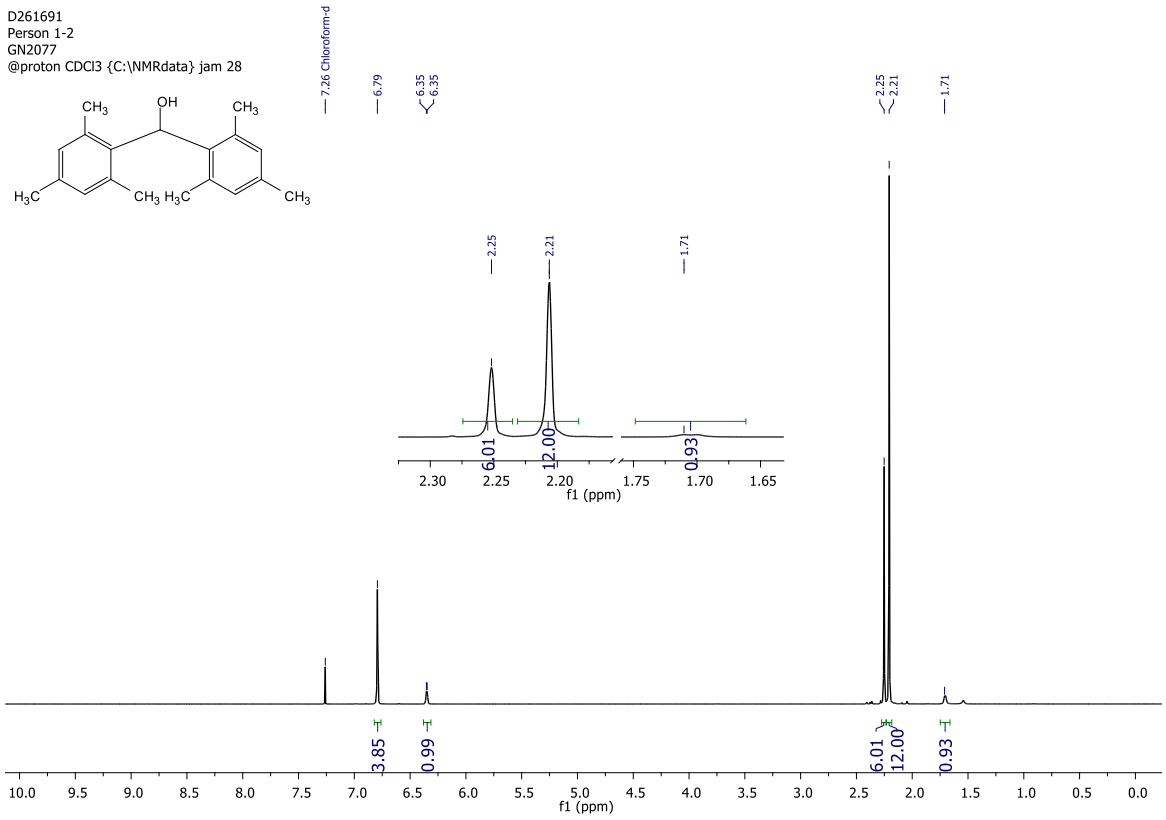


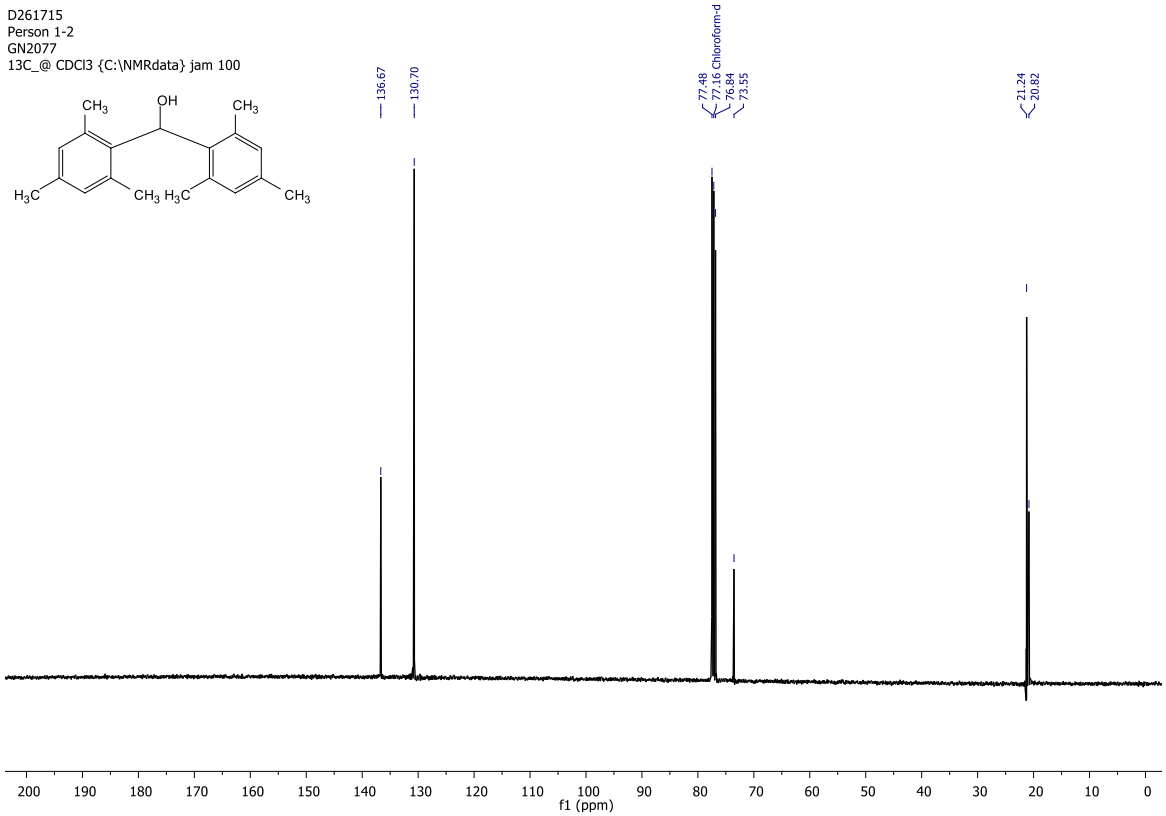
4,4'-Di-*tert*-butylbenzophenone, **440**



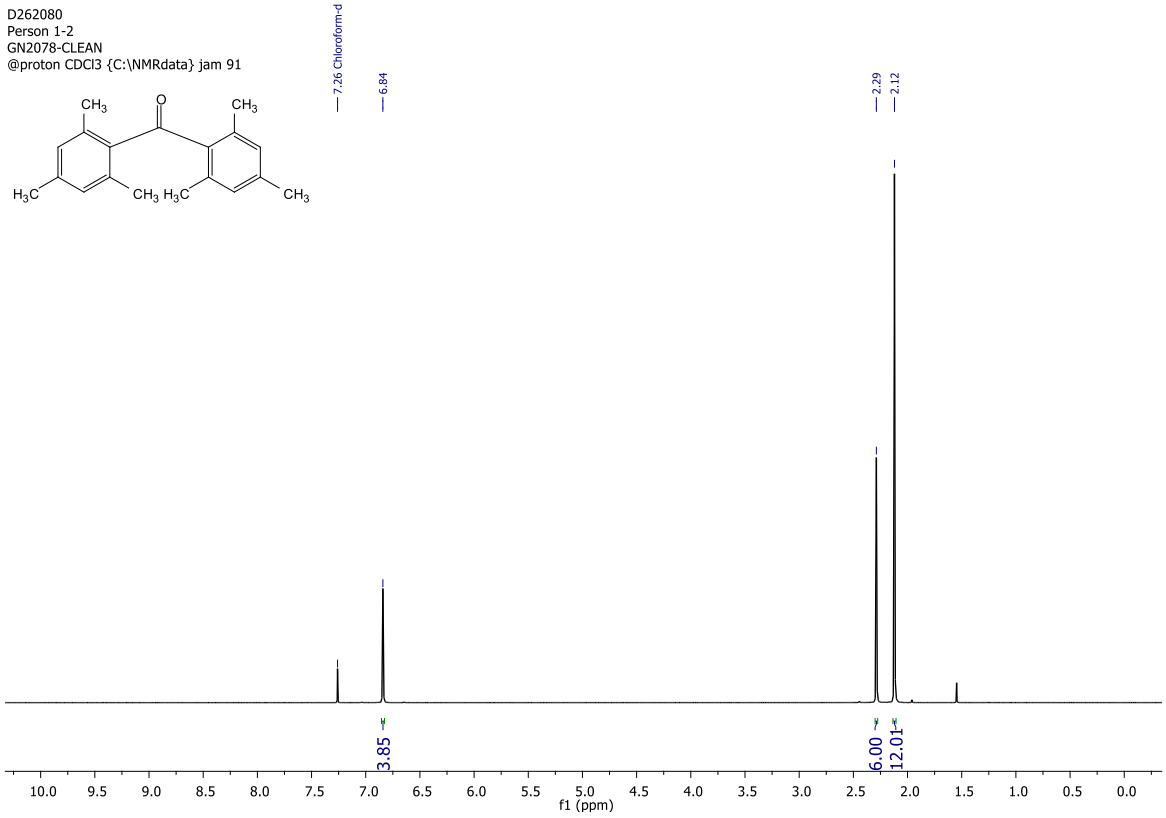


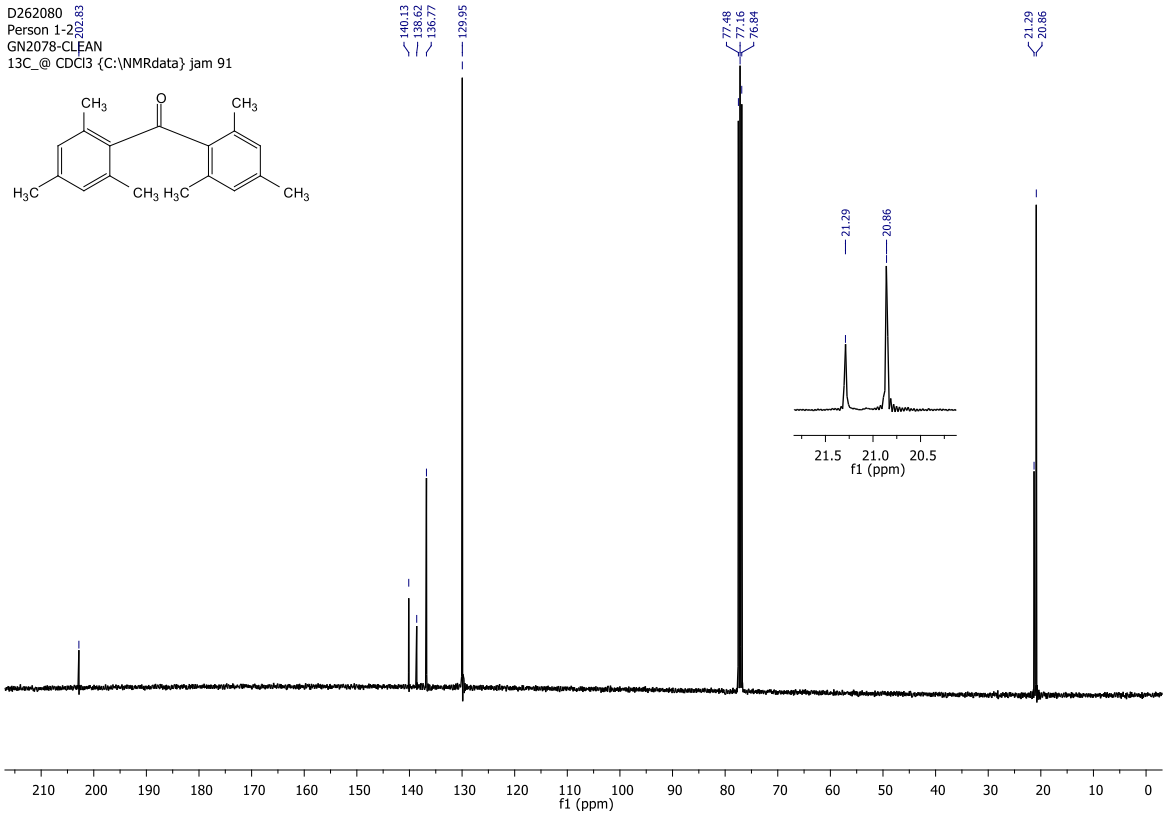
Dimesitylmethanol, **451**



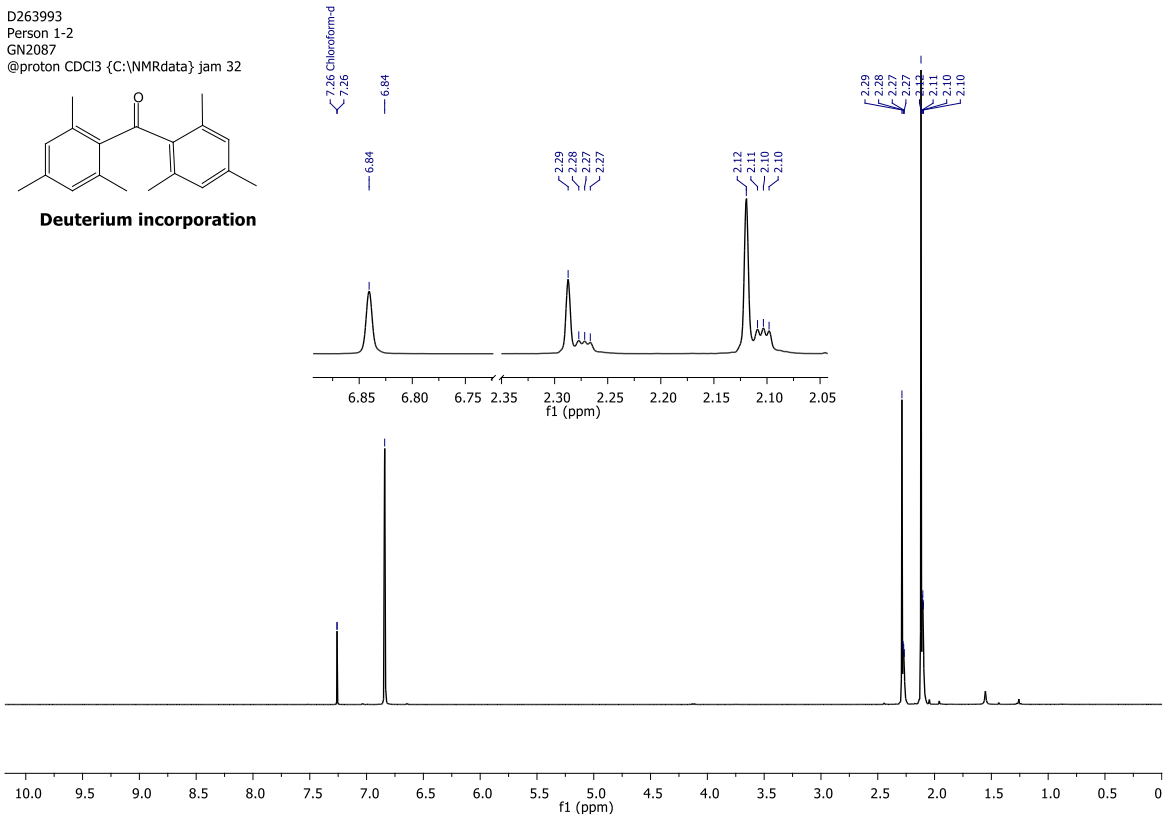


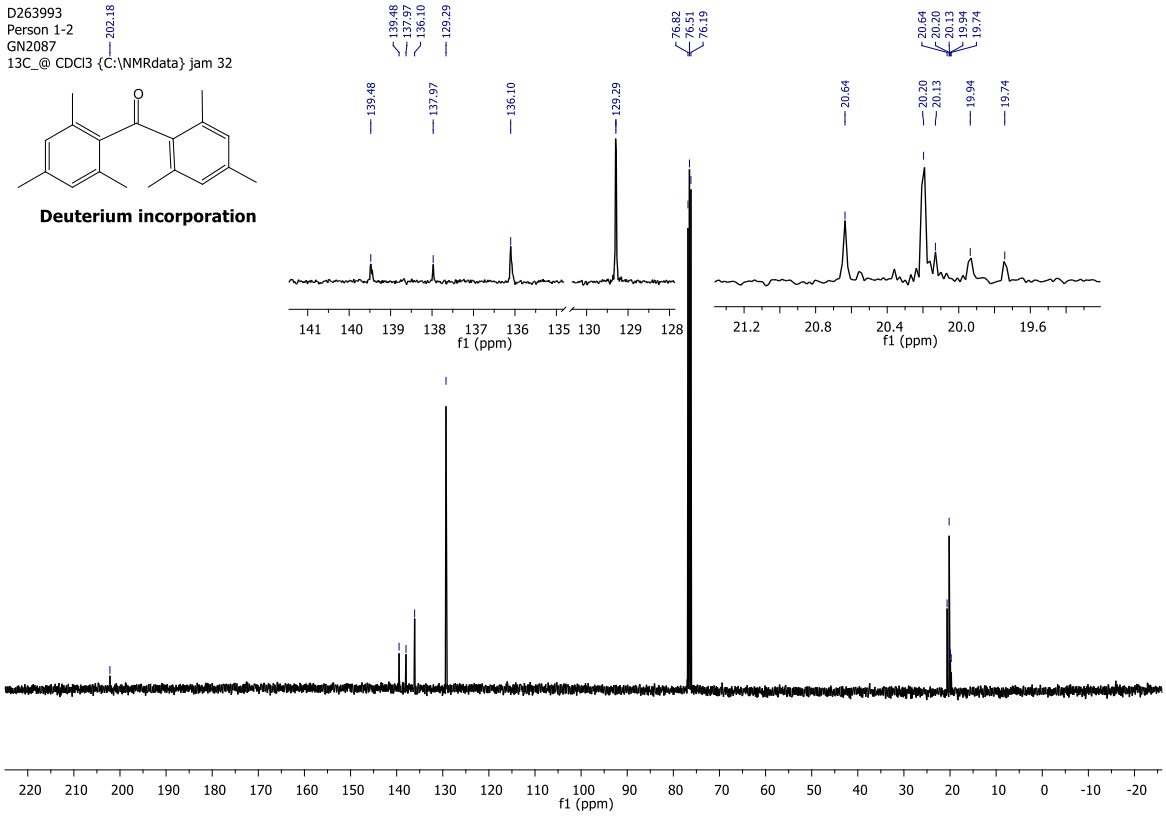
Dimesitylmethanone, **441**



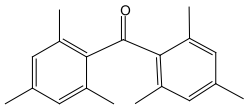


Polydeuterated dimesitylmethanone, **441-dmix**



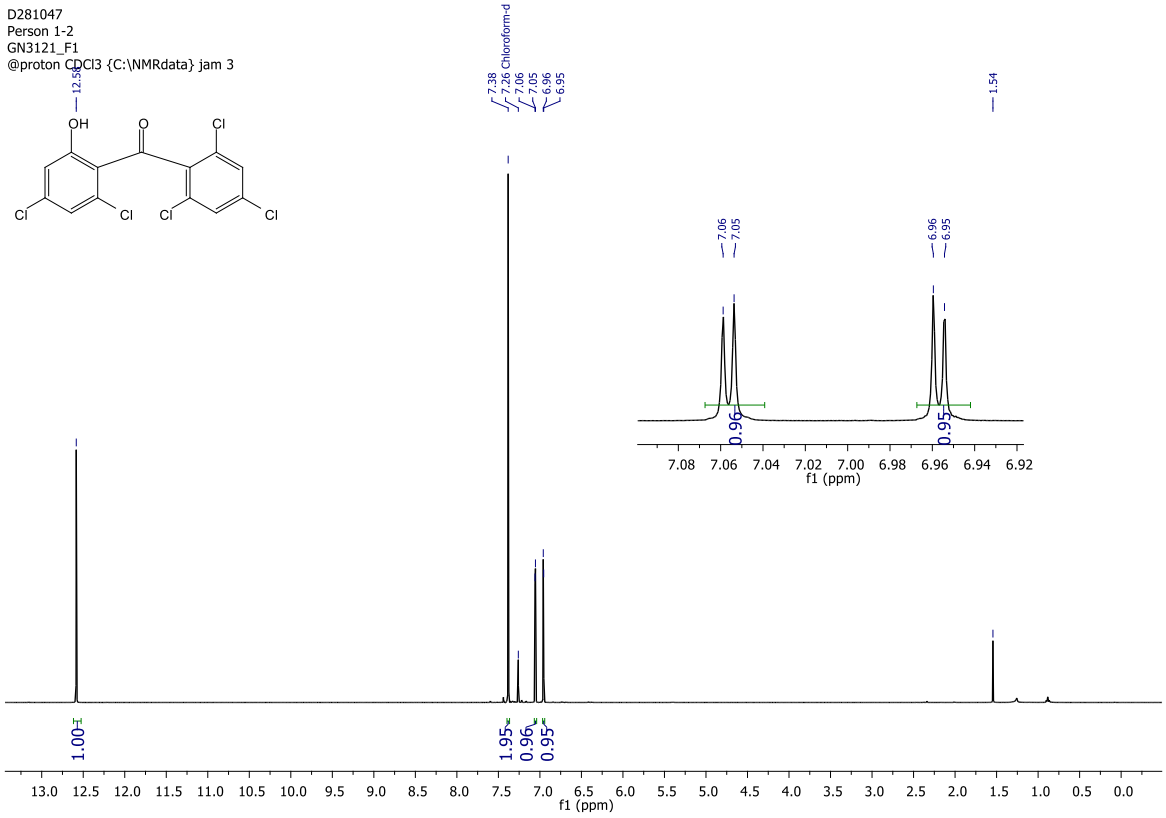


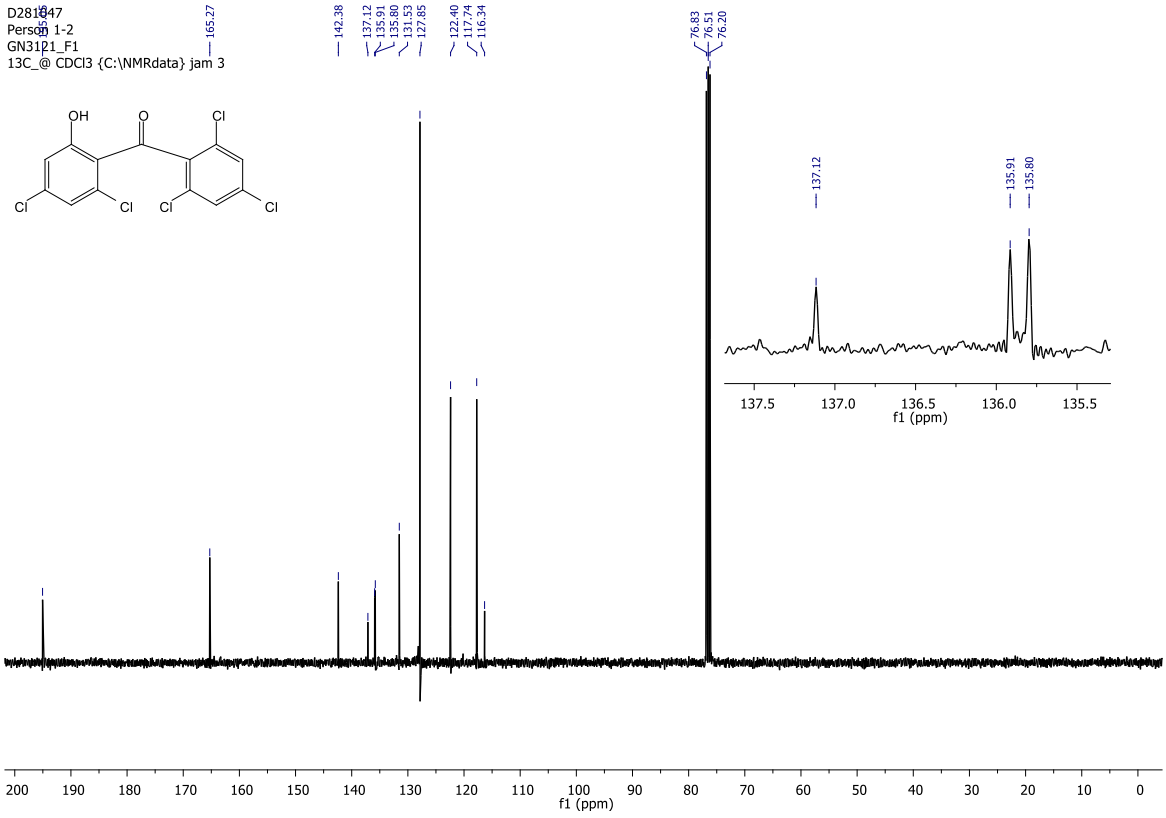
D263994
Person 1-2
GN2087
@2H.jap CHCl3 {C:\NMRdata} jam 33



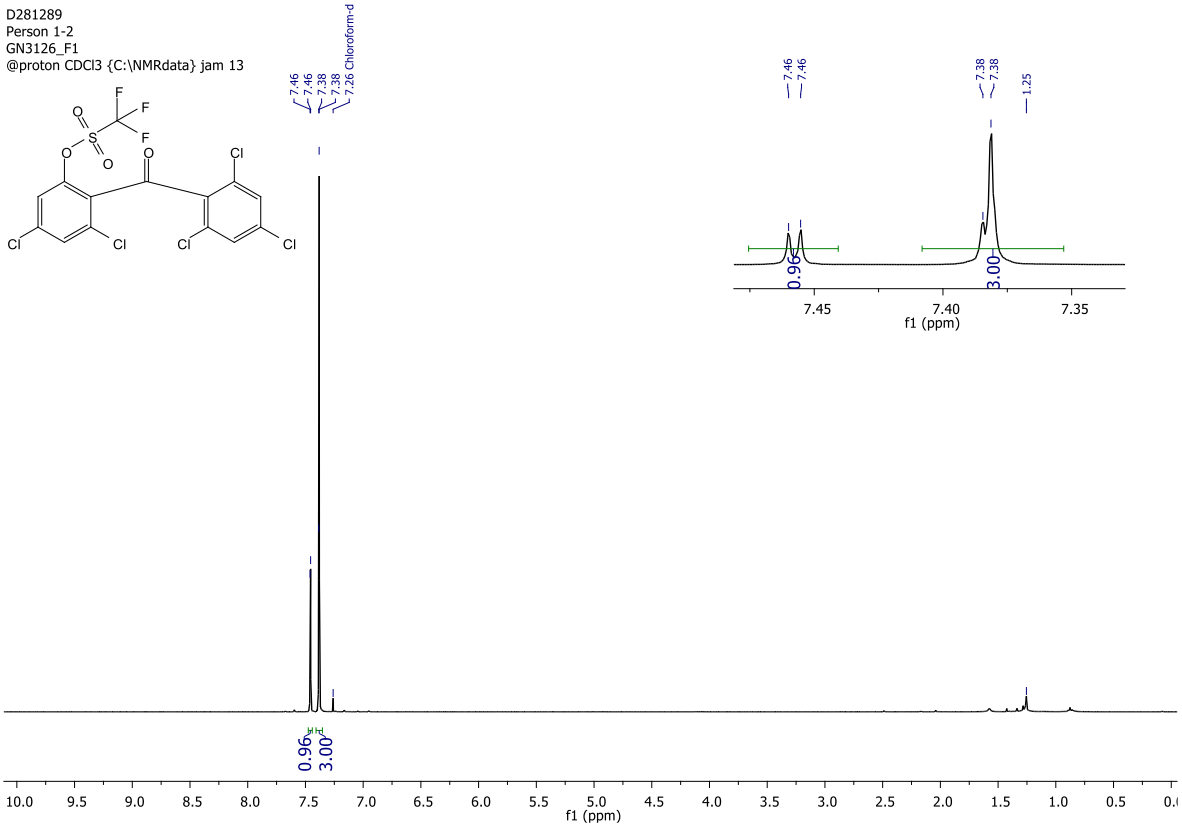
Deuterium incorporation

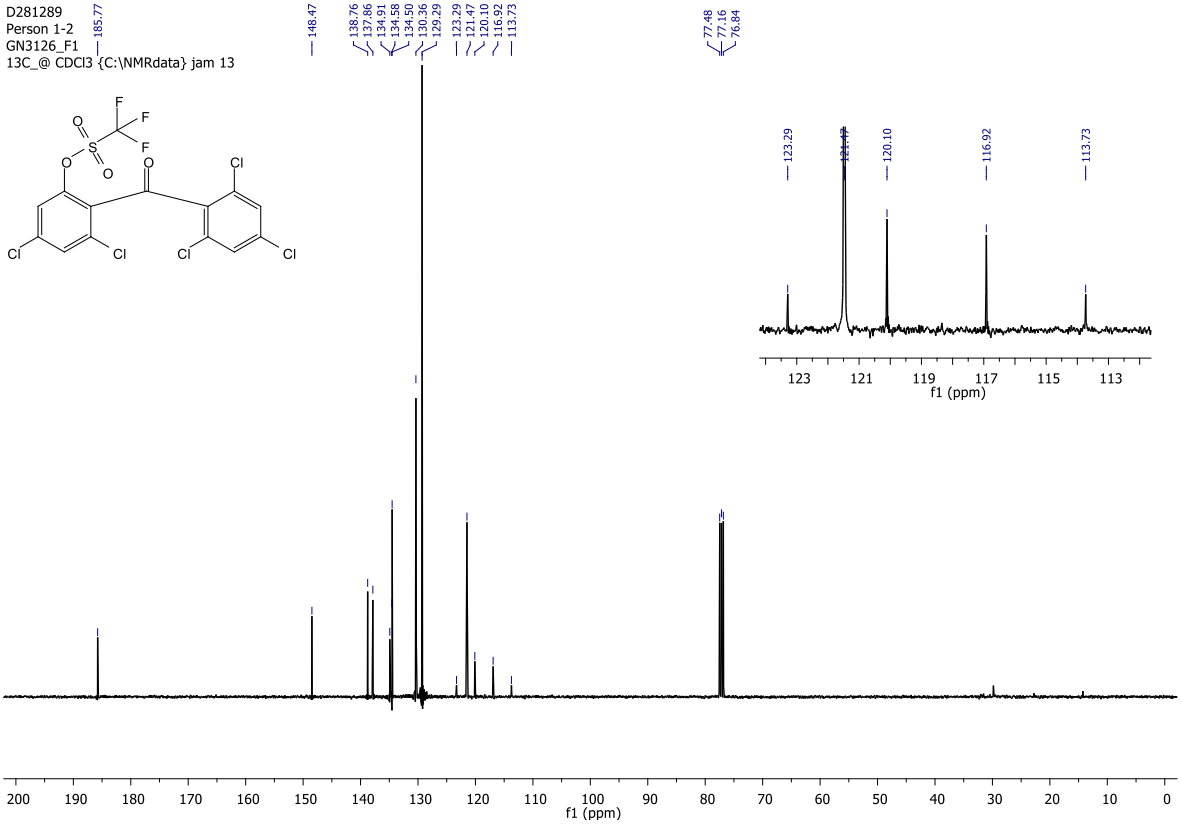
(2,4-Dichloro-6-hydroxyphenyl)(2,4,6-trichlorophenyl)methanone, **454**



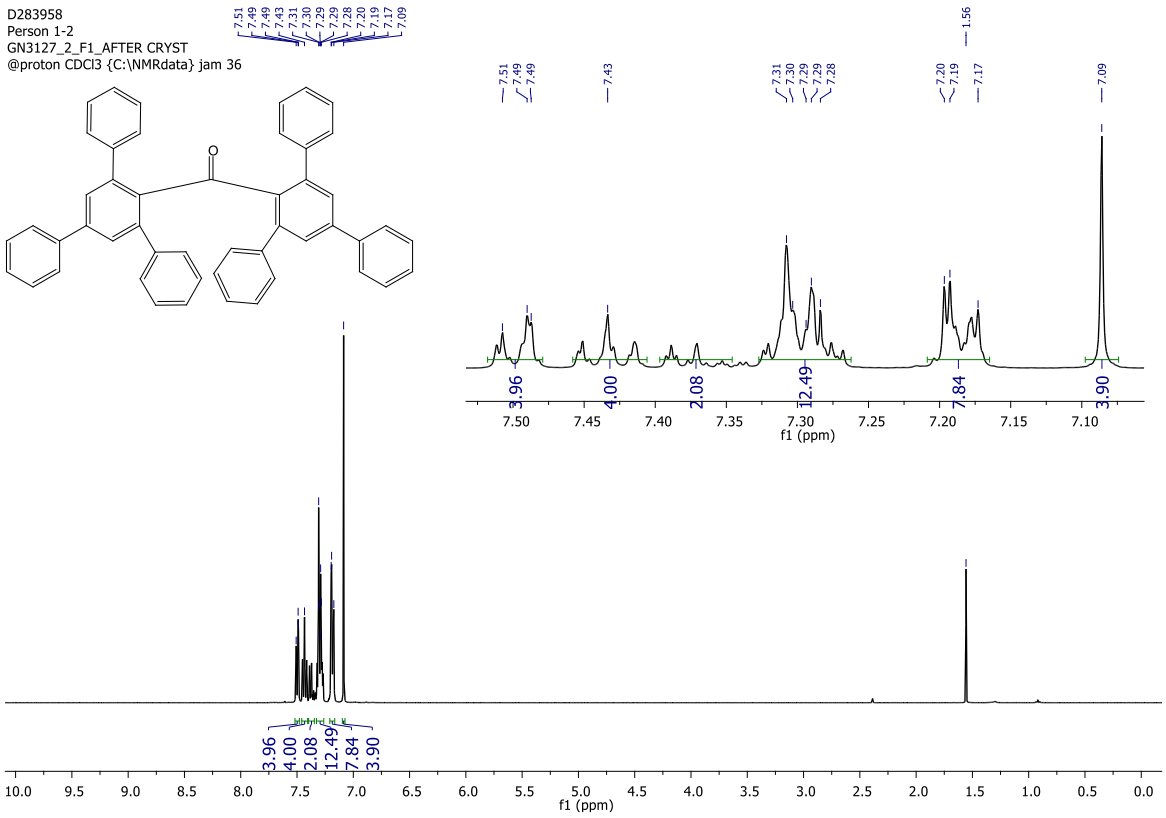


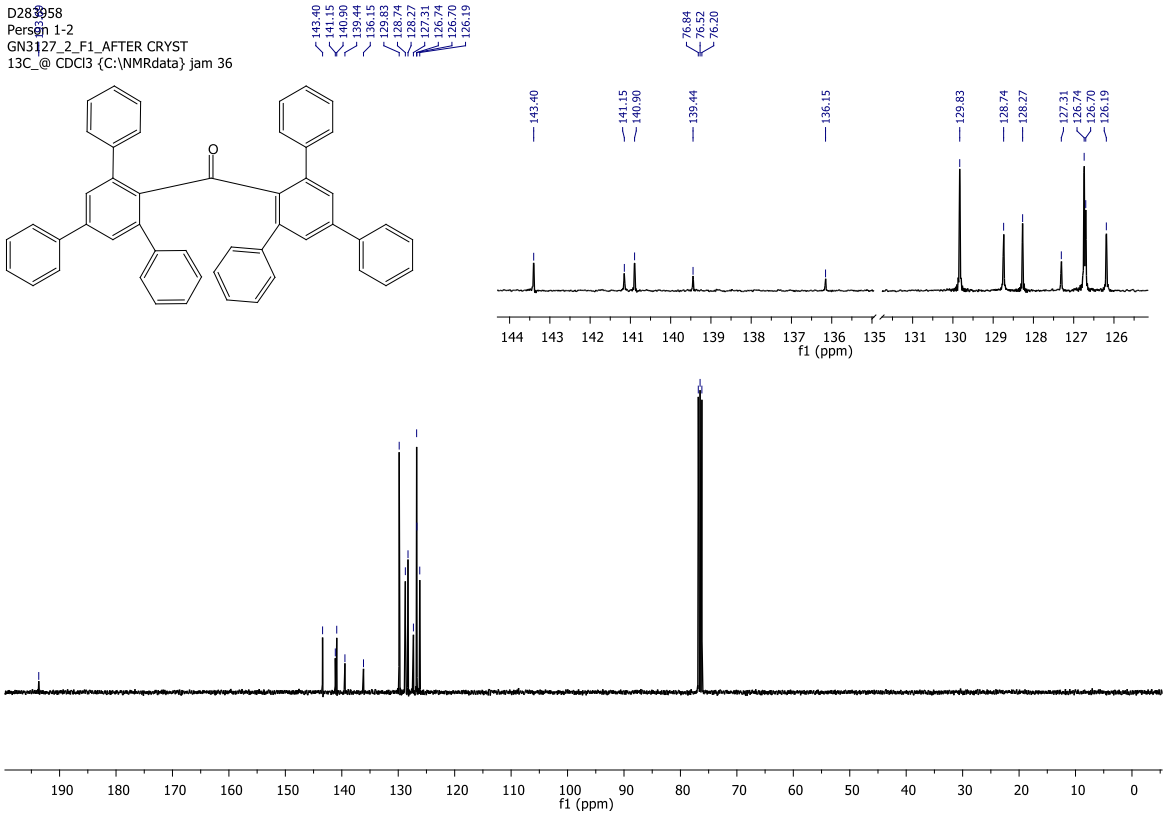
3,5-Dichloro-2-(2,4,6-trichlorobenzoyl)phenyl trifluoromethanesulfonate, **455**



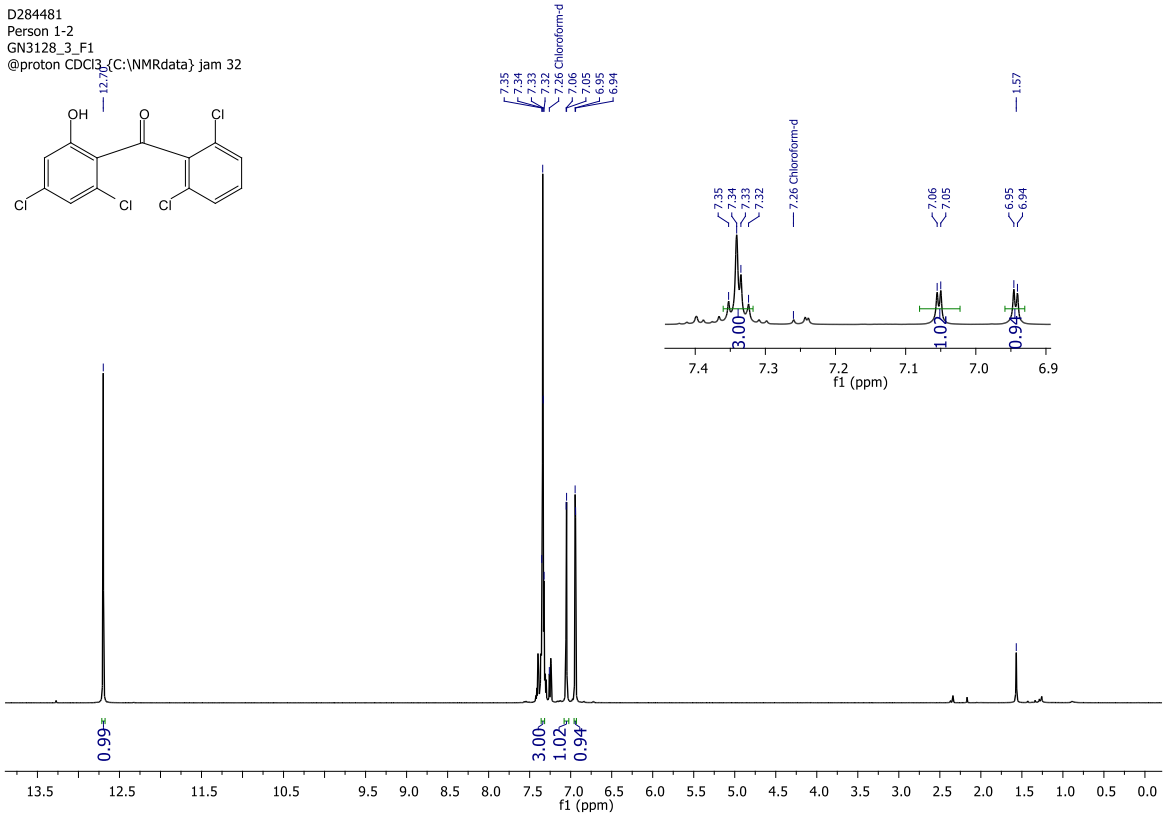


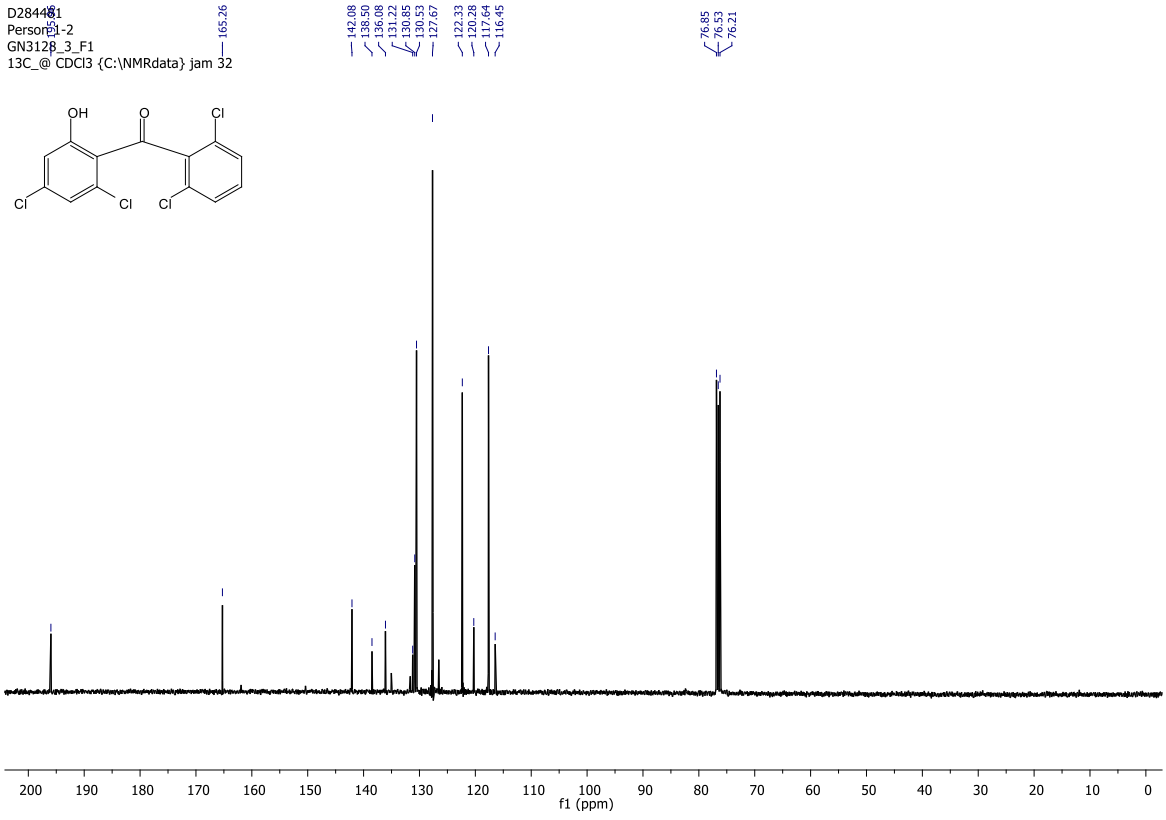
Bis(5'-phenyl-[1,1':3',1"-terphenyl]-2'-yl)methanone, **251**



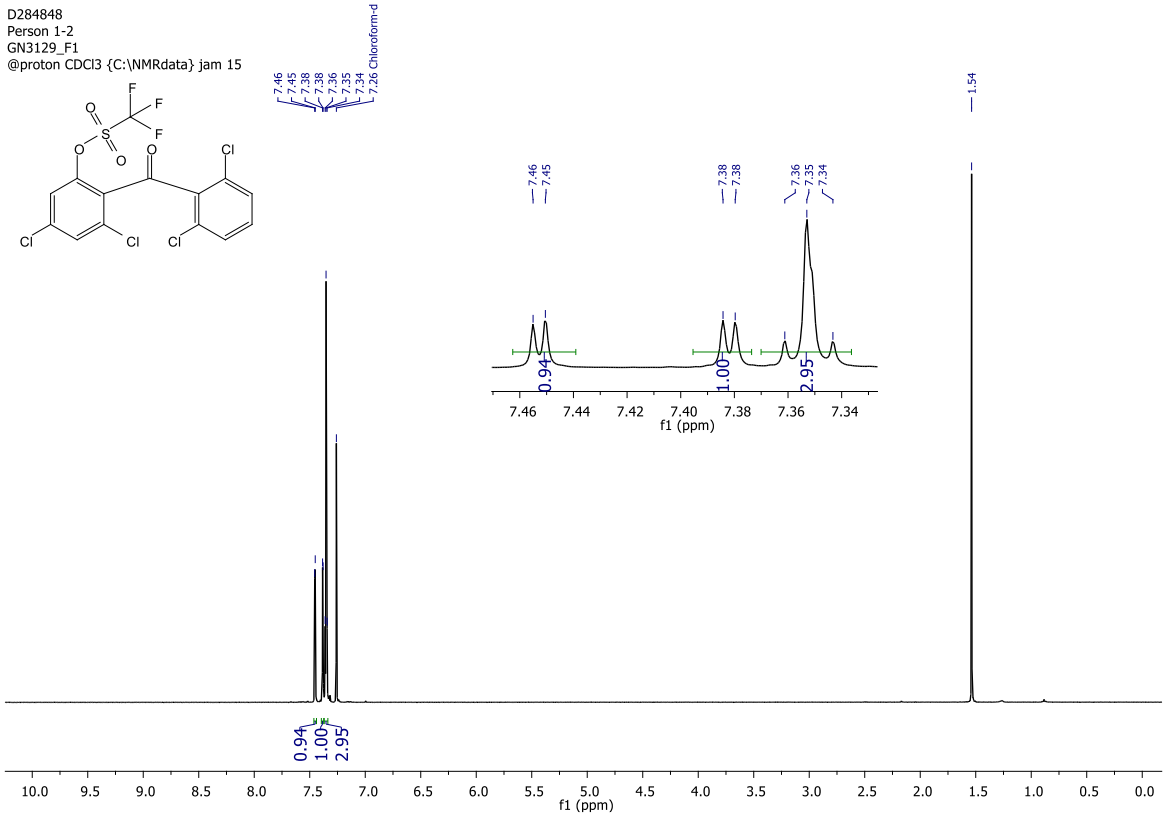


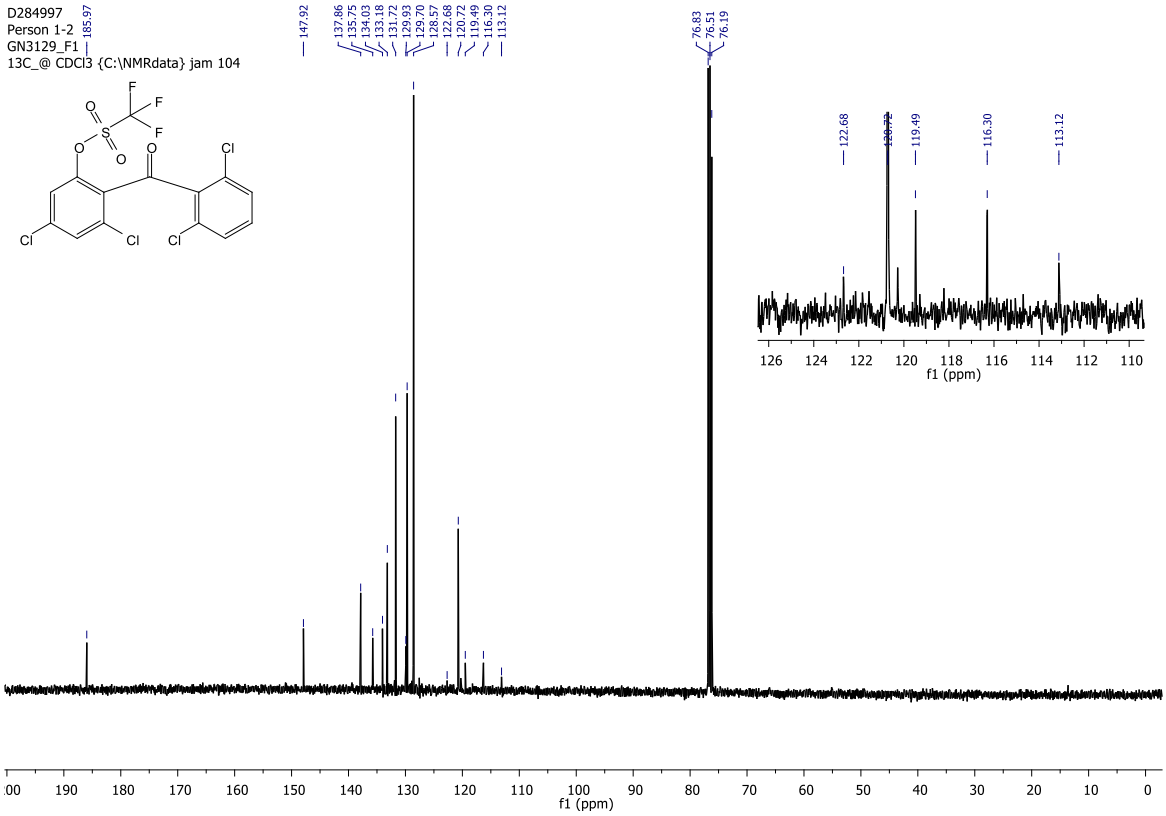
(2,4-Dichloro-6-hydroxyphenyl)(2,6-dichlorophenyl)methanone, **461**



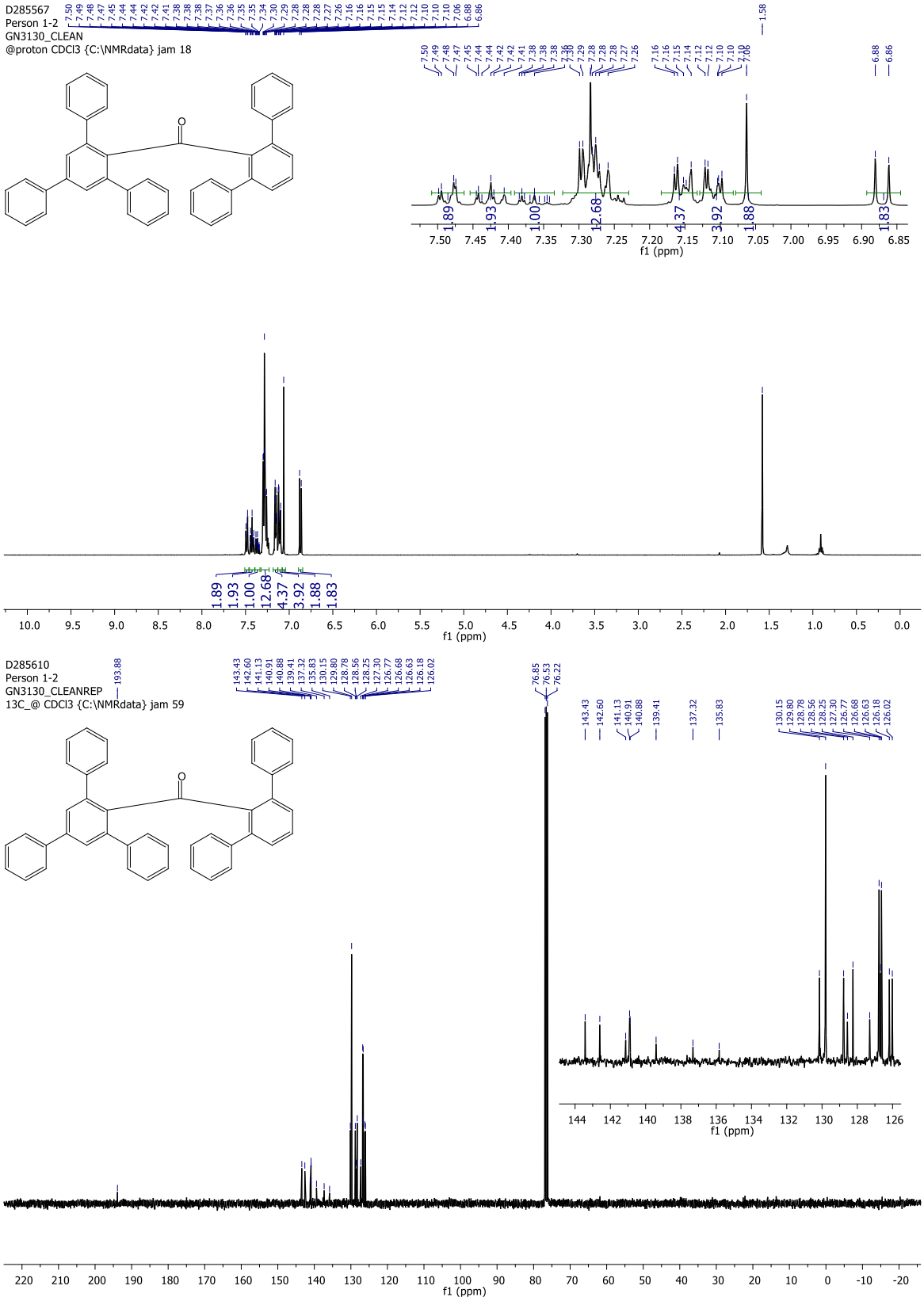


3,5-Dichloro-2-(2,6-dichlorobenzoyl)phenyl trifluoromethanesulfonate, **462**

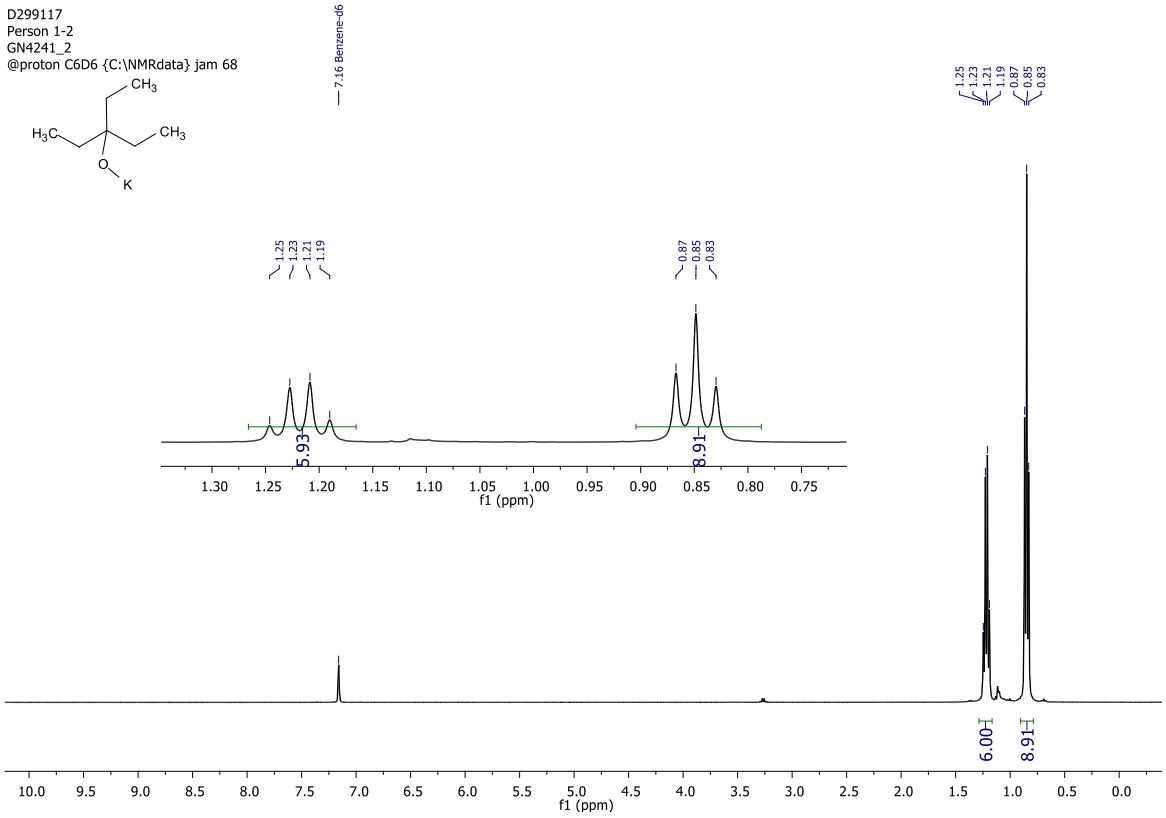


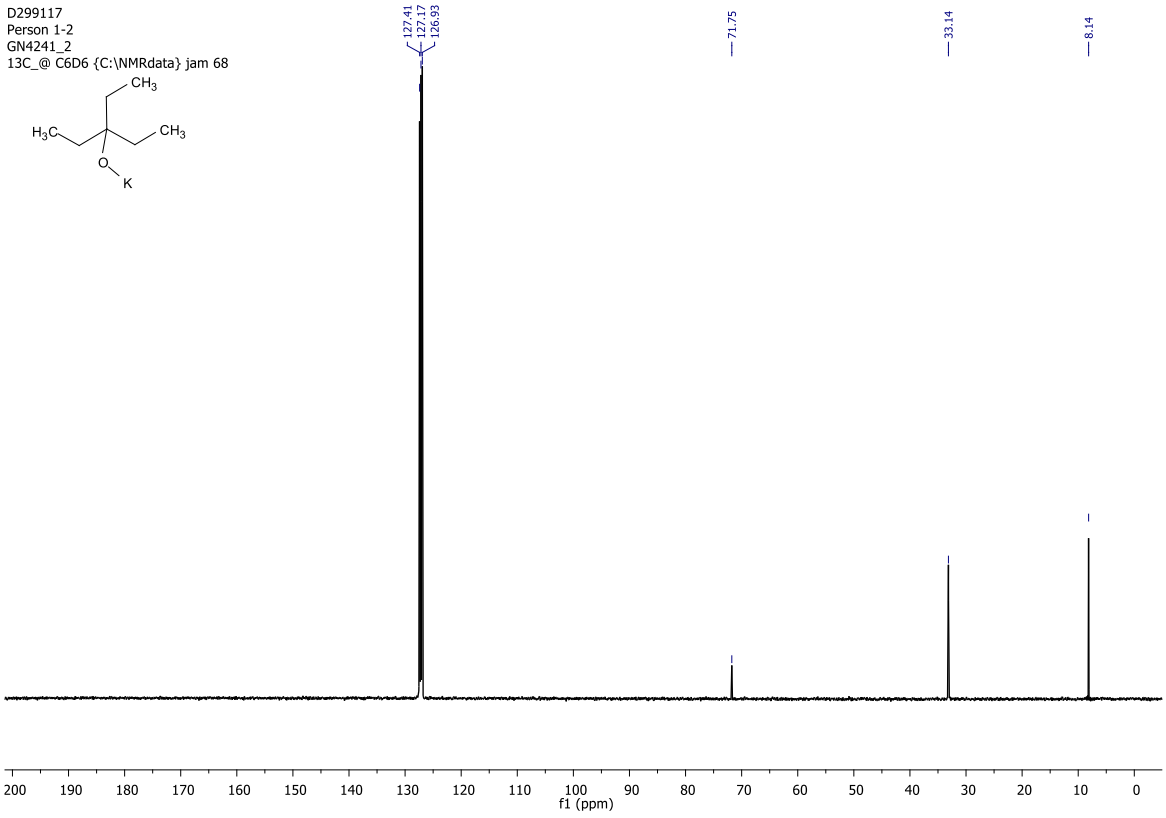


[1,1':3',1''-Terphenyl]-2'-yl(5'-phenyl-[1,1':3',1''-terphenyl]-2'-yl)methanone, **252**

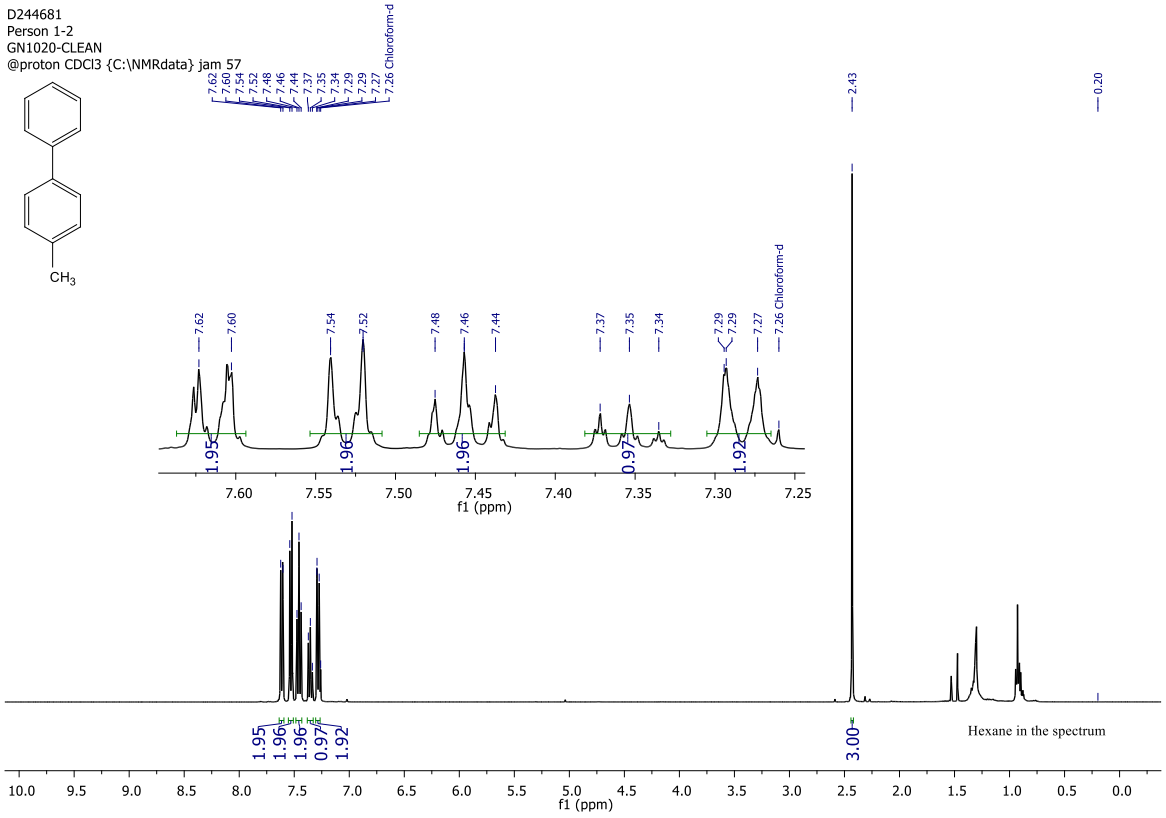


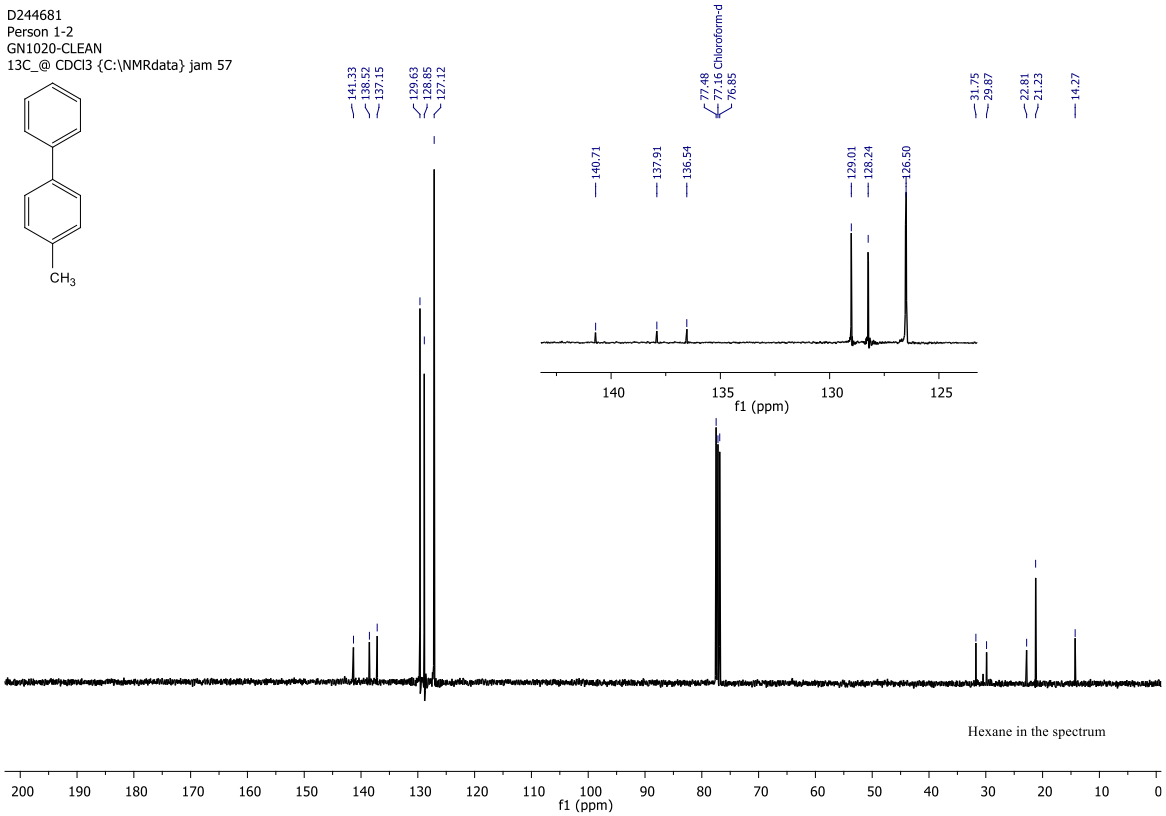
Potassium 3-ethylpentan-3-olate, **237**



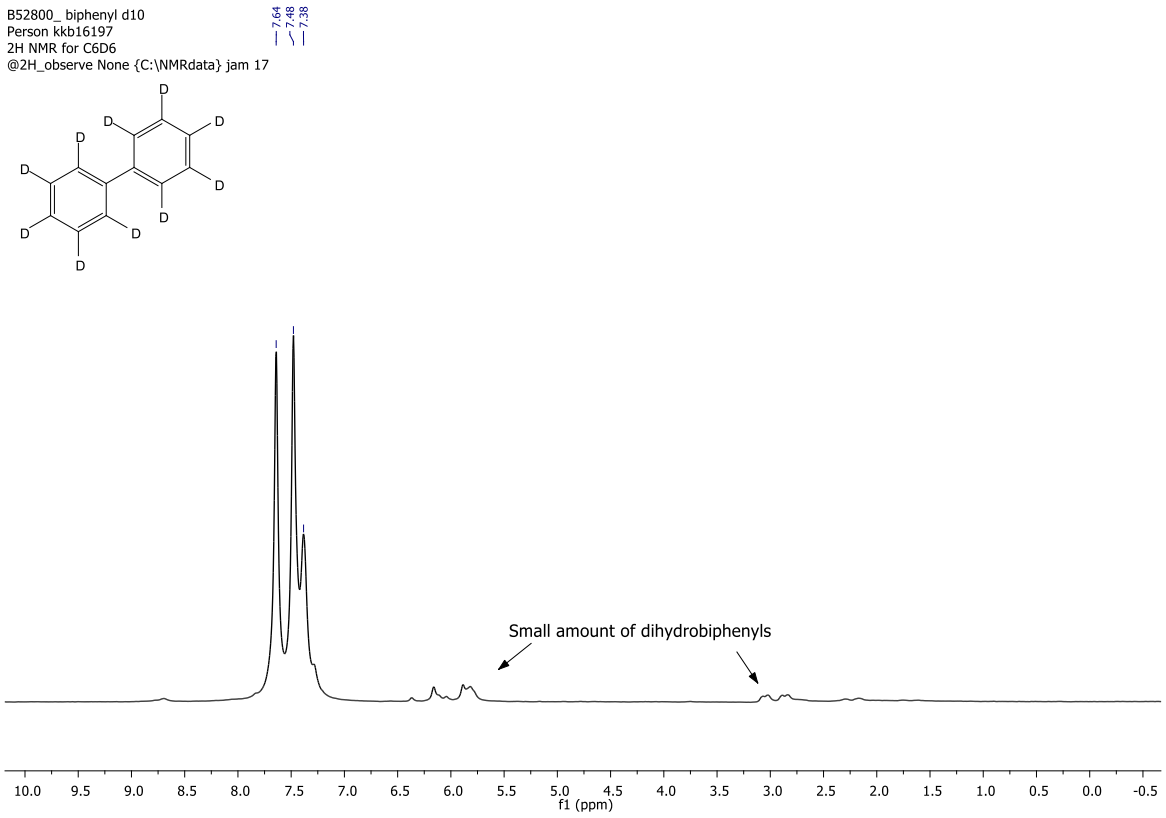


4-methyl-1,1'-biphenyl, **123**

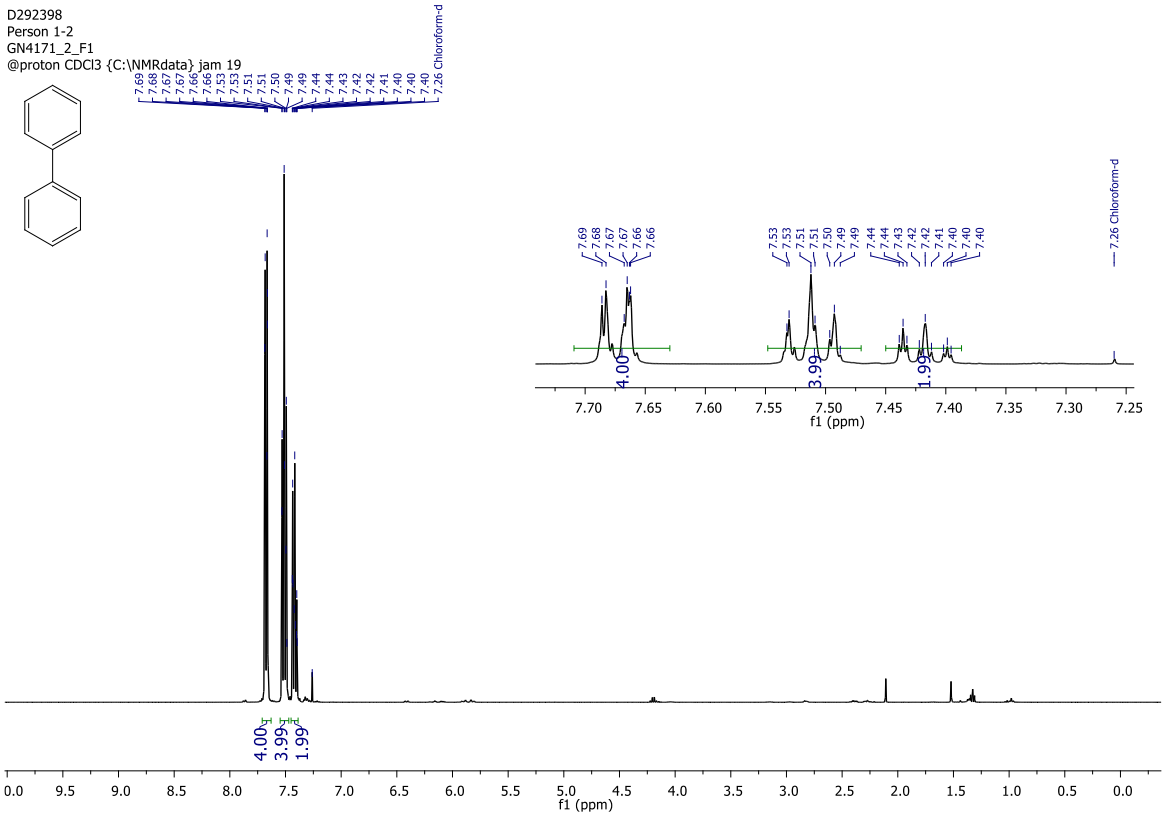


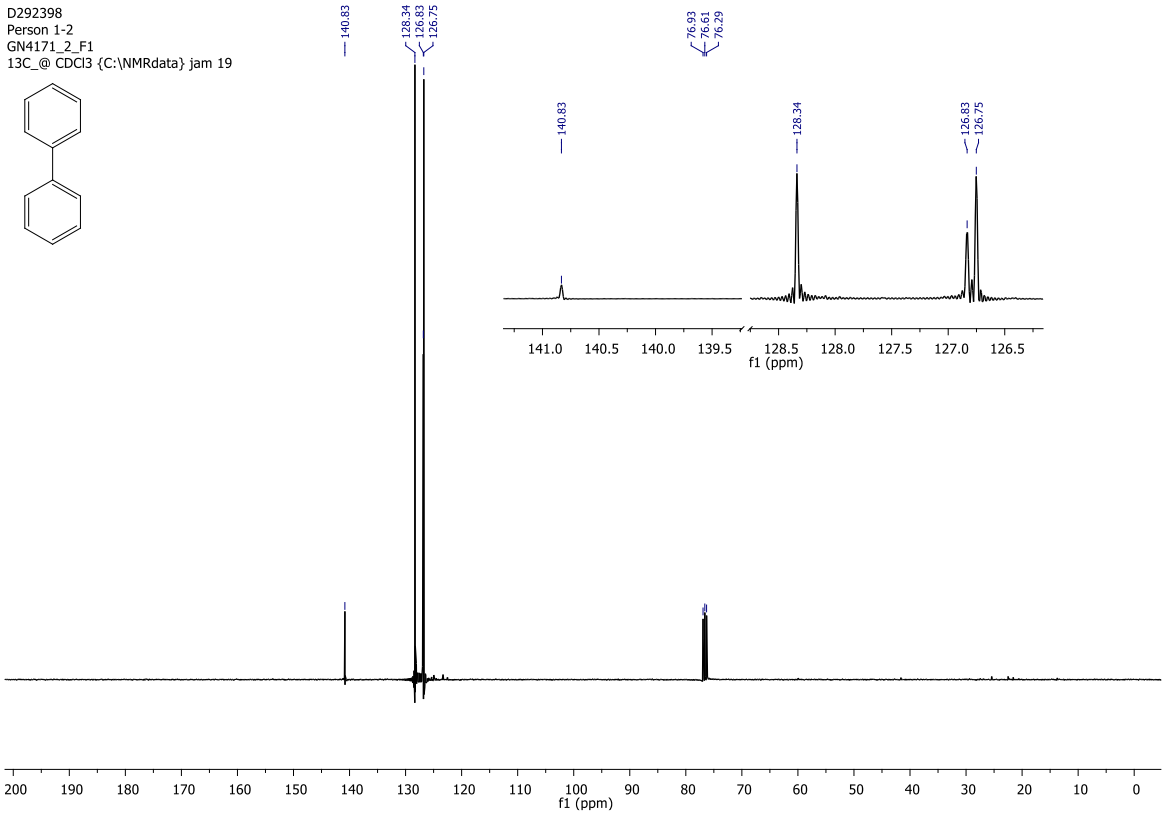


Byphenyl-d_{10}, 11-d_{10}



Biphenyl, **11**


D292398
Person 1-2
GN4171_2_F1
@proton CDCl3 {C:\NMRdata} jam 19
7.69 7.68 7.67 7.67 7.66 7.66 7.53 7.53 7.51 7.51 7.50 7.49 7.49 7.44 7.44 7.43 7.42 7.42 7.41 7.40 7.40 7.40 7.26 Chloroform-d
4.00
3.99
1.99
f1 (ppm)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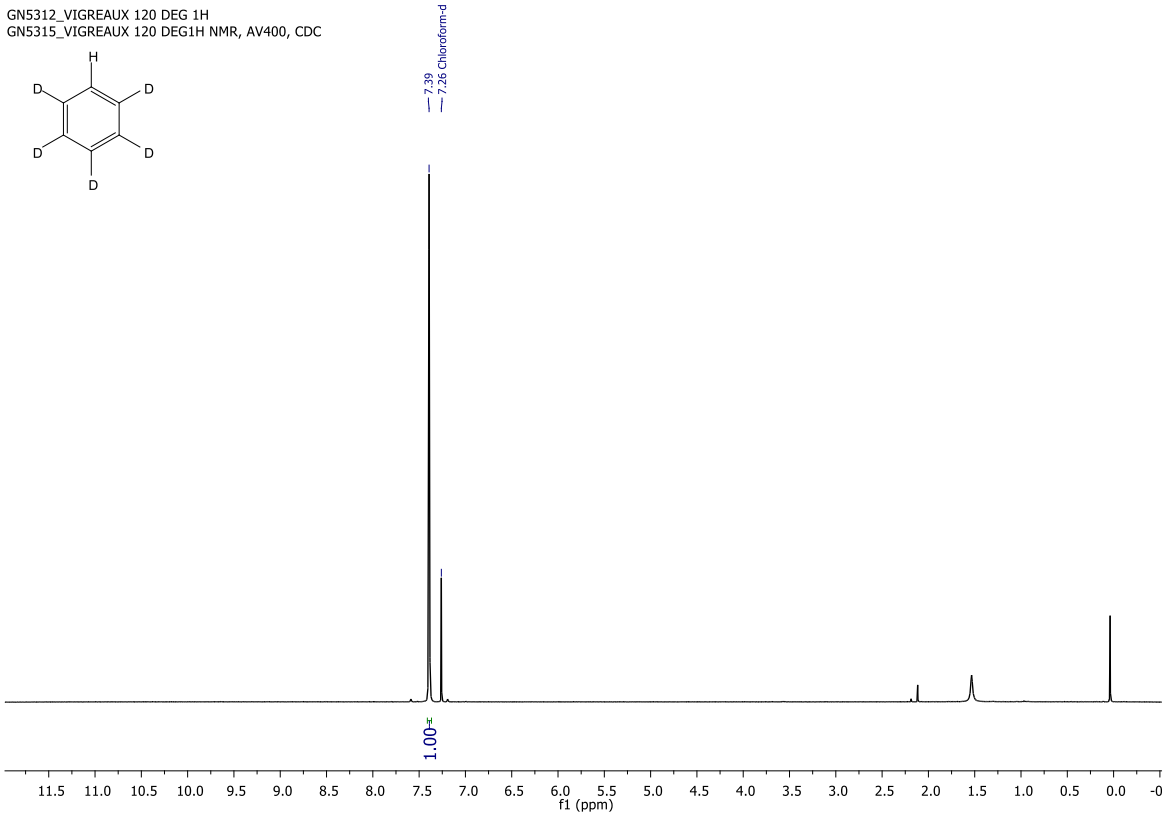
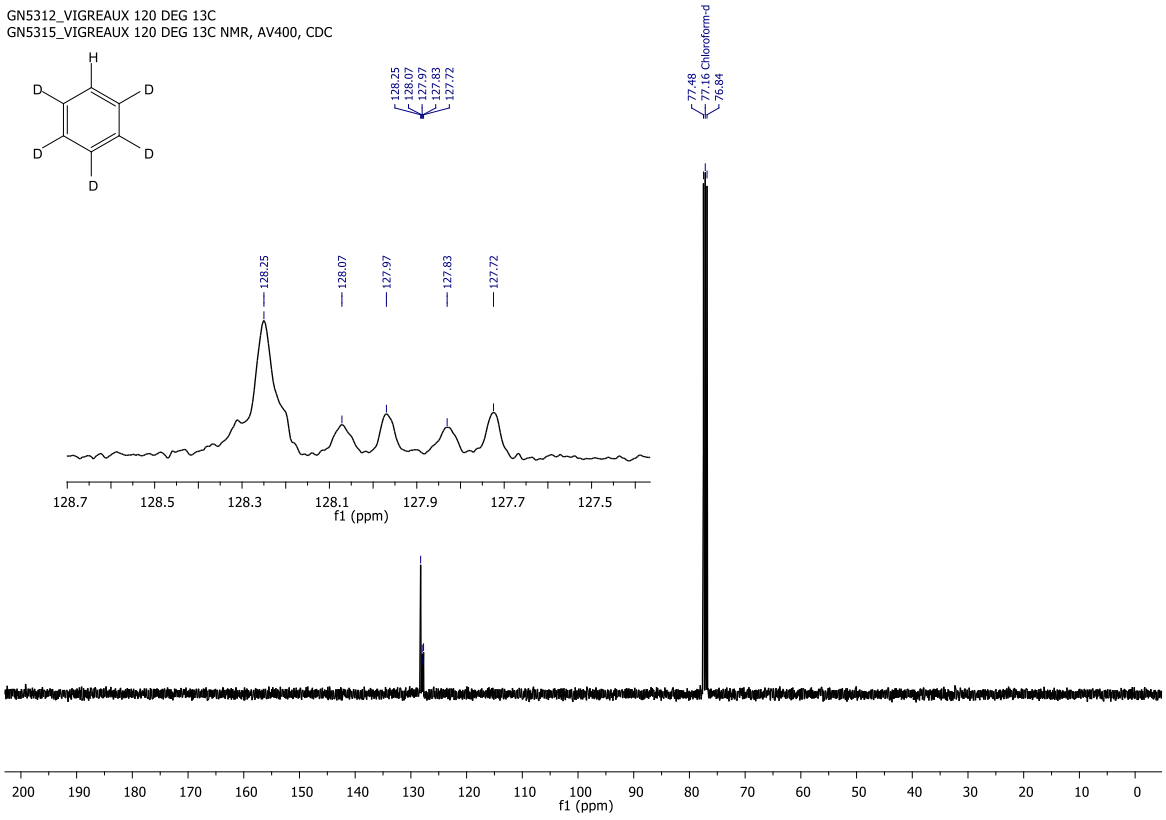
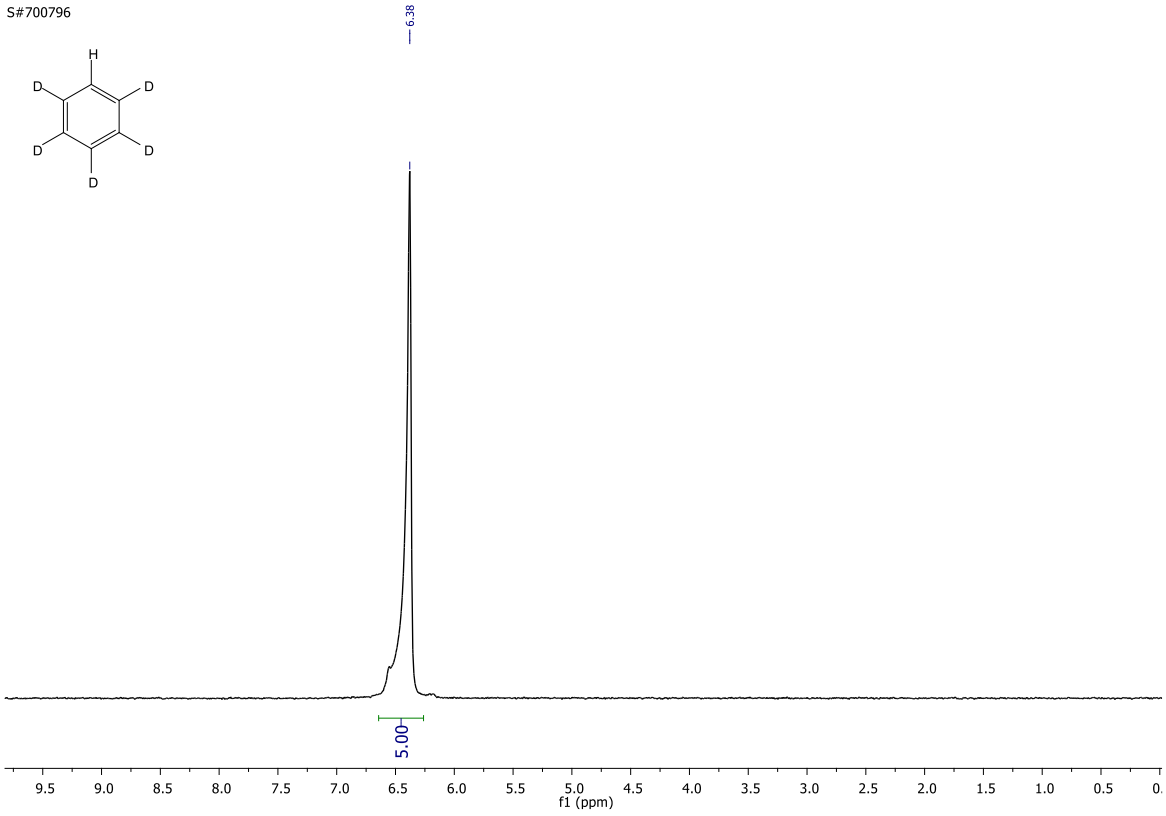
Benzene-d_5, **254** (^{1}HNMR, ^{13}CNMR, ^{2}HNMR shown)



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f1 (ppm)

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